

ORIGINAL ARTICLE

## Olopatadine versus levocetirizine in chronic urticaria: an observer-blind, randomized, controlled trial of effectiveness and safety

Amrita Sil<sup>1</sup>, Santanu Kumar Tripathi<sup>2</sup>, Anita Chaudhuri<sup>3</sup>, Nilay Kanti Das<sup>4</sup>, Avijit Hazra<sup>5</sup>, Chiranjib Bagchi<sup>6</sup> & Chowdhury Nazrul Islam<sup>7</sup>

<sup>1</sup>Department of Pharmacology, Burdwan Medical College, Burdwan, West Bengal, India, <sup>2</sup>Department of Clinical and Experimental Pharmacology, School of Tropical Medicine, Kolkata-73, West Bengal, India, <sup>3</sup>Department of Dermatology, Venereology and Leprology, Burdwan Medical College and Hospital, Burdwan, West Bengal, India, <sup>4</sup>Department of Dermatology, Venereology and Leprology, Medical College, Kolkata-73, West Bengal, India, <sup>5</sup>Department of Pharmacology, Institute of Postgraduate Medical Education & Research, Kolkata-20, West Bengal, India, <sup>6</sup>Department of Clinical and Experimental Pharmacology, School of Tropical Medicine, Kolkata and <sup>7</sup>Department of Pharmacology, Institute of Postgraduate Medical Education & Research, Kolkata-20, West Bengal, India

**Objectives:** Chronic urticaria (CU) is characterized by frequent appearance of wheals for  $\geq 6$  weeks. This study was undertaken to compare effectiveness and safety of olopatadine, a newer antihistamine with additional anti-inflammatory properties, in treating CU in comparison to the established second-generation antihistamine levocetirizine. **Methods:** A single center, assessor-blind, randomized (1:1), active-controlled, parallel group, Phase IV trial (CTRI/2011/08/001965) was conducted with 120 adult CU patients of either sex. Subjects received either olopatadine (5 mg b.i.d.) or levocetirizine (5 mg/day) for 9 weeks, continuously for first 4 weeks and then on demand basis for last 5 weeks. Primary outcome measures were urticaria activity score (UAS) and urticaria total severity score (TSS). Routine hematological and biochemical tests and treatment-emergent adverse events were monitored for safety. **Results:** Data from 54 subjects on olopatadine and 51 on levocetirizine were analyzed for effectiveness. UAS and TSS values declined significantly with both drugs over the treatment period but the reduction was greater with olopatadine. Adverse event profiles were comparable with sedation being the commonest complaint. **Conclusions:** Olopatadine is a safe and more effective alternative to levocetirizine in the treatment of CU.

**Key words:** chronic urticaria, dermatologic life quality index, olopatadine, randomized controlled trial, urticaria activity score, urticaria total severity score

### Introduction

Urticaria is characterized by the appearance of itchy wheals on the skin. Although most episodes of urticaria are transient, occasionally it may become recurrent or persistent without clearly identifiable triggers. Chronic urticaria (CU) has been defined as a distressing dermatosis characterized by evanescent wheals, itching, and erythema appearing daily or near daily (at least three times a week) for at least 6 weeks (1). It remains a vexing problem as it often responds incompletely to treatment, and patients remain uncomfortable and perturbed by the chronic pruritus. Epidemiological studies suggest a lifetime incidence of 15–25% for

urticaria (2,3), with greater propensity in middle-aged women (4). CU has been reported to affect 0.1–3% of the population (5,6). The prevalence in unselected dermatological patients was found to be around 1.85% (7,8).

Histamine is known to be an important mediator in urticaria. Second-generation  $H_1$ -receptor antagonists (antihistamines) are now considered first-line treatment in CU (9,10). Olopatadine hydrochloride is a selective  $H_1$ -receptor antagonist with the additional ability to inhibit release of inflammatory lipid mediators, such as leukotrienes and thromboxane  $A_2$ , from human polymorphonuclear leukocytes and eosinophils (11). It also hinders production of cytokines, such as interleukin (IL) 6 and IL-8 (12,13), and reduces histamine-enhanced TNF $\alpha$ -stimulated expression of adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1) and E-selectin (14). These data suggest that olopatadine may offer additional therapeutic benefits over that afforded by  $H_1$ -receptor antagonism alone.

PubMed search on 27 July 2012 using the keywords “olopatadine AND urticaria” and “olopatadine AND chronic urticaria” with the limits set to “clinical trial, controlled clinical trial, randomized controlled trial, multicentric study, meta-analysis, systematic review”, found only a single published randomized controlled trial comparing olopatadine and cetirizine in the English literature (15). Therefore, this superiority trial was undertaken to compare the effectiveness and safety of this newly introduced antihistamine, olopatadine with a standard second-generation antihistamine, levocetirizine (16), in management of CU.

### Methods

The study was designed as a single center, observer-blind, randomized (1:1), active-controlled, parallel group, Phase IV trial. Recruitment period was from March 2010 to February 2011. Eligible subjects were adults ( $>18$  years) of either sex suffering from CU and attending the dermatology outpatient department of a teaching hospital in eastern India. The operational definition of CU has been stated above (1,17). Exclusion criteria were pregnancy, lactation, advanced disease of vital organs, immunosuppression due to drug or disease, and history of alcohol or

