

Treatment of Chronic Idiopathic Urticaria with Levamisole: a Multicentre, Randomized, Double-blind, Controlled Trial

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The objective of this study was to evaluate the efficacy of treating chronic idiopathic urticaria (CIU) with levamisole in combination with levocetirizine. This was a multicentre, randomized, double-blind, controlled trial that included 132 patients with active CIU who were treated for 6 weeks with either levocetirizine alone (control group; $n = 65$) or levamisole plus levocetirizine (treatment group; $n = 67$). Response to therapy was evaluated by measuring the efficacy rate. After 2 weeks of treatment, there was no significant

difference in the efficacy rate between the treatment and control groups (54.84% and 42.37%, respectively). After 6 weeks of treatment, a statistically significant difference in the efficacy rate was observed between the groups (76.27% and 54.39% for the treatment and control groups, respectively). This study demonstrated that a combination of levamisole plus levocetirizine is more effective than levocetirizine alone and potentially provides a new, promising approach to the treatment of CIU.

KEY WORDS: CHRONIC IDIOPATHIC URTICARIA; LEVAMISOLE; LEVOCETIRIZINE; THERAPEUTIC EFFECT; EFFICACY RATE

Introduction

Chronic idiopathic urticaria (CIU) is characterized by persistent wheals and itching (pruritus) that continues for ≥ 6 weeks and has no identifiable cause, and affects up to 0.1% of the population, including both adults and children.¹ The aetiology of CIU is not completely understood; however, it is known that degranulation of mast cells or basophils,

which cause release of histamine and other inflammatory mediators, results in the development of urticarial lesions.² These lesions then attract T lymphocytes, monocytes, neutrophils, eosinophils and basophils to the inflamed skin.³ In patients with CIU there is evidence of immune cell dysfunction and cytokine abnormalities.²⁻⁴

The aim of the present study was to compare the efficacy of treatment with the

antihistamine levocetirizine alone with combination treatment with levocetirizine plus the immunomodulatory agent levamisole in patients who had active CIU.

Patients and methods

PATIENTS

This was a multicentre, randomized, double-blind, controlled clinical trial conducted in patients who had active CIU. It was approved by the Ethics Committee of the Affiliated Yancheng Hospital, Medical College of Southeast University, Yancheng, China. All patients provided written, informed consent prior to their participation in the study.

Patients were included in the study if they had CIU, i.e. episodes of hives with characteristic wheal and flare appearance, occurring regularly for a period of ≥ 6 weeks without an identifiable cause. Patients were only eligible for study inclusion if they had active moderate to severe CIU, defined as a pruritus score ≥ 2 , a number of wheals ≥ 1 and the largest wheal ≥ 1 cm (Table 1). Patients with other forms of urticaria, such as physical, drug-induced, acute or cholinergic urticaria were excluded from the study. Patients were also excluded if they were already undergoing an immunotherapy regimen or initiated an immunotherapy regimen during the course of the study. Female patients were excluded if they were

pregnant, lactating or not considered to be employing adequate measures to prevent conception. Patients were also excluded if they had any systemic or dermatological disease that had the potential to interfere with the evaluation of symptoms.

STUDY DESIGN

The study was conducted over a period of 6 weeks and included four study visits: (i) patient screening (visit 1); (ii) start of treatment (baseline, visit 2); (iii) 2 weeks after the start of treatment (visit 3); and (iv) 6 weeks after the start of treatment (visit 4).

At visit 1, the patients were screened. At visit 2, the patients were randomly assigned in a double-blind fashion to either the treatment group or the control group. Patients in the treatment group were given 50 mg levamisole orally three times daily (in total 150 mg/day) for 3 days consecutively every 2 weeks and 5 mg levocetirizine orally once daily. Patients in the control group were given 5 mg levocetirizine orally once daily and placebo administered using the same dosing schedule as for levamisole in the treatment group. Patients were treated for a period of 6 weeks. Efficacy was evaluated at visits 3 and 4.

