Original Article

Effectiveness and safety of levocetirizine 10 mg versus a combination of levocetirizine 5 mg and montelukast 10 mg in chronic urticaria resistant to levocetirizine 5 mg: A double-blind, randomized, controlled trial

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Abstract

Background: Chronic urticaria is a vexing problem for patients and treating physicians alike. The EAACI/GA²LEN/EDF/WAO guidelines advocate an increased antihistamine dosage up to four times the standard, before adding leukotriene receptor antagonists. Patients are frequently intolerant of these higher dosages. We conducted this study to determine whether the addition of leukotriene receptor antagonists to the standard antihistamine dose was comparable to higher dosages of antihistamines alone, in terms of efficacy, safety and quality of life changes. We compared levocetirizine 10 mg (double dose of standard) versus a combination of levocetirizine 5 mg and montelukast 10 mg in cases of chronic urticaria not responding to single daily dose of 5 mg levocetirizine.

Methods: A single-center, double-blind, randomized, active-controlled, parallel group phase IV trial (CTRI/2014/12/005261) was conducted on 120 patients of chronic urticaria of either sex not responding to 5 mg levocetirizine. Patients were randomized into receiving either levocetirizine 10 mg or levocetirizine 5 mg + montelukast 10 mg for 4 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: Fifty-two patients on levocetirizine 10 mg group and 51 patients on levocetirizine 5 mg + montelukast 10 mg group were analyzed. UAS and TSS reduced significantly in both treatment groups and reduction of score were comparable in between the groups ($P = 0.628$, $P = 0.824$, respectively). Among adverse effects, sedation was noted significantly more ($P = 0.013$) in levocetirizine 10 mg group. Quality of life was significantly improved in levocetirizine 5 mg + montelukast 10 mg group ($P = 0.031$).

Limitations: The limitation of the study was that the follow-up period was 4 weeks.

Conclusion: EAACI/GA²LEN/EDF/WAO guidelines need to be more flexible in allowing usage of montelukast before escalation of anti-histamine dosage.

Key words: Chronic urticaria, levocetirizine, montelukast

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Introduction

Chronic urticaria, a disease characterized by itching and wheals for >6 weeks, has a significant impact on the quality of life of those affected. It is a vexing problem for the treating dermatologist as well, when first-line therapy does not succeed.[1] Being a disease of mast cell release, the various mediators of allergic response are drug targets.[2,3] According to the EAACI/GA²LEN/EDF/WAO guidelines antihistamines in standard pharmacological doses are the first-line weapons, followed by an increased dosage up to fourfold if the symptoms persist after 2 weeks. The guidelines also state that leukotriene receptor antagonists are to be added only if patients do not respond to this increased dosage of antihistamines, with immunomodulators being the ultimate option for recalcitrant urticaria.[4]

Many patients do not tolerate a fourfold increased dosage of antihistamines. Although higher doses often are more effective, they also lead to increased incidence of adverse effects such as sedation, cognitive impairment, dry mouth and urinary retention.[5,6] To obviate this problem, a leukotriene receptor antagonist could be added to a standard dose of antihistamine. Although there are trials demonstrating the role of levocetirizine,[7-10] as well as leukotriene receptor antagonist (montelukast) as monotherapy,[11] and a combination of antihistamine with leukotriene receptor antagonist,[12] we were unable to find any previous double-blind, active control, parallel group trials which compared an escalated dose of levocetirizine with a combination of leukotriene receptor antagonist with standard dose (5 mg) of levocetirizine in treatment of difficult-to-treat/resistant chronic urticaria. Hence, we decided to observe through this study, whether earlier addition of leukotriene receptor antagonists could be useful for difficult-to-treat chronic urticaria patients.

In this study, we have compared the safety, effectiveness and quality of life changes of a double dose of antihistamine (levocetirizine 10 mg) with a combination of leukotriene receptor antagonist with single dose of antihistamine (levocetirizine 5 mg + montelukast 10 mg) in patients not responding to levocetirizine 5 mg alone.