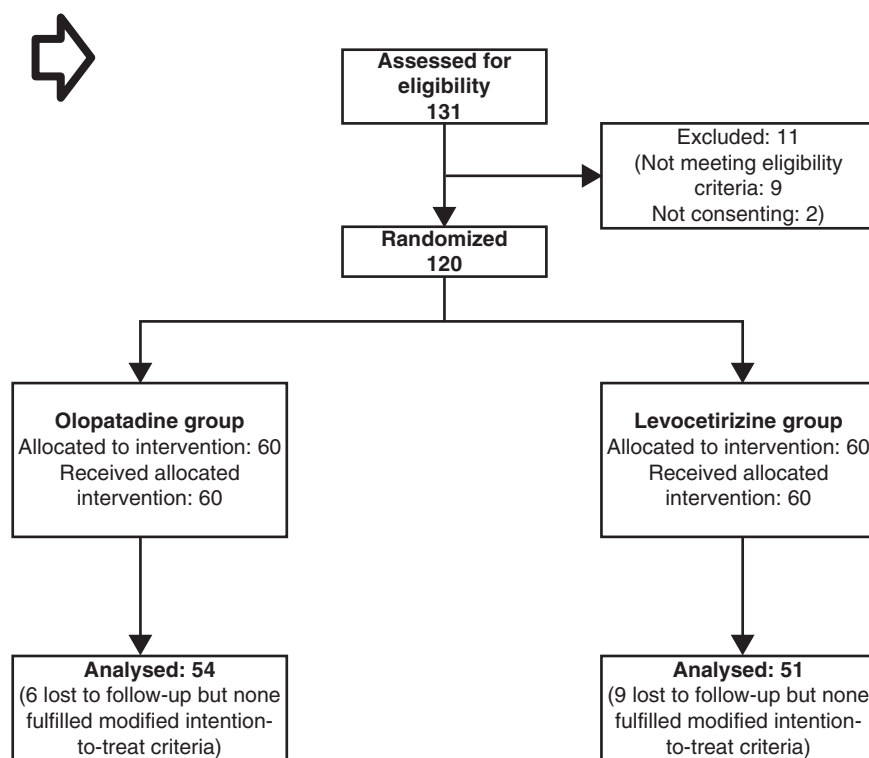


Figure 1. Flow chart of study participants.

substance abuse. Also excluded were drivers of any vehicle, machinery operators, those in whom sedation/drowsiness at workplace could be an issue, patients likely to change their sleep-wake cycle and those who had participated in any other trial in the past 3 months. The study was approved by the institutional ethics committee and written informed consent was obtained from all subjects. It was also registered with Clinical Trial Registry India – CTRI/2011/08/001965.

Consecutive eligible subjects were allocated, using a computer-generated random number list (simple, randomization with 1:1 allocation), to one of two oral treatment groups – olopatadine 5 mg b.i.d. (1 tablet twice daily) after food or levocetirizine 5 mg/day (1 tablet) in the evening after food. The dosage regime was chosen from the standard dose used in most published clinical trials of CU (18,19). A run-in period of 2 days was allowed prior to randomization. Allocation concealment was done by sequentially numbered opaque envelopes. The medicines were given continuously for 4 weeks following which they were continued on on-demand basis for further 5 weeks. This design was chosen to obtain control in 1 month and then taper all subjects to the least frequent dosing schedule which controls the urticaria (on-demand period). Subjects appeared for follow-up visits at the end of every week for 5 weeks and thereafter for a final visit at 9 weeks following randomization. For olopatadine hydrochloride, the formulation marketed by Ajanta Pharma Ltd, Mumbai (PATADIN tablets, Batch no. L0010A, Manufacturing date 01/2010, Expiry date 12/2011) was utilized. For levocetirizine, the formulation marketed by Systopic Laboratories Private Ltd, Mumbai (LEVOSIZ tablets, Batch no. 1140 LZ, Manufacturing date 09/2009, Expiry date 08/2011) was used. Both drugs were donated, on request, by the respective companies for trial purpose. These companies had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The physicians conducting study-related assessment were unaware of the exact identity of the drug being administered.

However, single- and double-blinding were precluded by the difference in the dosing regimen and by the fact that the tablets were not identical in appearance. Compliance was assessed by the traditional pill count method.

The primary outcome measures for effectiveness were urticaria activity score (UAS) (20) and urticaria total severity score (TSS) (21). UAS is a measure of disease activity derived from the wheal number and size (0: <10 small wheals [diameter <3 cm]; 1: 10–50 small wheals or <10 large wheals [diameter >3 cm]; 2: >50 small wheals or 10–50 large wheals; 3: almost whole body covered) and the itch severity score (0: none; 1: mild; 2: moderate; 3: severe). TSS is derived from the number and size of wheals, intensity of pruritus, duration of persistence of lesions, frequency of appearance of lesions, and frequency of antihistamine use with each parameter having a score of 0–3, maximum score being 18. TSS was a more comprehensive parameter than UAS; however, UAS being simpler to use is more commonly used by dermatologists. The secondary outcomes were patients' global assessment of disease activity improvement and physicians' global assessment of disease activity improvement, both scored on a 5-point Likert scale (0: no improvement; 1: mild improvement; 2: moderate improvement; 3: marked improvement; 4: excellent improvement) (22). These parameters were assessed at 1, 2, 3, 4, 5, and 9 weeks following randomization.

Safety assessment included vital signs, treatment-emergent clinical adverse events and routine hematological and biochemical tests. The laboratory tests were done at baseline and after 4 weeks of continuous therapy with trial medication. These included hemoglobin, total and differential leukocyte count, platelet count, creatinine, total and conjugated bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase (ALP), and fasting blood glucose.

