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Levocetirizine in the treatment of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study

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Conflicts of interest
None declared.

Summary

Background Chronic urticaria is a common skin condition. It is frequently a disabling disease because of the persistence of clinical symptoms, the unpredictable course and its negative influence on the quality of life.
Objectives To determine whether levocetirizine is efficacious in the treatment of chronic idiopathic urticaria.
Methods A randomized, double-blind, placebo-controlled study was conducted in 106 patients with a diagnosis of chronic idiopathic urticaria. A 1-week single blind placebo run-in period (baseline) was followed by a 6-week double blind active treatment period. The patients were randomized to receive one of the following treatments once daily: (a) oral levocetirizine 5 mg, or (b) oral placebo. The study ended after another 1-week single blind placebo washout period.
Results The evaluable population consisted of 100 patients. Levocetirizine administered once daily is effective and well tolerated in the treatment of the symptoms of chronic idiopathic urticaria and in improving the patient's quality of life. Levocetirizine was superior to placebo in reducing the mean total symptoms score as well as individual symptoms, the number of daily episodes and the number of weals, the overall severity of symptoms and the quality of life. The significant beneficial effects of levocetirizine lasted only during the active trial, while at follow-up there was a significant worsening of all the variables evaluated in this study, after the end of the active trial (week 7).
Conclusions A global assessment indicates that levocetirizine 5 mg once daily is an effective agent in patients with chronic idiopathic urticaria, as its action provides a rapid and satisfactory control of the symptoms and measures of subjective disease, although this is limited to the duration of treatment.

Levocetirizine is a newly developed selective H1 antagonist; it is the R-enantiomer or active isomer of the racemate cetirizine. Its small volume of distribution, smaller even than that of cetirizine, confers improved safety because of its lesser passage through the blood–brain barrier and low cerebral receptor binding.[1] Levocetirizine has twice the affinity for the H1 receptor compared with cetirizine and its potency as an antihistamine has been demonstrated by inhibition of histamine-induced weal and flare reactions.[2] Previous studies of the action of single doses of 5 mg levocetirizine on histamine-induced skin reactions in healthy male subjects compared its activity with that of other antihistamines at their therapeutic dosage: ebastine 10 mg, fexofenadine 180 mg, loratadine 10 mg and mizolastine 10 mg and desloratadine.[3,4] Assessment of their global anti-H1 activity over 24 h showed that levocetirizine had the greatest activity in suppressing skin reactivity to histamine. In addition, levocetirizine was superior to the other antihistamines because it induced longer lasting high levels of inhibition.

Gandon and Allain[5] assessed the effect of levocetirizine 5 mg after both single and repeated doses, on psychometric and cognitive functions compared with placebo, using the critical flicker fusion test. In addition, they evaluated secondary objectives including assessment of effects on a battery of tests including choice reaction time, body sway, and on learning memory. In addition, subjective perception of mood changes and vigilance were measured. They found that levocetirizine does not produce any deleterious effect on cognitive and psychometric functions compared with placebo.

The clinical efficacy of levocetirizine has been evaluated in several studies focusing on allergic rhinitis. In particular, it has been demonstrated that long-term treatment with this antihistamine (6 months) can improve the quality of life and symptoms and decrease the overall costs of persistent allergic rhinitis; these are some of the key criteria for the successful treatment of chronic disease.[4]

Levocetirizine has proven to be an effective and well-tolerated treatment for allergic rhinitis due to house dust mites and it was also effective for the relief of nasal congestion.[6] In addition, its efficacy in seasonal allergic rhinitis has been investigated. In patients with this disorder, treatment with levocetirizine produced a significant decrease in sneezing, rhinorrhoea, itching nose and itching eyes in comparison with the slow changes induced by placebo.[7] Different studies have demonstrated that a dose of 5 mg daily has the optimal benefit/risk ratio in the treatment of allergic rhinitis.[7,8]

H1 receptor antagonists are considered to be the first line of treatment for allergic rhinitis, as well as for urticaria. Up to now, no studies have been conducted to verify the efficacy of levocetirizine to treat urticaria. The aim of this study is to determine whether levocetirizine is efficacious in the treatment of chronic idiopathic urticaria.

Methods

A randomized, double-blind, placebo-controlled study was conducted in 106 patients with a diagnosis of chronic idiopathic urticaria (67 women and 39 men) ranging in age from 22 to 71 years (mean 40·2 ± SD 11·2 years).