Methods

The study was conducted as a single-center, double-blind, randomized (1:1) parallel group, active control trial. The recruitment period was from March 2014 to March 2015 and the total period of our study was 18 months. Patients >18 years of age of either sex presenting with history or symptoms of chronic urticaria and attending outpatient department of a teaching hospital in the eastern zone of India, were given levocetirizine 5 mg once daily, for 2 weeks. The study definition for chronic urticaria was a disease characterized by itching and wheals for >6 weeks.[1] If they failed to respond, they were screened and recruited into the trial, after providing informed consent. These (resistant) cases were defined as a persons with Urticaria Total Severity Score (TSS) ≥10 (minimum score of TSS = 10 derived by the number of wheals ≤10, size of wheals <1 cm, intensity of pruritus mild, duration of persistence <1 h, frequency of appearance daily or almost daily/week, frequency of antihistamine use daily or almost daily/week).[13] The exclusion criteria were pregnant and lactating women, patients having end-stage renal disease or those who were immunosuppressed due to drug or disease, patients with history of alcohol or substance abuse, participants working in night shifts or those likely to have a change of the usual sleep/wake cycle, patients allergic to levocetirizine, cetirizine or its parent compound hydroxyzine, montelukast and those who had a history of nonsteroidal anti-inflammatory drug intake over the last 15 days. Patients who had participated in any other clinical trial within the past 3 months, those not willing to provide written informed consent or not likely to comply with the trial protocol were also excluded from the study. The trial was approved by the Institutional Ethics Committee and has been registered in Clinical Trial Registry, India (CTRI/2014/12/005261). Computer-generated random number table was used for randomization, which was a simple randomization with 1:1 allocation to divide the patients equally into two groups. Allocation concealment was done by providing medicines in sequentially numbered, opaque sealed envelope (SNOSE).

A person unrelated to the trial packed the medicines in opaque envelopes serially according to the randomization sequence. These packs were handed over to the investigator, thus effectively blinding him to the medicine that the patient was going to receive. The tablets looked similar and were given in opaque envelopes, therefore blinding patients. Thus, double-blinding was achieved.

One treatment group was given tablet levocetirizine 10 mg while the other one was provided a combination of tablet levocetirizine 5 mg + montelukast 10 mg. Both the medications were to be consumed orally once at night after meals for 4 consecutive weeks. For levocetirizine 10 mg, the formulation marketed by Systopic Laboratories Private Limited (levosiz tablets, batch no. L 29013, manufacturing date: 10/2013, expiry date: 9/2015) was utilized. For levocetirizine 5 mg + montelukast 10 mg, the formulation marketed by Systopic Laboratories Private Limited (levosiz M tablets, batch no. LM 350913, manufacturing date: 09/2013, expiry date: 08/2015) was used. Both the medications were supplied by the Systopic Pharmaceuticals for trial purpose, and were provided free-of-cost to the patients participating in the study.

Follow-ups were carried out at weekly intervals for 4 weeks. The primary outcome measures were Urticaria Activity Score (UAS)[14] and Urticaria Total Severity Score (TSS).[13] UAS is the sum total of number and size of the wheals (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 the whole body is covered) and the itch severity score (0 - none; 1 - mild; 2 - moderate; 3 - severe). TSS is the measure of disease activity derived from number and size of wheals, the itch severity score, duration of persistence of lesions, frequency of appearance of wheals and frequency of administration of antihistamine with each of the parameters having score of 0–3, maximum score being 18. TSS includes more parameters as compared to UAS for determining disease activity, but UAS, being simpler, is used more commonly by dermatologists. The secondary outcomes were patient's global assessment of disease activity improvement and physician's global assessment of disease activity improvement, both of which were scored on a 5-point Likert scale (0 - no improvement; 1 - mild improvement; 2 - moderate improvement; 3 - marked improvement; 4 - excellent improvement).[15] The parameters were assessed on 1st, 2nd, 3rd and 4th treatment weeks following randomization.