Quality of life in urticaria patients was assessed by a validated vernacular (Bengali) version of Dermatology Life Quality Index (DLQI) [http://www.dermatology.org.uk/downloads/DLQI\_Ben

Table I. Demographic profile of study population.

| Category                           | Olopatadine group<br>(n = 54) | Levocetirizine group<br>(n = 51) | p value<br>(between groups) |
|------------------------------------|-------------------------------|----------------------------------|-----------------------------|
| <b>Age (in years)</b>              |                               |                                  |                             |
| Range                              | 19–80                         | 19–80                            |                             |
| Mean ± SD                          | 31.06 ± 13.98                 | 33.02 ± 12.05                    | 0.442                       |
| Median (IQR)                       | 26.5 (20.0–38.0)              | 32 (24.25–39.50)                 |                             |
| <b>Sex</b>                         |                               |                                  | 0.162                       |
| Male                               | 38 (70.37%)                   | 29 (56.86%)                      |                             |
| Female                             | 16 (29.63%)                   | 22 (43.14%)                      |                             |
| <b>Residence</b>                   |                               |                                  | 0.696                       |
| Urban                              | 26 (48.15%)                   | 22 (43.14%)                      |                             |
| Rural                              | 28 (51.85%)                   | 29 (56.86%)                      |                             |
| <b>Literacy</b>                    |                               |                                  | 0.445                       |
| None (Illiterate)                  | 9 (16.67%)                    | 6 (11.76%)                       |                             |
| Up to 4 years                      | 4 (7.41%)                     | 6 (11.76%)                       |                             |
| 5–10 years                         | 24 (44.44%)                   | 29 (56.86%)                      |                             |
| >10 years                          | 17 (31.48%)                   | 10 (19.62%)                      |                             |
| <b>Occupation</b>                  |                               |                                  | 0.216                       |
| Student                            | 11 (20.37%)                   | 8 (15.69%)                       |                             |
| Housewife                          | 6 (11.11%)                    | 15 (29.41%)                      |                             |
| Agricultural work                  | 12 (22.22%)                   | 8 (15.69%)                       |                             |
| Non-agricultural outdoor work      | 9 (16.67%)                    | 6 (11.76%)                       |                             |
| Non-agricultural indoor work       | 16 (29.63%)                   | 14 (27.45%)                      |                             |
| <b>Duration of illness (month)</b> |                               |                                  | 0.078                       |
| Range                              | 2–48                          | 2–48                             |                             |
| Mean ± SD                          | 13.84 ± 15.95                 | 11.41 ± 7.62                     |                             |
| Median (IQR)                       | 4.0 (2.0–24.0)                | 10.0 (8.0–12.0)                  |                             |
| <b>Subtypes of CU</b>              |                               |                                  | 0.077                       |
| Idiopathic                         | 20 (37.04%)                   | 22 (43.14%)                      |                             |
| Symptomatic dermatographism        | 13 (24.07%)                   | 10 (19.61%)                      |                             |
| Solar urticaria                    | 15 (27.78%)                   | 6 (11.76%)                       |                             |
| Cholinergic urticaria              | –                             | 4 (7.84%)                        |                             |
| Cold urticaria                     | 4 (7.41%)                     | 4 (7.84%)                        |                             |
| Aquagenic urticaria                | 2 (3.70%)                     | 5 (9.81%)                        |                             |

SD = Standard deviation; IQR = Interquartile range.

Literacy is expressed in terms of number of years of formal education.

The p value for between group comparisons is from Mann–Whitney U test (for age and duration of illness), Fisher's exact test (for sex and residence distribution) or chi-square test (for categorical variables; last three categories clubbed together for CU subtypes).

gali.pdf], which consisted of 10 questions, each scored between 0 and 3 (23). Permission was obtained from the developer (Finlay AY) for the use of the questionnaire.

The target sample size was 120, with 60 evaluable subjects in each group. This was calculated to detect a difference of 2 in TSS between groups, with 80% power, 5% probability of type 1 error standard deviation of 3.5 and possible 20% dropouts, considering a superiority trial. Continuous variables were compared between groups by independent samples *t*-test and within group by paired *t*-test. Mann–Whitney U test and Wilcoxon matched pairs signed-rank test were employed for comparison of unpaired and paired non-parametric data. Friedman's analysis of variance (ANOVA) was carried out with non-parametric data for within group repeated measures comparisons, followed by *post hoc* Dunn's test. Categorical data were compared between groups by chi-squared test or Fisher's exact test, as appropriate. MedCalc version 11.6 (Mariakerke, Belgium: MedCalc Software, 2011) and GraphPad Prism version 5 (San Diego, California, USA: GraphPad Software Inc., 20057) software were used for statistical analysis.

Effectiveness analysis was done on modified intention-to-treat basis with subjects reporting for at least two post-baseline follow-up visits. Missing values were dealt with by the last observation carried forward strategy. Pre- and post-treatment laboratory

values were compared in patients for whom both sets of data were available. For other safety analysis, all subjects who had received at least one dose of a study drug (essentially all 120 subjects) were considered.

## Results

The flow of study participants is depicted in Figure 1. Altogether, of the 120 subjects randomized, 105 (87.5%) comprised the intention-to-treat dataset, while the rest were lost to follow-up (termination of trial prior to 2 weeks of follow-up).

As seen from Table I, males outnumbered females and, patients were mostly in their thirties, indicating a preponderance of young adult subjects. Study groups were comparable at baseline with respect to age, sex, rural–urban status and distribution of income

Table II. Changes in primary outcome measures over the 9-week study period.