Approval for the study was obtained from the Ethics Committee and all patients gave their written informed consent. Prior to treatment, all patients completed screening; exclusion criteria were physical urticaria, or urticaria caused by medications, insect bites, food or other known causes, as well as a history of atopic diseases. Patients with significant concomitant illness (e.g. malignancies or hepatic, psychiatric, endocrine or other major systemic diseases) were also excluded.

Study design

The 106 patients were randomly assigned to receive levocetirizine or placebo once daily: Group A (53 patients) oral levocetirizine 5 mg; Group B (53 patients) placebo. They were not informed that the treatment would be divided up into specific periods. At the beginning of the trial, the tablets were encapsulated in a double-blind fashion, and sealed in envelopes by a pharmacist together with the instruction sheets. All treatments were dispensed by a third party. No medications that could interfere with the clinical evaluations were allowed during the trial.

A 1-week single-blind placebo run-in period (baseline) was followed by a 6-week double-blind active treatment period with the above substances. The study ended after another 1-week single-blind placebo washout period.

Apart from the initial screening visits, each patient was examined by the physician four times over the 8-week period: a first visit following the placebo run-in; a second visit after 3 weeks of active treatment; a third visit after 6 weeks of active treatment (end of treatment); and a final visit at the end of the second placebo washout period (follow-up) (Fig. 1).

Efficacy measures

Throughout the study, all patients recorded their symptoms in a daily diary, including pruritus, size of weals, number of weals, number of separate urticarial episodes. At each clinical visit the patient's diary was reviewed, the patient was interviewed and a physical examination was performed. Evaluations were made at each visit by the same investigator for each patient.

Efficacy measures were scored according to the following scales: pruritus: 0 (none), 1 (mild), 2 (moderate) and 3 (severe); number of weals: 0 (none), 1 (1–10 weals), 2 (11–20 weals), 3 (> 20 weals); size of weals (mean diameter): 0 (no lesion), 1 (< 1·27 cm), 2 (1·27–2·54 cm), 3 (> 2·54 cm); number of separate urticarial episodes: 0 (no episodes), 1 (1 episode), 2 (2–3 episodes), 3 (> 3 episodes). The maximum value of the total symptoms score (TSS) was 12. At each clinical visit, patients also completed a 10-cm visual analogue scale score (VAS) indicating the overall severity of their urticaria over the previous days from 0 (none) to 10 (worst).

Urticaria quality of life

At each clinical visit, a five-question urticaria quality of life (QoL) questionnaire was administered evaluating the following domains: cutaneous symptoms, emotions, practical problems. The questions were: 'Over the last week, how itchy, sore, painful or stinging has your skin been? Over the last week, how embarrassed or self-conscious have you been because of your skin? Over the last week, how much has your skin influenced the choice of clothes you wear? Over the last week, how much has your skin affected any social

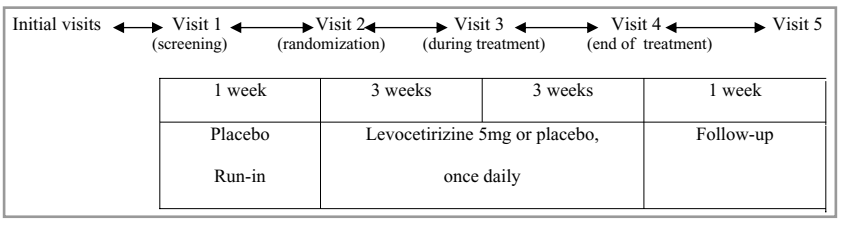

Fig 1. Schematic diagram of the study.

or leisure activities? Over the last week, has your skin prevented you from working or studying? If ''No'', over the last week how much has your skin been a problem at work or studying?'. These are part of the Dermatology Quality Life Index.[9] Patients scored their response to each question on a four-point scale ranging from 0 (no problems) to 3 (severe problems).

Safety

Safety and tolerability were assessed on the basis of the adverse events reported, or changes in vital signs, physical examination findings, and electrocardiograms recorded before and after the end of treatment. Laboratory safety parameters (haematology, serum biochemistry and urine analysis) were assessed before and after the treatment period.

Statistical analysis

The significance of differences in age, sex, baseline symptoms severity score, baseline QoL score, baseline duration of urticaria score, and baseline VAS was compared using the t-test for continuous data and the χ^2 test for categorical data.