Safety assessment was done by seeking treatment-emergent adverse effects as reported by the patient or elicited on direct questioning by the treating physician, and routine hematological and biochemical tests. Laboratory parameters were assessed at baseline and after 4 weeks of continuous therapy with trial medication. These

included hemoglobin, total leukocyte count, differential leukocyte count, platelets, erythrocyte sedimentation rate, liver function test (serum bilirubin, alkaline phosphatase, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase), fasting blood sugar, urea and creatinine. Quality of life was assessed by a validated Dermatology Life Quality Index (DLQI) questionnaire in the local (Bengali) language (http://www.dermatology.org.uk/downloads/DLQI_Bengali.pdf) which comprised ten questions.[16] The aim of the questionnaire was to measure the impact of urticaria on the life of the patient. The scoring of each of the questions varied from 0 to 3, where 0 meant "not relevant" or urticaria having "no effect at all" on quality of life, 1 meant "a little" effect, 2 and 3 meant "a lot" and "very much" effect. The DLQI was calculated by by the sum of the scores of answers to all questions, resulting in a maximum of 30 and a minimum of 0. A higher score represented a greater impairment of the quality of life.

The target sample size was 49 evaluable urticaria patients in each treatment group. This was calculated to detect a difference of 2 units in TSS between groups with 90% power and 0.05 probability of type 1 error, assuming a standard deviation of 3.5 for this parameter.[10] Considering a 20% possible dropout rate, the recruitment target was approximately 60 participants per group or 120 participants overall. Continuous variables were compared by independent samples *t*-test (between groups) and by paired *t*-test (within group). Mann–Whitney U-test and Wilcoxon matched pairs signed-rank test were employed for comparison of unpaired and paired nonparametric data. For repeated measures' comparison within group, Friedman's analysis of variance was carried out followed by *post hoc* Dunn's test as data were nonparametric in nature. 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) software was used for statistical analysis. Effectiveness analysis was done on modified intention-to-treat criteria, with all those participants who had reported for at least one post-baseline follow-up visit. Missing values were dealt with by the last observation carried forward strategy. Laboratory values were compared in patients for whom both pre- and post-treatment sets of data were available. All patients who had received at least one dose of a study drug (essentially all 120 subjects) were considered for other safety analysis.

Results

The flow of study participants is depicted in Figure 1. There were no changes to the protocol made after the commencement of the study. A total of 370 patients were diagnosed clinically as chronic urticaria and given 5 mg levocetirizine for 2 weeks. Among them, 137 (37.03%) cases were resistant to conventional 5 mg daily dose of levocetirizine and were screened for the study, but 17 patients did not meet the inclusion-exclusion criteria. Hence, 120 patients were recruited, of which 103 (85.83%) patients were analyzable as per modified intention-to-treat principle – 52 cases in levocetirizine 10 mg group and 51 cases in levocetirizine 5 mg + montelukast 10 mg group. 17 patients were lost to follow-up.

Most of the patients were young adult urban females in their thirties educated at or above secondary school level. Study groups were comparable with respect to age, sex, median duration of urticaria at presentation (median = 12 months) and subtypes of urticarial; 71.84% suffered from spontaneous urticaria [Table 1].