|                        | Olopatadine group<br>(n = 54) | Levocetirizine group<br>(n = 51) | p value<br>(between groups) |
|------------------------|-------------------------------|----------------------------------|-----------------------------|
| <b>UAS</b>             |                               |                                  |                             |
| Baseline               |                               |                                  | 0.549                       |
| Mean ± SD              | 33.57 ± 6.71                  | 34.32 ± 6.60                     |                             |
| Median (IQR)           | 35 (28–42)                    | 35 (28–42)                       |                             |
| First follow-up (1 w)  |                               |                                  | 0.006                       |
| Mean ± SD              | 3.76 ± 8.13*                  | 8.65 ± 9.86*                     |                             |
| Median (IQR)           | 0 (0–0)                       | 7 (0–14)                         |                             |
| Second follow-up (2 w) |                               |                                  | <0.001                      |
| Mean ± SD              | 3.50 ± 6.76*                  | 8.51 ± 8.67*                     |                             |
| Median (IQR)           | 0 (0–7)                       | 7 (0–12.5)                       |                             |
| Third follow-up (3 w)  |                               |                                  | <0.001                      |
| Mean ± SD              | 2.20 ± 6.50*                  | 10.43 ± 11.41*                   |                             |
| Median (IQR)           | 0 (0–0)                       | 7 (0–21)                         |                             |
| Fourth follow-up (4 w) |                               |                                  | 0.004                       |
| Mean ± SD              | 1.94 ± 5.99*                  | 8.92 ± 11.55*                    |                             |
| Median (IQR)           | 0 (0–0)                       | 0 (0–19.25)                      |                             |
| Fifth follow-up (5 w)  |                               |                                  | <0.001                      |
| Mean ± SD              | 6.09 ± 9.81*                  | 16.88 ± 12.14*                   |                             |
| Median (IQR)           | 0 (0–7)                       | 14 (7–21)                        |                             |
| End-of-study (9 w)     |                               |                                  | <0.001                      |
| Mean ± SD              | 8.17 ± 10.24*                 | 14.41 ± 10.70*                   |                             |
| Median (IQR)           | 7 (0–14)                      | 15 (13–16)                       |                             |
| <b>Urticaria TSS</b>   |                               |                                  |                             |
| Baseline               |                               |                                  | 0.633                       |
| Mean ± SD              | 15.24 ± 3.88                  | 14.63 ± 1.48                     |                             |
| Median (IQR)           | 15 (14–15)                    | 15 (13–16)                       |                             |
| First follow-up (1 w)  |                               |                                  | 0.009                       |
| Mean ± SD              | 4.81 ± 3.63*                  | 6.92 ± 4.05*                     |                             |
| Median (IQR)           | 3 (3–3)                       | 6 (3–11.75)                      |                             |
| Second follow-up (2 w) |                               |                                  | <0.001                      |
| Mean ± SD              | 4.89 ± 3.35*                  | 7.53 ± 3.87*                     |                             |
| Median (IQR)           | 3 (3–6)                       | 8 (3–10)                         |                             |
| Third follow-up (3 w)  |                               |                                  | <0.001                      |
| Mean ± SD              | 4.17 ± 2.94*                  | 7.39 ± 4.54*                     |                             |
| Median (IQR)           | 3 (3–3)                       | 7 (3–11)                         |                             |
| Fourth follow-up (4 w) |                               |                                  | 0.007                       |
| Mean ± SD              | 3.93 ± 2.45*                  | 6.50 ± 4.38*                     |                             |
| Median (IQR)           | 3 (3–3)                       | 3 (3–11)                         |                             |
| Fifth follow-up (5 w)  |                               |                                  | <0.001                      |
| Mean ± SD              | 3.75 ± 4.55*                  | 8.51 ± 4.36*                     |                             |
| Median (IQR)           | 1 (0–8)                       | 9 (4–12)                         |                             |
| End-of-study (9 w)     |                               |                                  | <0.001                      |
| Mean ± SD              | 4.83 ± 4.73*                  | 8.18 ± 3.85*                     |                             |
| Median (IQR)           | 4 (0–9)                       | 9 (6–10)                         |                             |

SD = Standard deviation; IQR = Interquartile range; w = weeks.

The p value for between group comparisons is from Mann–Whitney U test.

\*Denotes *p* < 0.001 for within group comparison between baseline and the particular visit (Friedman's ANOVA followed by *post hoc* Dunn's test).

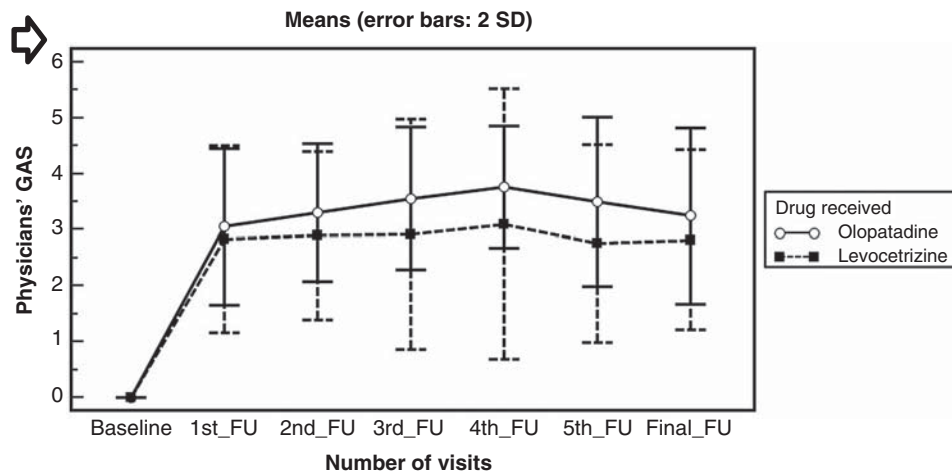


Figure 2. Line diagram of physicians' global assessment of disease activity improvement scale (physicians' GAS) of olopatadine and levocetirizine. FU = Follow up.

and occupation categories. The duration of urticaria at presentation was median 4 (interquartile range [IQR]: 2–24) months in the olopatadine arm and 10 (IQR: 8–12) months in the levocetirizine arm ( $p = 0.078$ ). There was also no significant difference between the two groups regarding the subtypes of CU.

Changes in disease activity scores are depicted in Table II. It is evident that UAS declined significantly in both treatment arms over the 9-week treatment period ( $p < 0.001$ ) – the decline becoming significant from the end of the first week itself. At baseline, the scores were comparable between groups. However, the overall reduction of UAS was greater with olopatadine (from median 35 [IQR: 28–42] to median 7 [IQR: 0–14]) than with levocetirizine (from median 35 [IQR: 28–42] to median 15 [IQR: 13–16];  $p < 0.001$ ). Changes in TSS showed a similar pattern. The decline was significant for both drugs, but the overall decline was greater for olopatadine (from median 15 [IQR: 14–15] to median 4 [IQR: 0–9]) than for levocetirizine (median 15 [IQR: 13–16] to median 9 [IQR: 6–10];  $p < 0.001$ ).