STUDY ASSESSMENTS

Patients assessed the severity of their CIU symptoms (including pruritus severity,

TABLE 1:
Scoring system used to assess the severity of chronic idiopathic urticaria symptoms

Score	Pruritus severity	No. of wheals	Size of largest wheal (cm)	No. of flares/day
0	None	0	0	0
1	Mild, noticeable but discrete, easy to tolerate	1 – 6	< 1	1
2	Moderate, obvious and unpleasant presence, but bearable	7 – 12	1 – 5	2
3	Severe, hard to bear	> 12	> 5	≥ 3

number of wheals, size of the largest wheal and number of flares per day) once a day. Each assessment parameter was scored on a four-point scale from 0 to 3, as detailed in Table 1, and the scores were recorded in a daily diary. Any side effects were also recorded in the daily diary. The diaries were checked by the investigator at each study visit to ensure proper completion. At each visit the investigator also evaluated CIU symptoms using the same assessment criteria (Table 1).

Response to therapy was evaluated by calculating the efficacy rate which was based on the total scores reduction index (TSRI), as follows: $TSRI = ([\text{total symptom scores before treatment} - \text{total symptom scores after treatment}] / \text{total symptom scores before the treatment}) \times 100\%$. Therapeutic effect was graded using the following scale: (i) cured – no pruritus, no wheals; (ii) significant improvement – $TSRI > 60\%$; (iii) improved – $TSRI 30\% - 60\%$; and (iv) no effect – $TSRI < 30\%$. The efficacy rate at each visit was calculated as $([\text{number of cured cases} +$

$\text{number of significantly improved cases}] / \text{total number of cases}) \times 100\%$.

STATISTICAL ANALYSIS

Statistical evaluation of the data was carried out using the SPSS® statistical package, version 12.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Statistical analyses were performed on the intent-to-treat (ITT) population, i.e. all randomized patients who received the study drug. The efficacy rate and the rate of occurrence of side-effects in the two study groups after 2 and 6 weeks' treatment were compared using either the χ^2 test or by direct calculation of the degree of significance according to Fisher's exact test. Baseline duration of CIU and demographic characteristics of the patients in the two study groups were compared using Student's *t*-test. The severities of the four CIU symptoms that were assessed (Table 1) were compared using an analysis of variance model. The statistical tests were two-tailed at the 5% level of significance ($P < 0.05$ was statistically significant).

TABLE 2:

Baseline demographics and disease severity characteristics of the intention-to-treat study population of patients with chronic idiopathic urticaria who were treated with either levamisole plus levocetirizine (treatment group) or levocetirizine plus placebo (control group) for 6 weeks

Variable	Treatment group (<i>n</i> = 67)	Control group (<i>n</i> = 65)	Total (<i>n</i> = 132)
Age (years)	36.8 ± 14.3	38.2 ± 15.6	37.5 ± 15.5
Sex, <i>n</i> (%)			
Male	26 (38.8)	26 (40.0)	52 (39.4)
Female	41 (61.2)	39 (60.0)	80 (60.6)
Weight (kg)	61.3 ± 16.6	63.1 ± 14.7	62.2 ± 14.5
Duration of urticaria (months)	26.3 ± 20.3	24.6 ± 23.6	25.5 ± 21.5
Pruritus severity (score) ^a	2.57 ± 0.50	2.55 ± 0.50	2.56 ± 0.50
Number of wheals (score) ^a	1.96 ± 0.59	1.95 ± 0.55	1.96 ± 0.57
Size of wheals (score) ^a	1.79 ± 0.61	1.73 ± 0.64	1.75 ± 0.64
Number of flares (score) ^a	1.68 ± 0.52	1.60 ± 0.49	1.64 ± 0.58

Data are mean ± SD unless otherwise stated.

^aThe scoring system is given in Table 1.