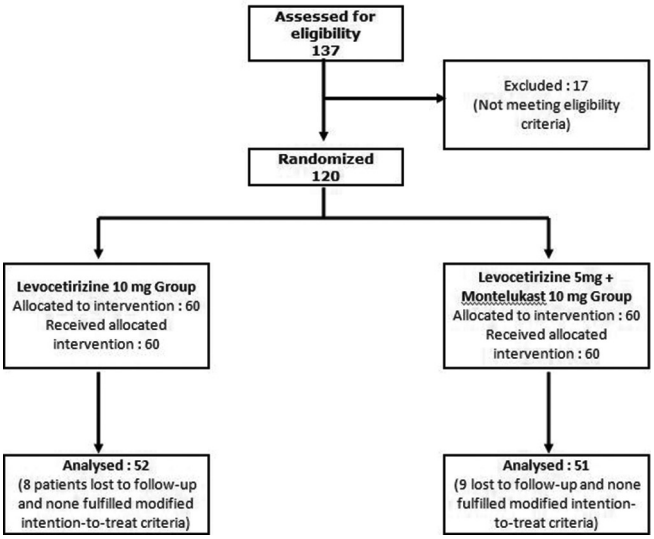

Figure 1: Flow of study participants

The changes in the UAS over the 4 treatment weeks are depicted in Table 2. It is evident that the UAS scores in both groups are declining over this time period and this decline is statistically significant ($P < 0.001$) in both the treatment arms. Furthermore, when individual follow-ups were compared to baseline, it was shown to vary significantly ($P < 0.001$) from first follow-up onward in both treatment arms. The scores in between the treatment groups were comparable at the baseline visit and the reduction of UAS remained comparable in both groups throughout subsequent visits. There was statistically significant ($P < 0.001$) reduction of TSS in both the treatment groups over this period of time; furthermore, when individual follow-ups were compared to baseline, it varied significantly ($P < 0.001$), but like UAS, the decline of TSS was comparable in both the treatment groups at baseline and subsequent visits [Table 2].

Assessment of disease severity by the physician showed that at baseline, the disease was severe (Physicians' global assessment of disease activity improvement scale value, 0–1) in both the treatment arms [Figure 2]. However, in subsequent visits, drug treatment decreased the disease severity significantly in individual treatment groups ($P < 0.001$) in both the treatment arms. Individual follow-ups when compared to baseline varied significantly ($P < 0.001$) from first follow-up onward. Comparison in between the treatment groups showed that the decrease of disease severity was comparable in between the groups on subsequent visits. The various grades of improvement of urticaria according to Physicians' global assessment are given in Table 3.

The opinion of patients regarding their baseline disease severity did not vary in between the two treatment groups. However, as the line diagram [Figure 3] suggests, their response to treatment was reflected in their assessment of disease severity in follow-ups, where the drugs prescribed significantly reduced their disease symptomatology in individual treatment groups ($P < 0.001$). Individual follow-ups when compared to baseline varied significantly ($P < 0.001$) from first follow-up onward in both treatment arms. Furthermore, the disease severity according to the patients' view decreased almost comparably in the levocetirizine 10 mg group and the levocetirizine 5 mg + montelukast 10 mg group during the 2nd, 3rd, 4th follow-ups.

Table 1: Demographic profile of study population

Category	Levocetirizine 10 mg group (*n*=52)	Levocetirizine 5 mg + montelukast 10 mg group (*n*=51)	*P* (between groups)
Age (years)			
Range	19-71	18-55	0.185
Mean±SD	36.21±13.66	32.96±10.84	
Median (IQR)	32 (26-42.5)	34 (23-42)	
Sex (%)			
Male	21 (40.38)	18 (35.29)	0.686
Female	31 (59.62)	33 (64.71)	
Residence (%)			
Urban	44 (84.62)	44 (86.27)	1.000
Rural	8 (15.38)	7 (13.73)	
Literacy (%)			
Illiterate	2 (3.85)	2 (3.92)	0.347
Primary	16 (30.77)	9 (17.65)	
Secondary	26 (50)	34 (66.67)	
Higher secondary and above	8 (15.38)	6 (11.76)	
Occupation (%)			
Student	3 (5.77)	9 (17.65)	0.348
Homemaker	27 (51.92)	23 (45.10)	
Agricultural worker	3 (5.77)	4 (7.84)	
Nonagricultural outdoor worker	10 (19.23)	6 (11.76)	
Nonagricultural indoor worker	9 (17.31)	9 (17.65)	
Duration of illness (months)			
Range	2-240	2–120	0.408
Mean±SD	32.33±45.38	19.39±23.83	
Median (IQR)	12 (8-24)	12 (8-18)	
Subtypes of CU (%)			
Spontaneous	35 (67.31)	39 (76.47)	0.656
Symptomatic dermatographism	13 (25)	8 (15.69)	
Solar urticaria	0	1 (1.96)	
Cholinergic urticaria	1 (1.92)	2 (3.92)	
Cold urticaria	1 (1.92)	0	
Aquagenic urticaria	2 (3.85)	1 (1.96)	

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 other categorical variables). SD: Standard deviation, IQR: Interquartile range, CU: Chronic urticaria

DLQI scores decreased significantly ($P<0.0001$) in both the treatment arms from baseline to 4th follow-up. However, the improvement of score was significantly better ($P = 0.031$) in levocetirizine 5 mg + montelukast 10 mg combination group (3.03 ± 2.29) as compared to levocetirizine 10 mg group (7.11 ± 6.31) at the end of treatment.