Rating of disease severity (Figures 2 and 3) showed that at study end the proportion of subjects rated as improved/very much improved, by the physicians was significantly greater for olopatadine than for levocetirizine ( $p = 0.005$ ). Patient global rating of disease activity improvement also showed trend favoring olopatadine ( $p = 0.002$ ).

DLQI in olopatadine group decreased significantly ( $p < 0.001$ ) from median 8 (IQR: 6–11.5) at baseline to median 0 (IQR: 0–1) at the end of 4 weeks of therapy. In levocetirizine group also it

decreased significantly ( $p < 0.001$ ) from median 8 (IQR: 5.5–14.5) at baseline to median 1 (IQR: 0–1) at end of continuous treatment. Intergroup comparison of DLQI returned  $p$  value of 0.639 at baseline and 0.161 at 4 weeks.

Heart rate and blood pressure values did not reveal any statistically significant changes (data not shown). A total of 100 subjects (52 on olopatadine and 48 on levocetirizine) had both baseline and follow-up laboratory data available for analysis. The changes are summarized in Table III. There was statistically significant lowering of eosinophil count in both treatment arms, but no significant difference between groups. Serum total bilirubin showed statistically significant rise in the levocetirizine arm. This is attributable to an increase in bilirubin in two patients, although none were clinically jaundiced at any time. Post-treatment ALP and creatinine values were significantly raised in the olopatadine arm, though still within the normal range. Apart from the two patients with raised bilirubin in the levocetirizine arm, laboratory test abnormalities in individual subjects were not considered significant enough to be reported as adverse event for any subject.

During the 9-week study period, 58 of the 60 patients on olopatadine spontaneously reported treatment-emergent adverse event. The corresponding figure for the levocetirizine arm was 56. The profile of clinical adverse events has been summarized in Table IV. These events were all mild to moderate in nature and were rated as possibly related to the study drug. Most resolved during the study period and none required drug withdrawal. No serious adverse events (events that were

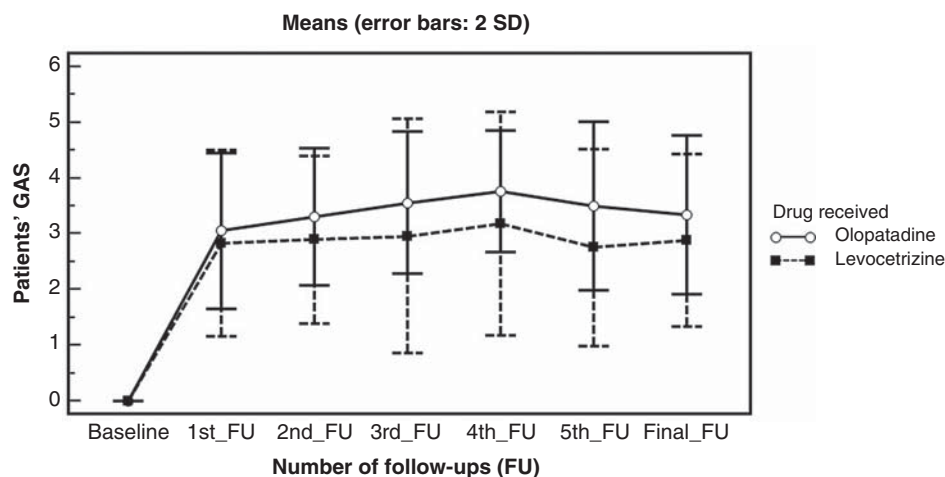


Figure 3. Line diagram of patients' global assessment of disease activity improvement scale (patients' GAS) of olopatadine and levocetirizine. FU = Follow up.

Table III. Changes in laboratory test parameters in the two treatment arms.