Results

Of the 150 patients who were screened at visit 1, a total of 132 were randomized (ITT population); 67 patients were included in the treatment group and 65 patients in the control group. Overall, 116 patients completed the study (87.9%). Five patients (three lost to follow-up and two for withdrawal of consent) in the treatment group and six patients (three lost to follow-up and three for withdrawal of consent) in the control group had discontinued the study by visit 3 (2 weeks after the start of treatment) and, in total, eight patients (four lost to follow-up and four for withdrawal of consent) in each group had discontinued the study by the last visit, visit 4 (6 weeks after the start of treatment). There were no statistically significant differences between the treatment and control groups in baseline demographics or clinical characteristics (Table 2).

Results for the efficacy rate evaluations after 2 and 6 weeks of treatment (visits 3 and 4, respectively) are given in Table 3. At visit 3 (2 weeks after the start of treatment), there was no statistically significant difference between the treatment group and control groups in the efficacy rate, whereas at the last visit, visit 4 (6 weeks after the start of treatment), there was a statistically significant difference between the two groups ($P < 0.05$).

No unexpected adverse events occurred during the study. The incidence of treatment-related adverse events was slightly higher (not statistically significant) in the treatment group than in the control group (23.8% and 19.8%, respectively); no serious adverse events occurred in either group.

Discussion

Levamisole was first used as an anthelmintic agent in 1969. Subsequently, its

TABLE 3:
Treatment efficacy after 2 and 6 weeks in patients treated with levamisole plus levocetirizine (treatment group) or levocetirizine plus placebo (control group) for chronic idiopathic urticaria

Time from start of treatment	Group	Patients, <i>n</i>					Effective rate	χ^2	Statistical significance
		Cured	Significantly improved	Improved	No effect	Efficacy ^a			
Visit 3 (2 weeks)	Treatment (<i>n</i> = 62)	14	20	17	11	34	54.84%	1.9	NS
	Control (<i>n</i> = 59)	8	17	20	14	25	42.37%		
Visit 4 (6 weeks)	Treatment (<i>n</i> = 59)	22	23	9	5	45	76.27%	6.2	$P < 0.05$
	Control (<i>n</i> = 57)	9	22	17	9	31	54.39%		

NS, not statistically significant ($P > 0.05$).

^aCured + significantly improved.

immunomodulatory effects have been recognized and investigated. Levamisole has a wide range of immunomodulatory applications resulting from its ability to stimulate and suppress immune responses to a variety of antigens and from its actions on a variety of immune cell types. An increase in monocyte chemotaxis is considered to be one of its most important actions.⁵ Levamisole acts on both T and B lymphocytes, although its effects on T lymphocytes are more pronounced.⁶ Like other T-cell adjuvants,⁷ levamisole appears preferentially to stimulate delayed-type hypersensitivity, involving a proliferation of T helper (Th) 1 cells and/or a decrease in the number of Th2 cells produced; furthermore, levamisole suppresses interleukin (IL)-4 gene expression and serum IgE levels. Levamisole augments mitogen-induced T-cell proliferation and potentiates the T-cell proliferation-inducing activity of IL-2, resulting in up-regulation of the cytokine, IL-18, which is involved in skewing the immune balance towards a Th1 response by stimulating interferon (IFN)- γ production.^{8,9} Research has also suggested that levamisole restores depressed immune function rather than raising it above homeostatic levels.⁶

Previous studies have demonstrated that there is dysfunction of immune cells and an

abnormality of the relevant cytokines (increase in IL-4 and IL-10 levels and/or reduction of IL-2 and IFN- γ) in patients with CIU.²⁻⁴ In contrast, other studies have suggested that there is a Th0 or a mixture of Th1 and Th2 cytokine profile rather than a Th2 cytokine profile in patients with CIU.^{10,11}

The present study indicated that a combination of levamisole with levocetirizine is more effective than levocetirizine alone for the treatment of CIU. One possible mechanism for this activity is that levamisole restores depressed immune function and thereby modulates the production of related cytokines and antibodies; however, more studies are required to investigate this mechanism further. This study provides a new potentially promising approach for the treatment of CIU.

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Conflict of interest

The authors had no conflicts of interest to declare in relation to this article.

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