A total of 97 cases (49 in levocetirizine 10 mg group and 48 in levocetirizine 5 mg + montelukast 10 mg group) had both baseline and post-baseline (after 4 weeks) laboratory parameters available for analysis. The laboratory values were within normal limits during therapy and there were no significant changes from baseline [Table 4]. Sedation rate was significantly higher ($P = 0.013$) in levocetirizine 10 mg group. Besides sedation, the other treatment-emergent adverse events noted were dizziness, fatigue, constipation, breathlessness, paresthesias of upper limbs, loss of hair, sleep disturbance and pedal edema [Table 5]. Causality assessment was done using the World Health Organization-Uppsala Monitoring Centre scale.[17] Only "sedation" fell in the "probable" category and the rest in the "possible" category. No serious adverse events were encountered during the study period.

Discussion

The natural course of chronic urticaria is unpredictable, and thus any research on it may be intriguing for a researcher. However, the disease is exasperating for patients, as well as for the treating physician. One study had prospectively evaluated 220 patients up to 3 years and found that only 35% were free of symptoms after 1 year and among the rest, at the end of 3 years, only 47% achieved remission.[18] This highlights the fact that the therapy needs to be continued on long-term basis. For any long-term treatment regime, it is desirable that the medication should not impose significant impact on the daily activity of the patients and should be having minimum side effects. It is also desirable that

Table 2: Changes in urticaria activity score and total severity score in both treatment arms

UAS	Levocetirizine 10 mg group (*n*=52)	Levocetirizine 5 mg+montelukast 10 mg group (*n*=51)	*P* (between groups)
Baseline			
Mean±SD	3.40±1.27	3.13±1.17	0.572
Median (IQR)	4 (2.5-4)	3 (3-4)	
First follow-up			
Mean±SD	1.58±1.56*	1.73±1.59*	0.598
Median (IQR)	1 (0-3)	1 (0-2.75)	
Second follow-up			
Mean±SD	1.54±1.51*	1.69±1.74*	0.855
Median (IQR)	1 (0-3)	1 (0-3.75)	
Third follow-up			
Mean±SD	1.56±1.61*	1.75±1.76*	0.629
Median (IQR)	1 (0-3)	1 (0-3.75)	
Fourth follow-up			
Mean±SD	1.5±1.62*	1.62±1.62*	0.628
Median (IQR)	1 (0-3)	1 (0-3)	
P (within group)	<0.001	<0.001	
Urticaria TSS	**Levocetirizine 10 mg group (*n*=52)**	**Levocetirizine 5 mg+montelukast 10 mg group (*n*=51)**	***P* (between groups)**
Baseline			
Mean±SD	13.81±2.43	13.25±2.72	0.301
Median (IQR)	14 (12.5-15.5)	14 (12-15)	
First follow-up			
Mean±SD	9.35±4.82*	9.14±4.6*	0.886
Median (IQR)	10 (3-13)	10 (3-13)	
Second follow-up			
Mean±SD	9.10±4.84*	9±5.06*	0.928
Median (IQR)	9 (3-12)	10 (3-14)	
Third follow-up			
Mean±SD	9.02±4.84*	9.14±4.98*	0.825
Median (IQR)	10 (3-13)	10 (3-14)	
Fourth follow-up			
Mean±SD	8.71±4.93*	8.88±4.82*	0.824
Median (IQR)	9.5 (3-12)	10 (3-13)	
P (within group)	<0.001	<0.001	

