



An open-label prospective clinical study to assess the efficacy of increasing levocetirizine dose up-to four times in chronic spontaneous urticaria not controlled with standard dose

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Title page

Title: An open-label prospective clinical study to assess the efficacy of increasing levocetirizine dose up-to four times in chronic spontaneous urticaria not controlled with standard dose

Running title: Levocetirizine up-dosing in chronic urticaria

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Abstract

Objective

The EAACI/GA²LEN/EDF/WAO recommendation of increasing antihistamines' dose up-to 4-times in urticaria not adequately controlled with the standard dose is largely based on expert opinion. The objective of this study is to test the current urticaria guidelines of up-dosing antihistamines as second-line treatment.

Methods

This was an open-label study conducted prospectively on 113 patients with chronic spontaneous urticaria. All patients were treated with sequentially increasing doses of levocetirizine (5mg, 10mg, 15mg and 20mg/day) every week till the patients became completely asymptomatic or dose of 20mg/day reached. Urticaria Activity Score (UAS)-7, urticaria-related quality-of-life (CU-Q2oL) and patients' global assessment were used to assess treatment response.

Results

Twenty-one (18.58%) patients became asymptomatic with levocetirizine 5mg/day, while fifty required higher doses of levocetirizine for complete control: 29/92 (31.52%), 6/63 (9.52%) and 15/57 (26.31%) with 10mg, 15mg and 20mg/day, respectively. The percentage of patients experiencing >75% improvement increased with increasing doses of levocetirizine: 26.54%, 53.98%, 60.17% and 69.91% with 5mg, 10mg, 15mg and 20mg/day respectively. Sequential up-dosing of levocetirizine produced a progressive improvement in both urticaria

control (UAS-7) as well as quality-of-life (CU-Q2oL) without significantly increasing somnolence.

Conclusions

Our results support the current recommendations of increasing antihistamines up-to 4-times the standard dose in patients who fail the first-line treatment.

Clinical trial registry number (CTRI/2016/07/007099)

Key words: Chronic urticaria, levocetirizine, up-dosing

JUST ACCEPTED

Introduction

Chronic urticaria, defined as recurrent urticarial episodes occurring at least twice a week for 6 weeks or more, affects approximately 0.5-1% of population at some point of their life.¹ It can have a significant negative impact on the quality-of-life of patients.²⁻⁴ Second-generation non-sedating antihistamines are recommended as the first-line therapy, because of the good evidence for their efficacy and excellent safety profile. The EAACI/GA²LEN/EDF/WAO guidelines recommend increasing the dose of antihistamines up-to 4-times in patients not responding to the conventional doses. However, it is largely based on expert opinion and lacks high quality evidence.^{5,6} Though a few studies have examined the efficacy of up-dosing with non-sedating antihistamines in chronic urticaria, and shown promising results, not all the studies are comparable due to heterogeneity of the study population due to different types of urticaria and use of different outcome measures. The need for additional well-controlled, well-designed clinical trials to clarify the choice of non-sedating antihistamines, their dose and duration in treating chronic urticaria not responding to standard therapy has been stressed previously.¹ We conducted the present study with the objective to test the validity of the current recommendation of increasing the dose of antihistamines up-to 4-times with levocetirizine in chronic spontaneous urticaria not responding to standard dose.

Methods

Study participants

Adult (≥ 18 years) patients with chronic spontaneous urticaria presenting to the department of Dermatology and Venereology, All India Institute of Medical Sciences, New Delhi, India were screened for inclusion in the study. Chronic spontaneous urticaria was defined as urticarial episodes occurring at-least 3 times a week lasting for 6 weeks or more with no identifiable cause on history or examination. Patients with physical urticaria, contact

urticaria, drug-induced urticaria and urticarial vasculitis were excluded. Other exclusion criteria included pregnancy, lactation, hepatic or renal dysfunction, abnormal laboratory parameters (hemogram/serum biochemistry) or electrocardiogram at screening, regular use of systemic corticosteroids, cyclosporine, methotrexate or any other immunosuppressant in the last 4 weeks; antihistamines or leukotriene-receptor antagonists in the last 7 days.