| Category                          | Olopatadine group<br>(n = 52) | Levocetirizine group<br>(n = 48) | p value<br>(between groups) |
|-----------------------------------|-------------------------------|----------------------------------|-----------------------------|
| Hemoglobin (g/dL)                 |                               |                                  |                             |
| Baseline                          | 11.54 ± 1.12                  | 11.56 ± 1.34                     | 0.935                       |
| Fourth follow up                  | 11.95 ± 1.40                  | 11.31 ± 1.64                     | 0.037                       |
| Before-after p value              | 0.068                         | 0.362                            |                             |
| TLC (cells/ µL)                   |                               |                                  |                             |
| Baseline                          | 7290 ± 2017.40                | 7756.25 ± 888.92                 | 0.014                       |
| Fourth follow up                  | 7200 ± 1515.93                | 7634.31 ± 1433.57                | 0.027                       |
| Before-after p value              | 0.892                         | 0.281                            |                             |
| Differential eosinophil count (%) |                               |                                  |                             |
| Baseline                          | 7.31 ± 5.40                   | 5.85 ± 4.45                      | 0.021                       |
| Fourth follow up                  | 5.25 ± 4.14                   | 5.13 ± 4.72                      | 0.507                       |
| Before-after p value              | 0.002                         | 0.021                            |                             |
| ESR (mm in first hour)            |                               |                                  |                             |
| Baseline                          | 15.64 ± 14.03                 | 19.73 ± 18.78                    | 0.541                       |
| Fourth follow up                  | 16.38 ± 10.81                 | 22.38 ± 33.17                    | 0.448                       |
| Before-after p value              | 0.384                         | 0.380                            |                             |
| Bilirubin (mg/dL)                 |                               |                                  |                             |
| Baseline                          | 0.91 ± 0.30                   | 0.81 ± 0.20                      | 0.041                       |
| Fourth follow up                  | 0.91 ± 0.28                   | 1.12 ± 0.80                      | 0.078                       |
| Before-after p value              | 0.904                         | 0.014                            |                             |
| ALT (U/L)                         |                               |                                  |                             |
| Baseline                          | 47.63 ± 34.21                 | 45.56 ± 43.92                    | 0.792                       |
| Fourth follow up                  | 38.75 ± 29.28                 | 47.92 ± 55.51                    | 0.299                       |
| Before-after p value              | 0.048                         | 0.808                            |                             |
| AST (U/L)                         |                               |                                  |                             |
| Baseline                          | 36.48 ± 26.81                 | 39.67 ± 27.47                    | 0.559                       |
| Fourth follow up                  | 35.63 ± 28.52                 | 49.27 ± 54.85                    | 0.118                       |
| Before-after p value              | 0.838                         | 0.252                            |                             |
| ALP (U/L)                         |                               |                                  |                             |
| Baseline                          | 211.42 ± 79.26                | 200.44 ± 69.02                   | 0.463                       |
| Fourth follow up                  | 237.33 ± 121.19               | 175.83 ± 79.15                   | 0.004                       |
| Before-after p value              | 0.035                         | 0.077                            |                             |
| Creatinine (mg/dL)                |                               |                                  |                             |
| Baseline                          | 0.92 ± 0.17                   | 0.88 ± 0.15                      | 0.233                       |
| Fourth follow up                  | 0.94 ± 0.20                   | 0.99 ± 0.19                      | 0.213                       |
| Before-after p value              | 0.413                         | < 0.001                          |                             |
| Fasting blood glucose (mg/dL)     |                               |                                  |                             |
| Baseline                          | 94.77 ± 26.01                 | 99.48 ± 41.83                    | 0.497                       |
| Fourth follow up                  | 95.73 ± 23.17                 | 104.63 ± 37.27                   | 0.152                       |
| Before-after p value              | 0.841                         | 0.295                            |                             |

SD = Standard deviation; IQR = Interquartile range.

The p value for between group comparison of variables is from Student's independent samples t-test when normally distributed or Mann-Whitney U test when otherwise. Those for within group comparison is from paired t-test when normally distributed or Wilcoxon matched pairs signed-rank test when otherwise.

fatal/life-threatening/incapacitating/disabling or requiring hospitalization for management) were encountered and there were no hospitalizations during the study period.

Compliance was rated for all subjects who completed the study as per protocol. In the olopatadine arm, the rating was excellent (missed doses <10% of total scheduled doses) for 50, good (10–20% missed doses) for 2 and fair (20–30% missed doses) for the rest 2. The corresponding figures in the levocetirizine arm were not significantly different at 48, 3, and 0. These compliance break points were fixed *a priori* and were assessed at baseline and at the end of continuous therapy with medications.

## Discussion

The natural course of CU is unpredictable and often recalcitrant. One study prospectively evaluated 220 patients for up to 3 years and found that only 35% were symptom-free after 1 year and among the rest, at study end, only 47% achieved remission (24). This highlights the fact that CU treatment needs to be long term,

for which it is desirable that medication should impose tolerable pill, adverse event and monetary burden. There is, therefore, need for comparative evaluation of any new drug that is introduced against existing remedies. This prompted us to undertake the trial. Levocetirizine was the comparator drug in our study as it is now well-established in the treatment of CU and has a simple dosing regimen. Recent studies have shown it to be equivalent or better than loratadine and desloratadine in chronic idiopathic urticaria (16,18,25).

The study was designed as an observer-blind, randomized, controlled trial. A double-blind trial is ideal but we did not have access to the logistical requirements to ensure true double-dummy packaging of the study medication due to the difference in dosing regimen. However, the observer who assessed subjects was different from the one who dispensed the study drugs and this observer was strictly prohibited from asking questions regarding the dosing regimen.

The median duration of urticaria symptoms well exceeded 6 weeks in both groups and the cases belonged mostly to the idiopathic or physical urticaria categories. The primary outcome measures for effectiveness were UAS (20) and TSS (21). Both these scores are semi-objective methods of evaluating disease activity in urticaria. UAS is used most often, but, unlike UAS, TSS incorporates the need for antihistamines and can reflect the changing pill burden on the patient. Also duration of persistence of symptoms and frequency of appearance of wheals are considered in TSS. We, therefore, decided to utilize both.

The results show that olopatadine 5 mg b.i.d. is effective in CU, with substantial symptom relief to be expected at the end of only 1 week of treatment. The extent of improvement is likely to be greater than with levocetirizine 5 mg/day. Clinical studies of olopatadine in Japanese patients with pruritic dermatoses showed significant symptom reduction and at least comparable efficacy to other agents currently used in Japan (26). Takahashi et al. evaluated the effects of olopatadine, cetirizine and fexofenadine during a 24-h period in a double-blind, randomized, crossover comparison of skin responses induced by histamine iontophoresis (27). Olopatadine completely suppressed the wheal response induced by a 0.2-mA histamine iontophoresis, while fexofenadine and cetirizine were less effective. Effects of olopatadine on histamine-induced skin responses were also evaluated by Hashimoto et al. in 10 healthy subjects in comparison with placebo, fexofenadine and bepotastine (28). Olopatadine significantly suppressed histamine-induced wheal-flare-itch and was more effective than fexofenadine and bepotastine. Our results are in concordance with these studies. It is worth mentioning that

Table IV. Treatment-emergent clinical adverse events encountered over 9 weeks.