P value for between-group comparisons is from Mann–Whitney U-test. **P*<0.001 for within group comparison between the baseline visit and the particular visit (Freidman's ANOVA followed by *post hoc* Dunn's test). UAS: Urticaria activity score, TSS: Total severity score, SD: Standard deviation, IQR: Interquartile range, ANOVA: Analysis of variance

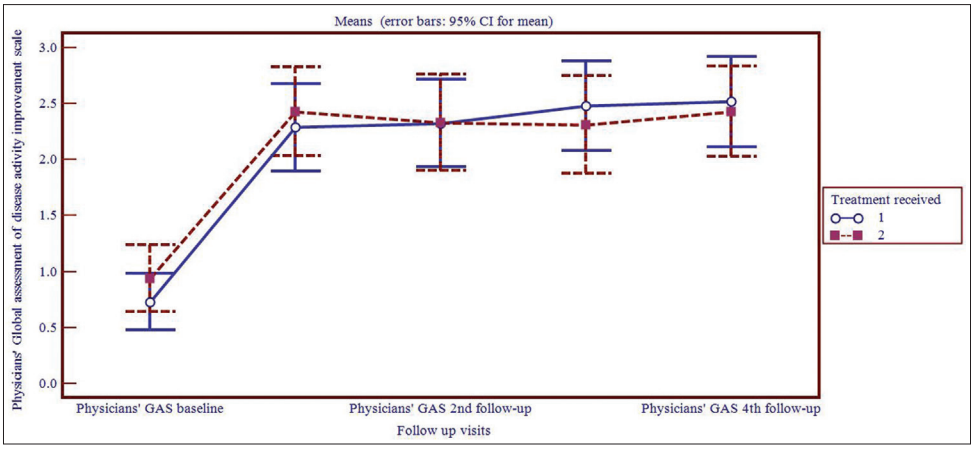

Figure 2: Line diagram of physician's global assessment of disease activity improvement scale in 1 = levocetirizine 10 mg and 2 = levocetirizine 5 mg + montelukast 10 mg group

Table 3: Grades of improvement of urticaria according to physicians' global assessment of disease activity improvement scale value

Grades	Levocetirizine 10 mg group (*n*=52)	Levocetirizine 5 mg + montelukast 10 mg group (*n*=51)	Number of patients (*n*=103)	Percentage of patients
0 - No improvement	6	8	14	13.6
1 - Mild improvement	8	5	13	12.6
2 - Moderate improvement	12	11	23	22.3
3 - Marked improvement	5	11	16	15.5
4 - Excellent improvement	21	16	37	35.9

Table 4: Changes in laboratory parameters in the two treatment arms

Category	Levocetirizine 10 mg group (*n*=52)	Levocetirizine 5 mg + montelukast 10 mg group (*n*=51)	*P* (between groups)
Hemoglobin (g/dl)			
Baseline	12.68±1.62	12.43±1.39	0.397
Fourth follow-up	12.65±1.54	12.39±1.65	0.401
Before-after *P* value	0.604	0.732	
TLC (cells/µl)			
Baseline	7175±1836.54	7541.18±1631.71	0.436
Fourth follow-up	7089.81±1843.66	7574.51±1862.46	0.319
Before-after *P* value	0.578	0.394	
Eosinophils (%)			
Baseline	4.96±4.54	5.37±3.38	0.099
Fourth follow-up	5.64±4.40	5.61±3.66	0.757
Before-after *P* value	0.589	0.772	
ESR (mm in 1st h)			
Baseline	35.75±14.10	34.02±12.85	0.509
Fourth follow-up	34.81±12.57	33.64±12.80	0.466
Before-after *P* value	0.572	0.761	
Bilirubin (mg/dl)			
Baseline	0.73±0.13	0.71±0.10	0.425
Fourth follow-up	0.71±0.12	0.74±0.14	0.249
Before-after *P* value	0.495	0.111	
ALT (U/L)			
Baseline	35.63±4.79	35.51±4.74	0.895
Fourth follow-up	35.73±3.57	35.10±4.62	0.438
Before-after *P* value	0.876	0.411	
AST (U/L)			
Baseline	35.46±5.61	35.76±6.05	0.793
Fourth follow-up	35.42±4.72	35.29±4.00	0.882
Before-after *P* value	0.949	0.069	
ALP (U/L)			
Baseline	124.48±11.34	125.57±17.05	0.703
Fourth follow-up	123.40±7.98	125.53±10.92	0.261
Before-after *P* value	0.329	0.983	
Urea (mg/dl)			
Baseline	22.52±3.92	23.29±3.02	0.265
Fourth follow-up	22.06±2.78	22.14±2.94	0.881
Before-after *P* value	0.444	0.037	
Creatinine (mg/dl)			
Baseline	0.64±0.13	0.63±0.12	0.778
Fourth follow-up	0.65±0.16	0.60±0.11	0.053
Before-after *P* value	0.646	0.069	