Study design

This was an open-label clinical trial conducted prospectively over a period of 1 year (November 2014 to October 2015). At the screening visit (week 0), patients fulfilling the inclusion criteria and consenting to participate in the study were subjected to a detailed history, examination and laboratory evaluation (complete blood count, erythrocyte sedimentation rate, serum biochemistry, electrocardiogram, urine and stool examination). The patients were asked to record the Urticaria activity score (UAS)-7,^{7,8} which served as the baseline urticaria severity, and asked to return after 7 days. The UAS-7 is a validated patient-reported outcome measure derived by summing the score for number of wheals (0: none, 1: <20, 2: 21-50, 3: >50) per day and intensity of pruritus (0: none, 1: mild, 2: moderate, 3: severe) for 7 consecutive days. No treatment was given during this period, except for levocetirizine 5mg as per need as rescue medication. At the next visit (week 1), the baseline weekly UAS-7 score was noted, and the patients were asked to fill the Hindi translation of Chronic urticaria quality-of-life questionnaire (CU-Q2oL),⁹ a validated urticaria-specific quality-of-life instrument, and rate the level of somnolence on a four-point Likert scale (0- none, 1-mild, 2-moderate, 3-severe), following which they received levocetirizine 5mg/day for 1 week. At the next visit (week 2), patients who became urticaria-free (UAS-7 as 0), left the trial. Patients who did not achieve complete control of urticaria with this treatment were treated with sequential up-dosing of levocetirizine every week till they became completely asymptomatic, as follows: 10mg/day (at week 2), 15mg/day (week 3) and 20mg/day (week 4)

for patients who remained symptomatic with levocetirizine 5mg/day, 10mg/day and 15mg/day, respectively. At every visit, patients who remained symptom-free in the preceding week left the trial (Figure 1). The UAS-7, CU-Q2oL, degree of somnolence and patient's global assessment of treatment response (-1: worsening, 0: no change, 1: <25% improvement, 2: 25-50% improvement, 3: 50-75% improvement, 4: >75% improvement) were recorded at every follow-up visit, in addition to any adverse event experienced by the patient. The study was conducted after approval from Institute ethics committee, and registered with the Clinical trials registry-India (CTRI/2016/07/007099).

Statistical analysis

A previous study¹⁰ on up-dosing of antihistamines had shown an overall success rate of approximately 50%. Keeping a precision of $\pm 10\%$ and confidence level of 95%, sample size of ninety-six patients was calculated. The primary outcome measure was the proportion of patients becoming urticaria-free with sequential up-dosing of levocetirizine. The secondary outcome measures were the patients' global assessment of response, mean change in UAS-7 and CU-Q2oL scores, and degree of somnolence experienced by the patients with different doses of levocetirizine. Data was analysed as per intention-to-treat protocol using Stata 14.1 software (*StataCorp. LP 2015. College Station, Texas 77845 USA*).

Results

One hundred and thirteen patients participated in the study. Ten patients were lost to follow-up (five patients at week 2, four at week 3, and one at week 4). Demographic and baseline characteristics of the study population are summarised in Table 1. All 113 patients were treated with levocetirizine 5mg per day. Of these, 92 (81.4%) patients required up-dosing till 10mg levocetirizine, 63 (55.8%) till 15mg and 57 (50.4%) till 20mg/day, as per the study protocol.

Proportion of patients becoming asymptomatic with sequential up-dosing of levocetirizine

Overall, 71 (62.83%) patients achieved complete control of urticaria with sequential up-dosing of levocetirizine. Twenty-one (out of 113, 18.58%) patients became completely asymptomatic with levocetirizine 5mg/day. Of the 92 patients who continued to have urticaria with this dose, 50 (54.34%) became urticaria-free with levocetirizine up-dosing: 29/92 (31.52%), 6/63 (9.52%) and 15/57 (26.31%) patients became asymptomatic with levocetirizine 10mg, 15mg and 20mg/day, respectively (Figure 2). The cumulative response rate increased with increasing doses of levocetirizine as follows: 18.58% (n=21), 44.24% (n=50), 49.55% (n=56) and 62.83% (n=71) with levocetirizine 5mg, 10mg, 15mg and 20mg/day, respectively.

Patients' global assessment of treatment response

Overall, 79 (69.91%) patients reported >75% improvement to increasing doses of levocetirizine. Thirty (26.54%) patients achieved it with levocetirizine 5mg/day, while 49 (48.67%) patients responded to higher-than-standard doses. The cumulative percentage of patients experiencing >75% improvement with increasing doses of levocetirizine beyond 5mg is as follows: 53.98% (n=61), 60.17% (n=68) and 69.91% (n=79), with levocetirizine 10mg, 15mg and 20mg/day respectively. The percentage of patients with less than 25%, 50% and 75% improvement to sequential up-dosing of levocetirizine to 20mg/day was 12.39% (n=14/113), 20.35% (n=23/113) and 30.09% (n=34/113), respectively (Figure 3).