For the efficacy analyses and comparison of the VAS in each study group, and at different visits, a repeated measures analysis of variance was performed. To compare the efficacy and the VAS in the two groups at different visits an analysis of variance was performed. In all instances, $P < 0{\cdot}05$ was considered statistically significant.

Results

The 106 patients were randomized, 53 to treatment with levocetirizine (36 women and 17 men ranging in age from 22 to 71 years, mean 41·1 ± SD 11·8 years); 53 with placebo (32 women and 21 men ranging in age from 22 to 69 years, mean 39 ± SD 10·5 years). The two groups were balanced with respect to baseline demographic data, including patient age and sex, duration of disease, overall symptom severity and perceived QoL. Two patients in the levocetirizine group and four patients in the placebo group discontinued treatment during the first study week. The reasons for discontinuation were: noncompliance ($n = 2$); heart attack ($n = 1$); and the need to take oral corticosteroids because of aggravation of the urticaria ($n = 3$; among them two came from the placebo group and one from the levocetirizine group). The evaluable population thus consisted of 100 patients. The patient demographics and baseline characteristics are shown in Table 1.

Table 1 Baseline patients' data (only patients who completed the study)

Patients' data	Levocetirizine	Placebo
Sex		
Male	17 (33%)	20 (41%)
Female	34 (67%)	29 (59%)
Age (years), mean ± SD	41·2 ± 11·9	36·9 ± 10·7
Symptom severity (overall score)[a]	9·4 ± 1·6	9·3 ± 1·1
Quality of life (overall score)[b]	6·6 ± 2·7	6·2 ± 2·4
Duration of urticaria (months)	11·7 ± 12·5	8·9 ± 4·1
Baseline visual analogue scale	8·7 ± 0·9	8·6 ± 1·0

[a]Mean of four domains scored on 0–3 scale. [b]Mean of five domains scored on 0–3 scale.

Efficacy analysis

At all study visits, patients from the levocetirizine group reported a significant improvement in overall chronic idiopathic urticaria compared with the placebo group, and this effect was maintained in the follow-up analysis ($P < 0{\cdot}05$).

The mean TSS value decreased by 81% at the end of therapy with respect to the baseline evaluation in the group treated with levocetirizine, and by 1% in the group treated with placebo. At the end of the active treatment, total disappearance of the symptoms was recorded in 27 (53%) vs. 0 patients treated with levocetirizine or placebo, respectively. Controls conducted 1 week after the end of active treatment showed that the positive effects persisted and were still statistically significant between the two groups, although to a lesser degree compared with those obtained during active therapy. At follow-up, total disappearance of the symptoms was recorded in 12 (24%) patients treated with levocetirizine, and in three (6%) patients treated with placebo.

Number of weals

The treatment group was statistically superior to the placebo group in terms of reduction of the number of weals score throughout the trial ($P < 0{\cdot}05$). In particular, in the levocetirizine group the drug determined a reduction in the number of weals score at all visits except follow-up, when the score was higher than the one reported at week 7.

During the six active treatment weeks levocetirizine therapy produced a 79% reduction in the score for number of weals compared with baseline ($P < 0{\cdot}05$). At follow-up, the reduction in number of weals score compared with baseline was 58% in the treatment group ($P < 0{\cdot}05$), although there was significant worsening with respect to the score at the end of active treatment ($P < 0{\cdot}05$). In the placebo group there were only slight, not significant, changes in the scores for number of weals during the trial.

Number of separate urticarial episodes

The levocetirizine group was statistically superior to the placebo group in terms of the reduction of the number of urticarial episodes scores throughout the trial ($P < 0{\cdot}05$).

During the first three active treatment weeks levocetirizine therapy produced an 84% reduction in the number of separate

episodes score compared with baseline ($P < 0{\cdot}05$). This marked effect did not persist after the end of the active treatment, and there was a worsening, although not significant, of the score, with an increase by 33% with respect to the fourth week of the trial.

At the follow-up visit, again, there was a significant worsening of the score after the end of the active treatment period (100%; $P < 0{\cdot}05$), although this value is significantly lower than the corresponding baseline assessment (− 58%; $P < 0{\cdot}05$). In the placebo group there were only slight, not significant, changes in the scores for the number of urticarial episodes during the trial.