| Adverse event       | Olopatadine group<br>(n = 60) | Levocetirizine group<br>(n = 60) | p value<br>(between groups) |
|---------------------|-------------------------------|----------------------------------|-----------------------------|
| Sedation            | 34 (56.67%)                   | 37 (61.67%)                      | 0.711                       |
| Dryness of mouth    | 12 (20.00%)                   | 9 (15.00%)                       | 0.632                       |
| Constipation        | 4 (6.67%)                     | –                                | 0.119                       |
| Nausea              | 2 (3.33%)                     | 2 (3.33%)                        | 1.000                       |
| Palpitation         | 2 (3.33%)                     | –                                | 0.496                       |
| Cough               | 1 (1.67%)                     | 3 (5.00%)                        | 0.619                       |
| Fatigue             | 1 (1.67%)                     | 1 (1.67%)                        | 1.000                       |
| Increased appetite  | 1 (1.67%)                     | 2 (3.33%)                        | 1.000                       |
| Loose stools        | 1 (1.67%)                     | 1 (1.67%)                        | 1.000                       |
| Epigastric distress | –                             | 1 (1.67%)                        | 1.000                       |

The numbers represent counts (percentages) within respective groups. The p value is from Fischer's exact test.

there is a dearth of clinical trials with olopatadine in CU. An earlier open-label Indian trial on chronic idiopathic urticaria showed that the mean UAS score declined significantly from 3.7 at baseline to 1.9 at 2 weeks and further to 1.2 at 4 weeks (19). It is also noteworthy that in our study the beneficial effects were present not only during the first 4 weeks of continued treatment but also during the subsequent 5 weeks of on-demand use. Thus, patients continue to get benefit along with reduction of the pill burden.

Olopatadine, by virtue of its property of inhibiting the release of leukotrienes and thromboxane A<sub>2</sub> from human polymorphonuclear leukocytes and eosinophils, reducing histamine-induced secretion of IL-6 and IL-8 and histamine-enhanced TNF $\alpha$ -stimulated adhesion molecule expression, is a novel antihistamine (11,14). Expression of ICAM-1 and E-selectin are also inhibited at therapeutic doses. Although speculative, these additional activities may account for greater improvement seen with olopatadine as compared to levocetirizine.

Regarding changes in laboratory parameters, similar to our study, Anuradha et al. have also reported that differential eosinophil count gets lowered with antihistamine treatment in CU (18). Relatively large changes were noted in some liver function test parameters in two patients on levocetirizine. Although, clinically asymptomatic, these two were considered to have suffered potential drug-induced hepatotoxicity and were withdrawn from levocetirizine. Though ALP in the olopatadine group was raised at 4 weeks, the individual value for all subjects, as well as the group mean, was within normal limits. The levocetirizine group showed significantly raised post-treatment creatinine value, though the individual values and group mean were within normal limits. Thus, it may be concluded that both drugs are safe for continued treatment so far as the biochemical parameters are concerned.

Regarding treatment-emergent clinical adverse events, these were common but mostly in the form of mild sedation or anticholinergic effects like dryness of mouth and constipation. There were no cognitive or psychomotor impairment in any subject. The frequency of individual adverse effects was comparable between the groups. Olopatadine is known to have sedative effect and can potentially impair psychomotor performance (27). In our study, 57% of the patients on olopatadine complained of sedation, which was, however, mild and did not require drug withdrawal. Levocetirizine being excluded from the brain should report less central nervous system effects. However, in our study as well as in other trials, a small proportion of patients reported sedation after taking levocetirizine (29). Study subjects showed mostly excellent compliance. The lack of troublesome adverse events helped in this regard. High degree of compliance in patients suffering from this chronic ailment would favor long-term therapy.

Urticaria patients may suffer from depression and impaired quality of life. Simple aspects of daily life, such as choice of clothes, shopping, looking after home or garden, studying, sleeping, sexual activities, become demanding. DLQI provides an assessment of the quality of life in such patients. The significant decline in DLQI scores in both the treatment arms indicates that these medications have a favorable effect on the quality of life.

This study has its share of limitation. Double dummy method of double blinding could not be used due to logistical reasons. Classifying the urticaria into subtypes was solely based on clinical examination and the numbers were not sufficient to attempt subgroup comparison. The large number of follow-ups may be a reason behind the 12.5% attrition rate. However, this was necessary to detect the trend in response to therapy. Also, whether

beneficial effects are sustained to any extent after drug discontinuation was not assessed. Finally, we did not attempt formal cost comparisons. However, the unit price of the study drugs in the Indian market suggests that cost should not be a major impediment to treatment and it is expected, from the reduction in symptom intensity noted, that there should be definite improvement in the quality of life.

To conclude, olopatadine is a safe and more effective alternative to levocetirizine in the treatment of CU in adult patients. It remains to be explored if the drug is also safe and beneficial in other patient groups, such as children, with this disorder. Urticaria is a chronic disorder, and any drug used to treat the condition needs an enduring assessment of adverse effects, and so does olopatadine. A more comprehensive long-term trial can give us a deeper insight to both the potential and drawbacks of the molecule.

## Acknowledgement

The authors would like to acknowledge the permission from Prof. Andrew Y Finlay regarding the use of Dermatology Life Quality Index (Bengali version). Also, the support of Dr. Soumya Mukherjee, Assistant Professor, Department of Pathology and laboratory technician of the Department of Biochemistry, Burdwan Medical College is thankfully acknowledged.

**Declaration of interest:** There was no commercial sponsor for this study. Study medication was donated by respective manufacturers and provided to the subjects free of charge. The teaching hospital where the trial was conducted provided complimentary laboratory investigations as required. None of the authors stand to gain financially from the conduct of the study or publication of the results.