Urticaria severity

The mean reduction in UAS-7 from baseline with varying doses of levocetirizine was 7.43 ± 5.69 (n=113), 12.64 ± 7.19 (n=92), 11.94 ± 8.31 (n=63), and 15.27 ± 8.92 (n=57) with levocetirizine 5mg, 10mg, 15mg and 20mg/day, respectively. The additional reduction in

mean UAS-7 with step-wise increase in levocetirizine dose beyond the standard dose of 5mg is as follows: 6.23 ± 5.33 (5-10mg/day), 1.19 ± 3.44 (10-15mg/day), and 3.96 ± 4.14 (15-20mg/day). The mean UAS-7 values with increasing doses of levocetirizine are plotted in Figure 4.

Quality-of life

The mean reduction in CU-Q2oL scores from baseline with increasing doses of levocetirizine was 10.44 ± 9.62 (n=113), 16.57 ± 11.42 (n=92), 16.75 ± 14.47 (n=63) and 20.26 ± 15.12 (n=57) with levocetirizine 5mg, 10mg, 15mg and 20mg/day, respectively. The additional reduction in mean CU-Q2oL scores with sequential up-dosing of levocetirizine beyond 5mg/day is as follows: 7.25 ± 7.17 (5-10mg/day), 1.49 ± 6.07 (10-15mg/day), and 4.67 ± 8.14 (15-20mg/day). The mean CU-Q2oL values with increasing doses of levocetirizine are plotted in Figure 5.

Somnolence and other treatment-related adverse effects

Overall, twenty-two (out of 113, 19.46%) patients experienced at-least some degree of somnolence. Of these, only five (22.72%) patients developed it at higher-than-standard dose; four at 10mg, and one at 20mg per day. The percentage of patients tolerating the standard dose, but developing somnolence at a higher dose was 4.34% (n=4/92) and 1.75% (n=1/57) for 10mg and 20mg/day, respectively. On up-dosing, the degree of somnolence increased from mild to moderate in 2 patients (from 5mg to 10mg/day), while a decrease was noted in one patient (from moderate at 5mg, to mild at 10mg, and none at 15 and 20mg/day). None of the patients reported severe degree of somnolence. Three patients developed headache, and two developed joint pains and generalised body ache during the course of treatment. These were not thought to be treatment-related, and disappeared on continuing the treatment. None of these complaints, including somnolence necessitated withdrawal from the study.

Discussion

The results of our study show that sequential up-dosing of levocetirizine up-to 4-times the standard dose benefits majority of the patients with chronic spontaneous urticaria. While more than 80% patients required treatment with higher-than-standard doses of levocetirizine, the proportion of patients achieving complete urticaria control increased to more than two-folds and three-folds on doubling and quadrupling the standard dose of 5mg per day, respectively. A similar trend was noted for patients reporting >75% reduction in urticaria severity, which was taken as the cut-off for significant improvement in the present study. Sequential up-dosing of levocetirizine led to a gradual improvement in both, the severity of symptoms as well as the quality-of-life. This improvement was more apparent on increasing the dose to 10mg (from 5mg) and 20mg (from 15mg), as compared to a hike from 10mg to 15mg per day. As there is only little additional benefit from increasing the levocetirizine dose to 15mg for patients not responding to 10mg/day, a direct increase to 20mg circumventing the 15mg-step maybe more appropriate for such patients. As up-dosing the antihistamines was found to be beneficial to more than half the patients not responding to standard dose, our results suggest that there may be some merit in the current recommendation of up-dosing the antihistamines as second-line treatment. However, it is noteworthy that a sizeable proportion (~46%) of patients not completely controlled with the standard levocetirizine dose still remained symptomatic despite maximal recommended up-dosing. Approximately 30% patients did not have significant improvement on up-dosing of levocetirizine, and would be the ideal candidates for more aggressive therapy in the form of systemic immunosuppressives or omalizumab.

Our results are in accordance with some of the previous studies. In a retrospective questionnaire-based survey, 40%, 42% and 54% of the 238 patients who had up-dosed their antihistamines in view of unsatisfactory response to a single tablet of antihistamine, reported

having significant added benefit from 2, 3 and 4 tablets of an antihistamine, while approximately a quarter of patients did not perceive any additional benefit.¹¹ Though a few prospective trials have shown the effectiveness of up-dosing of various second-generation antihistamines in chronic urticaria, many were limited by a small sample size, and did not analyse patient-reported outcome measures, such as patient satisfaction or impact on quality-of-life.^{10,12–16} We could find only two studies examining the efficacy of levocetirizine up-dosing.^{10,16} In one series, all 20 patients with chronic urticaria became asymptomatic with sequential up-dosing of levocetirizine.¹⁶ The other was a randomized trial on 80 patients, where effectiveness of up-dosing of levocetirizine was compared with that of desloratadine. The success rate more than doubled by increasing the dose above the conventional dose for either drug (13 patients became symptom-free at 5mg, in comparison to 28 patients at 10mg and 20mg) and levocetirizine was found to be statistically superior to desloratadine in improving symptoms and quality-of-life.¹⁰