Size of weals

The treatment group was statistically superior to the placebo group in terms of reduction in the size of weals. In particular, in the levocetirizine group the drug determined a reduction in the score for the size of weals at all visits except follow-up, when this score was higher than the one reported at week 7.

During the 6 weeks of active treatment levocetirizine therapy produced a 75% reduction in the scores for size of weals compared with baseline ($P < 0{\cdot}05$). At follow-up, the reduction in the score for size of weals compared with baseline was 50% in the treatment group ($P < 0{\cdot}05$), although there was a significant worsening with respect to the end of active treatment score ($P < 0{\cdot}05$). In the placebo group there were only slight, nonsignificant changes in the score for the size of weals during the trial.

Pruritus

Levocetirizine was statistically superior to placebo in reducing mean scores for pruritus throughout the trial ($P < 0{\cdot}05$). In particular, in the levocetirizine group the drug determined a reduction in pruritus intensity at all visits except follow-up, when the pruritus score was higher than the one reported at week 7.

At the end of the active treatment, a reduction in pruritus severity by 85% was recorded compared with baseline in the levocetirizine group ($P < 0{\cdot}05$). At follow-up, the reduction in pruritus severity compared with baseline was 69% in the treatment group ($P < 0{\cdot}05$). In the placebo group there were only slight, nonsignificant changes in the pruritus score during the trial.

Quality of life

There was a significant improvement in overall QoL with respect to baseline in the levocetirizine group, while in the placebo group there was a minor, but nonsignificant improvement. However, in the follow-up assessment there was a worsening, although nonsignificant, of the QoL evaluation with respect to the end of active treatment. In the placebo group there were only slight, nonsignificant changes in the QoL score during the trial.

Visual analogue scale score

There was a significant improvement in the VAS with respect to baseline in the levocetirizine treatment group, while there were only slight changes among patients treated with placebo. Patients in the active treatment group indicated a mean decrease from baseline of 82% after 3 weeks of active treatment, 87% after 6 weeks and 74% at follow-up ($P < 0{\cdot}05$). In the placebo group there were only slight, nonsignificant improvements in the VAS during the trial.

Safety

No clinically significant changes in vital signs, laboratory parameters or electrocardiogram criteria occurred during the study in any group. No patient reported any side-effects during the course of therapy in any study group.

Discussion

Urticaria is a condition characterized by the development of itchy, erythematous cutaneous swellings (weals). In particular, chronic urticaria is characterized by the occurrence of weals daily or almost daily for a period of at least 6 weeks.[10] It is a fairly common disorder, occurring in at least 0·1% of the population.[11] Despite an exhaustive and expensive diagnostic approach, searches for the aetiology of chronic urticaria are mostly frustrating, because in most cases the causative agent is unknown, and a physical urticaria and urticarial vasculitis are excluded. In these cases a diagnosis of chronic idiopathic urticaria is made.

However, recent research suggests that an autoimmune process may be causal in a significant subpopulation of patients, featuring the presence of circulating functional autoantibodies either to the high affinity IgE receptor or to IgE.[12,13]

In any case, the pathogenesis of urticaria involves the release of a wide array of potential vasoactive mediators that arise from the activation of mast cells in the skin.[14–16] Among them, histamine is released from preformed granules and is capable of eliciting the classic triple response consisting of vasodilation (erythema), increased vascular permeability (oedema), and an axon reflex that increases the extent of the reaction, particularly the erythema. In addition, various lipid-derived vasoactive factors are liberated by mast cells. However, because the signs and symptoms associated with chronic urticaria are mediated primarily by histamine, antihistamines are the mainstay of treatment.

Although the disfigurement can be remarkable and the pruritus intense, chronic urticaria is not life-threatening. Nevertheless, the symptoms can cause great misery, including such symptoms as sleep disruption, fatigue, social isolation, energy loss and emotional difficulties.[17] This is enhanced by the fact that the course and duration of chronic urticaria are highly variable and unpredictable. Spontaneous remissions may often occur within 12 months, but a substantial number of patients may have symptoms lasting periodically for years.[11,18]

Therefore, the treatment of chronic urticaria should improve both symptoms and QoL, the latter an important goal in the management of patients with chronic urticaria.