Values are mean±SD. *P* value for between-group comparison is from Mann–Whitney rank sum test, whereas for within group before-after comparison, it is from Wilcoxon test. SD: Standard deviation, TLC: Total lymphocyte count, ESR: Erythrocyte sedimentation rate, ALT: Alanine transaminase, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase

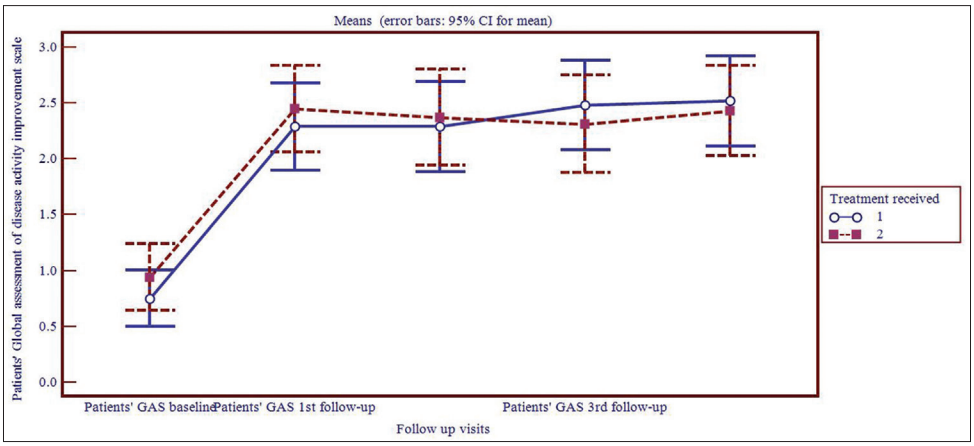

Figure 3: Line diagram of patient's global assessment of disease activity improvement scale in 1 = levocetirizine 10 mg and 2 = levocetirizine 5 mg + montelukast 10 mg group

Table 5: Treatment-related adverse events in the two treatment groups

Category	Levocetrizine 10 group (*n*=52)	Levocetirizine 5 mg + montelukast 10 mg group (*n*=51)	*P* (between groups)
Sedation	13	3	0.013
Dizziness	0	3	0.118
Constipation	1	0	1.000
Fatigue	2	1	1.000
Breathlessness	0	1	0.495
Sleep disturbance	0	1	0.495
Hair loss (scalp)	0	1	0.495
Pedal edema	0	1	0.495
Paresthesia of arm	1	0	1.000

The numbers represent counts in individual groups. *P* value is from Fisher's exact test

the pill burden should be low as well, as it should impose minimum monetary-burden, especially in a developing country like ours, where most of the individuals are not protected by health-care insurance.

Histamine and leukotrienes are important mediators in the pathogenesis of urticaria; in principle, a combination of antihistamine and montelukast is a more rational approach in treating this condition, instead of targeting only histamine by increasing the dose of antihistamines in resistant chronic urticaria.