A major concern with up-dosing of antihistamines has been the fear of increased somnolence at higher doses. However, we found that more than three-quarters of the patients who experienced somnolence, developed so on the standard 5mg dose, suggesting that up-dosing only marginally increases the risk of somnolence. Similar results have been obtained by others as well.^{10,12–16} Staevska *et al*¹⁰ reported that 75% of their patients had either no change or even a reduction in somnolence throughout the study, which they attributed to better sleep-quality leading to prolonged wakefulness during the day, and development of tolerance to antihistamine's sedative effect.

Our study has certain limitations. As this study was conducted in a tertiary-care referral hospital, we may have recruited more patients with difficult-to-treat urticaria. Additionally, long-term control of symptoms was not assessed. In conclusion, our study demonstrates the efficacy of up-dosing of levocetirizine in treating chronic spontaneous urticaria not

responding to standard dose without significantly increasing somnolence, and provides support for the current urticaria guidelines.

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Legends:

Table 1. Demographic and baseline characteristics of patients

Figure 1 showing the study design

Figure 2. Percentage of patients becoming asymptomatic with increasing doses of levocetirizine: 5mg, 10mg, 15mg and 20mg/day

Figure 3. The cumulative percentage of patients with differing levels of improvement with increasing doses of levocetirizine: 5mg, 10mg, 15mg and 20mg/day

Figure 4. The mean UAS-7 scores with increasing doses of levocetirizine

Figure 5. The mean CU-Q2oL scores with increasing doses of levocetirizine

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Table 1. Demographic and baseline characteristics of patients

Age (years)	
Mean±SD	31.68±11.48
Median	29.00
Range	16-67
Gender (n, %)	
Males	47 (41.6%)
Females	66 (58.4%)
Duration (Mean±SD, months)	
33.33±36.85	
Angioedema (n, %)	
Present	33 (29.2%)
Absent	80 (70.8%)
UAS-7	
Mean±SD	19.95±8.74
Median	19.00
Range	5-40
CU-Q2oL	
Mean±SD	47.71±13.52
Median	46.00
Range	25-87

SD, standard deviation; UAS-7, urticaria activity score-7; CU-Q2oL, chronic urticaria quality-of-life questionnaire

Patients with chronic spontaneous urticaria fulfilling the inclusion criteria (n=113)

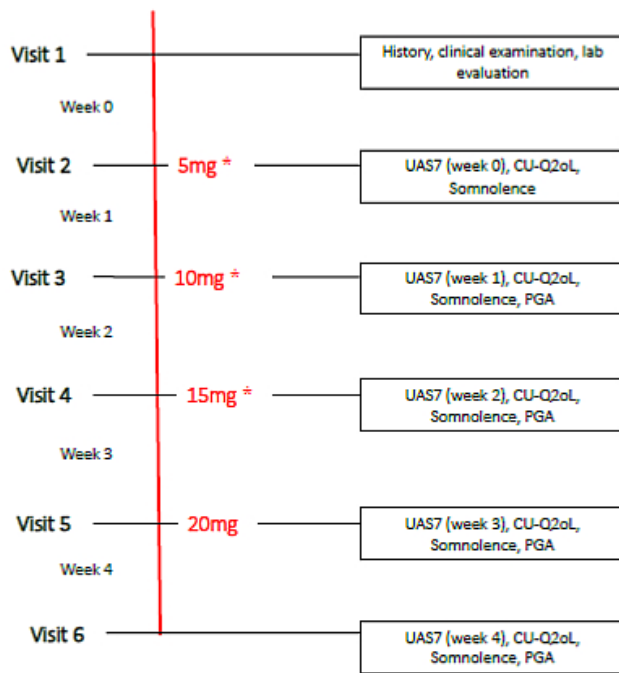


Fig 1 showing the study design.

— Levocetirizine dose,
 UAS7, Urticaria activity score-7; CU-Q2oL, Chronic urticaria quality-of-life questionnaire; PGA, Patient global assessment of response
 *Patients leave the trial when UAS-7 becomes zero