This is the first study to evaluate the efficacy of 5 mg levocetirizine in the treatment of chronic idiopathic urticaria in a double-blind, placebo-controlled trial. We have demonstrated that this new antihistamine taken once daily is effective and well tolerated in the treatment of chronic idiopathic urticaria symptoms and in improving the patient's QoL. Levocetirizine was superior to placebo in reducing the mean TSS as well as individual symptoms, number of daily episodes and number of weals, VAS and QoL.

These beneficial effects of levocetirizine appeared during the first 3 weeks and lasted throughout the duration of the active trial, showing the excellent ability of the drug to control chronic idiopathic urticaria.

In the placebo group there were only slight variations in the parameters, that could be attributed to the spontaneous course of chronic idiopathic urticaria.

Interestingly, focusing attention only on the levocetirizine group, we could observe that the significant beneficial effects of this drug lasted only during the active trial, while at follow-up there was a significant worsening of all the variables evaluated in this study, with respect to the end of the active trial (week 7). Notwithstanding this decrease, the condition was still better than at baseline. At the end of active treatment urticaria disappeared in 27 (53%) individuals belonging to the levocetirizine group and in none belonging to the placebo group. At the end of follow-up, 14 of them (52%) suffered a relapse of the urticaria.

This could be explained by the fact that antihistamines are substantially symptomatic agents. Mediators other than histamine, such as the newly generated eicosanoid lipid-derived mediators, predominantly prostaglandin D_2 and leukotriene C_4, and preformed mediators, have been suggested to be important contributory factors in the clinical management of chronic urticaria and responsible for the late-phase reactions.[19–21] Hence, chronic idiopathic urticaria should not be treated with antihistamines alone, but could require specific agents such as antileukotrienes, as shown in other studies.[22–25] The underlying complex mechanism could be responsible for the relapse of symptoms observed at follow-up.

In addition, the efficacy of levocetirizine as a symptomatic agent has been highlighted by the perfect correlation between the objective evaluation of chronic urticaria by means of the Breneman scale[26] and patients' perception of the disability referred by means of QoL impairment and VAS (Figs 2 and 3). The QoL issue allows clinicians to assess the extent and nature of the disability suffered, so that an appropriate management regimen can be implemented. The safety profile of levocetirizine was excellent in this study, with a complete absence of adverse events.

In conclusion, a global assessment indicates that levocetirizine 5 mg once daily is an effective agent in patients with chronic idiopathic urticaria, as its action provides a rapid and satisfactory control of the symptoms and subjective disease measures, although this is limited to the duration of treatment.

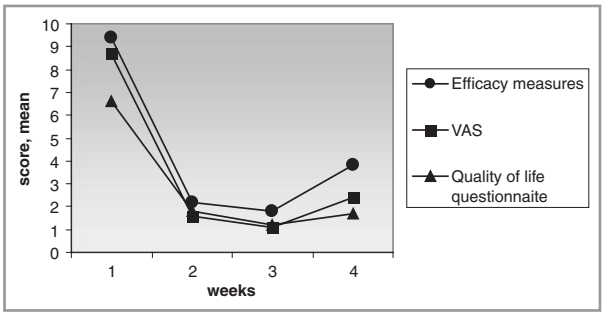

Fig 2. Overall mean symptoms scores, visual analogue scale (VAS) score and quality of life questionnaire by week of treatment in levocetirizine group. 1, 2, 3, 4 refer to baseline, after the 3rd and 6th weeks of active treatment and at follow-up.

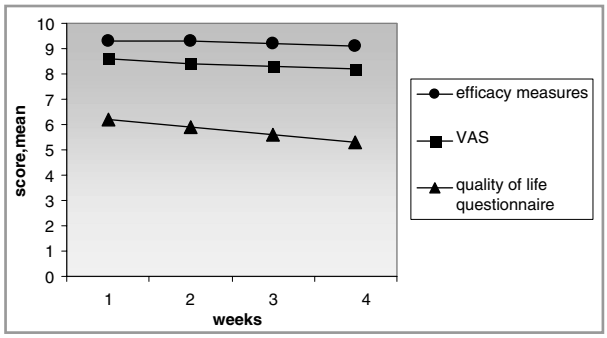

Fig 3. Overall mean symptoms scores, visual analogue scale (VAS) score and quality of life questionnaire by week of treatment in placebo group. 1, 2, 3, 4 refer to baseline, after the 3rd and 6th weeks of active treatment and at follow-up.

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