This study showed that most of the patients were women homemakers in their mid-thirties. Previous studies in other parts of the globe also found a greater incidence of chronic urticaria in middle-aged females similar to our study population.[19,20]

The primary effectiveness variables, UAS[13] and TSS[14] are semiobjective methods of evaluating the activity/severity of urticaria, but TSS is superior to UAS since it incorporates the duration of persistence of symptoms and frequency of appearance of wheals. The results show that there was significant improvement in UAS and TSS in both the groups over 4 treatment weeks. Furthermore, both the scores decreased from baseline significantly ($P < 0.001$) during all the follow-ups in both the treatment arms, showing that both the study drugs were quite effective in relieving symptoms of urticaria. A significant reduction in both UAS and TSS was evident from the 1st week onward. Thus, urticaria, though vexing for its persistence, is rapidly managed with the present day antihistamines with higher dose or in combination with montelukast. This is the silver lining and needs to be emphasized to all patients of urticaria, particularly to those who do not respond to treatment with conventional initial standard dose of antihistamines, to uplift their morale and impart positive outlook to the disease.

Trials conducted by Erbagci[14] and Agcaoili *et al*.[11] demonstrated the definite role of montelukast as monotherapy, whereas Bagenstose *et al*. demonstrated the effective role of leukotriene receptor antagonist (zafirlukast) as add-on therapy to cetirizine in chronic urticaria.[12]

One systematic review of randomized controlled trials, showed equivocal response of leukotriene receptor antagonist (montelukast) monotherapy,[21] but combined therapy of antihistamine with leukotriene receptor antagonist seemed to be beneficial according to most of the studies.[12,22]

The laboratory parameters showed no changes in our study, which show that both the drugs were safe in this regard. In our study, 13 (25%) patients on levocetirizine 10 mg complained of sedation whereas 3 (5.88%) patients complained of sedation in levocetirizine 5 mg + montelukast 10 mg group, suggesting lower side effect profile of montelukast. Our study showing lower incidence of sedation is corroborative with the studies conducted by Erbagci[13] and Agcaoili *et al*.[11] Sedation being one of the prime barriers in compliance with long-term antihistamines, less sedation with levocetirizine 5 mg + montelukast 10 mg is definitely a welcome sign and is a step forward in urticaria management. There was one

patient who complained of scalp hair loss and another one who complained of pedal edema; both of them were from levocetirizine 5 mg + montelukast 10 mg group. The causality assessment showed merely a "possible association" in both cases and laboratory parameters did not suggest any specific reason for the manifestation.

Thus, a combination of levocetirizine 5 mg + montelukast 10 mg has comparable effectiveness with reduced side effects than a double dose of levocetirizine (i.e., 10 mg) which skews the benefit-risk ratio in favor of levocetirizine 5 mg + montelukast 10 mg against levocetirizine (10 mg). Needless to say with four times the dose of levocetirizine, the sedation would increase furthermore. Study participants showed very good compliance. The lack of troublesome or serious adverse events helped in this regard. High degree of compliance in the patients suffering from this chronic ailment favors the long-term therapy with either of the treatment regime.

Chronic urticaria may limit the daily activities, lead to depression and the social burden of the disease is huge. The combination of montelukast with levocetirizine by virtue of its effect on a significantly improved DLQI may help patients have a better quality of life.

For all these reasons, it is more rational to introduce a leukotriene inhibitor (e.g., montelukast) in combination with standard initial dose of antihistamine instead of increasing the dose of antihistamine alone. Hence, our study highlights that EAACI/GA²LEN/EDF/WAO guideline needs to be more flexible in its recommendation regarding the introduction of leukotriene inhibitors after four times the standard dose.[4] The study, being a double-blind randomized controlled trial, also provides a strong evidence (level 1b) for subsequent amendment of the existing guideline.

The limitations of the study were that the follow-up period was less, urticaria specific quality of life instrument was not used and study population included various types of urticaria and autologous serum skin test was not performed.

Conclusion

Both levocetirizine 10 mg and a combination of levocetirizine 5 mg + montelukast 10 mg can effectively treat cases of recalcitrant chronic urticaria; Sedation is much more common with higher doses of levocetirizine; quality of life is better in the montelukast arm; hence, instead of increasing the dose of antihistamines alone, the addition of leukotriene receptor inhibitors to a standard antihistamine dose can be considered in recalcitrant chronic urticaria.

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Conflicts of interest

There are no conflicts of interest.

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