## References

- Greaves MW, Sabroe RA. Allergy and the skin I: Urticaria. *Br Med J*. 1998;316:1147–1150.
- Sheldon JM, Mathews KP, Lovell RG. The vexing urticaria problem: present concepts of etiology and management. *J Allergy*. 1954;25:525–560.
- Kozel MM, Mekkes JR, Bossuyt PM, Bos JD. The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. *Arch Dermatol*. 1998;134:1575–1580.
- Lindelof B, Sigurgeirsson B, Wahlgren CF, Eklund G. Chronic urticaria and cancer: an epidemiological study of 1155 patients. *Br J Dermatol*. 1990;123:453–456.
- Warin RP. Food and factors in urticaria. *J Hum Nutr*. 1976;30:179–186.
- Sabroe RA, Greaves MW. The pathogenesis of chronic idiopathic urticaria. *Arch Dermatol*. 1997;133:1003–1008.
- Hellgren L, Hersle K. Acute and chronic urticaria. A statistical investigation on clinical and laboratory data in 1204 patients and matched healthy controls. *Acta Allergol*. 1964;19:406–420.
- Sehgal VN, Rege VL. An interrogative study of 158 urticaria patients. *Ann Allergy*. 1973;31:279–283.
- Kaplan AP, Horakova Z, Katz SI. Assessment of tissue fluid histamine levels in patients with urticaria. *J Allergy Clin Immunol*. 1978;61:350–354.
- Phanuphak P, Schocket AL, Arroyave CM, Kohler PF. Skin histamine in chronic urticaria. *J Allergy Clin Immunol*. 1980;65:371–375.
- Ohmori K, Hayashi K, Kaise T, Ohshima E, Kobayashi S, Yamazaki T, et al. Pharmacological, pharmacokinetic and clinical properties of olopatadine hydrochloride: A new antiallergic drug. *Jpn J Pharmacol*. 2002;88:379–397.
- Giustizieri ML, Albanesi C, Fluhr J, Gisondi P, Norgauer J, Girolomoni G. H1 receptor mediates inflammatory responses in human keratinocytes. *J Allergy Clin Immunol*. 2004;114:1176–1182.
- Ciprandi G, Cirillo I, Vizzaccaro A, Tosca MA. Levocetirizine improves nasal obstruction and modulates cytokine pattern in patients with seasonal allergic rhinitis: a pilot study. *Clin Exp Allergy*. 2004;34:958–964.
- Furukawa H, Takahashi M, Nakamura K, Kaneko F. Effect of an antiallergic drug (Olopatadine hydrochloride) on TARC/CCL17 and

- MDC/CCL22 production by PBMCs from patients with atopic dermatitis. *J Dermatol Sci*. 2004;36:165–172.
15. Okubo Y, Shigoka Y, Yamazaki M, Tsuboi R. Double dose of cetirizine hydrochloride is effective for patients with urticaria resistant: a prospective, randomized, non-blinded, comparative clinical study and assessment of quality of life. *J Dermatolog Treat*. 2011;Epub ahead of print.
  16. Staevska M, Popov TA, Kralimarkova T, Lazarova C, Kraeva S, Popova D, et al. The effectiveness of levocetirizine and desloratidine in up to 4 times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol*. 2010;125:676–682.
  17. Philpott H, Kette F, Hissaria P, Gillis D, Smith W. Chronic urticaria: the autoimmune paradigm. *Intern Med J*. 2008;38:852–857.
  18. Anuradha P, Maiti R, Jyothirmai J, Mujeebuddin O, Anuradha M. Loratidine versus levocetirizine in chronic idiopathic urticaria: A comparative study of efficacy and safety. *Indian J Pharmacol*. 2010;42:12–16.
  19. Godse KV. Olopatadine in chronic idiopathic urticaria. *Indian J Dermatol*. 2009;54:191–192.
  20. Erbagci Z. The leukotriene receptor antagonist montelukast in the treatment of chronic idiopathic urticaria: a single-blind, placebo-controlled, crossover clinical study. *J Allergy Clin Immunol*. 2002;110:484–488.
  21. Bajaj AK, Upadhyay A, Damisetty R, Dhar S. Autologous serum therapy in chronic urticaria: Old wine in a new bottle. *Indian J Dermatol Venereol Leprol*. 2008;74:109–113.
  22. Bonifati C, Berardesca E. Clinical outcome measures of psoriasis. *Reumatismo*. 2007;59:64–67.
  23. Finlay AY. Quality of life indices. *Indian J Dermatol Venereol Leprol*. 2004;70:143–148.
  24. Kozel MM, Mekkes IR, Bossuyt PM, Bos JD. Natural course of physical and chronic urticaria and angioedema in 220 patients. *J Am Acad Dermatol*. 2011;45:387–391.
  25. Potter PC, Kapp A, Maurer M, Guillet G, Jian AM, Hauptmann P, et al. Comparison of the efficacy of levocetirizine 5 mg and desloratidine 5 mg in chronic idiopathic urticaria patients. *Allergy*. 2009;64:596–604.
  26. Ohmori K, Hayashi K, Kaise T, Ohshima E, Kobayashi S, Yamazaki T, et al. Pharmacological, pharmacokinetic and clinical properties of olopatadine hydrochloride, a new antiallergic drug. *Jpn J Pharmacol*. 2002;88:379–397.
  27. Takahashi H, Zhang Y, Morita E. Evaluation of the antihistamine effects of olopatadine, cetirizine and fexofenadine during a 24 h period: a double-blind, randomized, crossover, placebo-controlled comparison in skin responses induced by histamine iontophoresis. *Arch Dermatol Res*. 2008;300:291–295.
  28. Hashimoto T, Ishii N, Hamada T, Dainichi T, Karashima T, Nakama T, et al. Effects of olopatadine hydrochloride, a histamine H1 receptor antagonist, on histamine-induced skin responses. *Dermatol Res Pract*. 2010; Epub 2010 Sep 16.
  29. Dubuske LM. Levocetirizine: the latest treatment option for allergic rhinitis and chronic idiopathic urticaria. *Allergy Asthma Proc*. 2007;28:724–734.