

The leukotriene receptor antagonist montelukast in the treatment of chronic idiopathic urticaria: A single-blind, placebo-controlled, crossover clinical study

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Background: Chronic idiopathic urticaria (CIU) might be refractory to standard therapies. For the patients with severe unremitting CIU who have failed to benefit from conventional therapy with antihistamines, other effective and safe therapeutic modalities are required.

Objective: A randomized, single-blind, placebo-controlled crossover study was conducted to evaluate the efficacy and safety of the new selective leukotriene antagonist montelukast sodium in the treatment of refractory CIU.

Methods: Thirty patients with refractory CIU were enrolled in the trial. After informed consent was obtained, patients were randomly assigned to 2 groups. The patients in group A received 10 mg/d montelukast and a nonsedating H₁ antihistamine (cetirizine) when needed for 6 weeks. After a 2-week washout period, they received placebo for 6 weeks and the same H₁ antihistamine as needed. Group B received the treatment vice versa. Improvement was monitored by using the self-estimated urticaria activity score, which is the sum of the wheal number score and the itch severity score, and the antihistamine counts used in each study period.

Results: More significant decreases occurred in urticaria activity scores with montelukast therapy compared with those with placebo therapy ($P < .001$). H₁ antihistamine use was also significantly less frequent during the montelukast period ($P < .001$).

Conclusion: The present study results suggest that montelukast might be an effective and safe therapeutic agent in the treatment of refractory CIU. (*J Allergy Clin Immunol* 2002;110:484-8.)

Key words: Chronic idiopathic urticaria, treatment, leukotriene antagonist, montelukast, placebo, urticaria activity score, crossover study

Chronic idiopathic urticaria (CIU) is a common cutaneous disorder with a complex pathophysiologic mechanism for which there is usually no identifiable specific

Abbreviations used

ASST:	Autologous serum skin test
CIU:	Chronic idiopathic urticaria
CU:	Chronic urticaria
LRA:	Leukotriene receptor antagonist
LT:	Leukotriene
NSAID:	Nonsteroidal anti-inflammatory drug
UAS:	Urticaria activity score

causative agent.¹ The pathogenic mechanisms vary, but cutaneous mast cell activation with release of histamine and other vasoactive or proinflammatory mediators is thought to be the final common pathway for lesion induction in most cases. Other inflammatory cells, including lymphocytes and polymorphonuclear cells, have also been implicated.² Although histamine is considered to be the principal mediator in the immediate urticarial responses, a subsequent late-phase allergic reaction caused by additional substances, including the cysteinyl leukotrienes (LTs), which are potent lipid mediators, seems to prolong the inflammatory process in some types of urticaria, particularly in certain chronic forms.^{1,2}

Cysteinyl leukotriene receptor antagonists (LRAs) are currently used for the treatment of mild-to-moderate asthma and rhinitis.³ LRAs have been recently shown to be moderately effective in some patients with atopic dermatitis.⁴⁻⁶ Some anecdotal case reports⁷⁻¹⁰ and study results have suggested that the LRAs montelukast and zafirlukast might also be effective in the treatment of chronic urticaria (CU), including steroid-dependent cases,¹¹⁻¹⁴ particularly in the control of the severe urticaria-angioedema exacerbations related to cold,¹⁵ pressure,¹⁶ food additives, and nonsteroidal anti-inflammatory drugs (NSAIDs).¹⁷ Nevertheless, in a recent study montelukast was not found to be more effective than placebo in decreasing the early and late cutaneous allergic responses.¹⁸ Moreover, low doses of a new LRA, pranlukast, have been reported to cause provocation of aspirin-sensitive urticaria in 2 patients.¹⁹ Therefore the potential therapeutic effect of LRAs in the control of CU is yet to be determined with further placebo-controlled clinical studies with larger patient populations.

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TABLE I. Baseline patient characteristics in the study groups

Patient characteristics	Group A (montelukast → placebo, n = 15)	Group B (placebo → montelukast, n = 15)
Sex		
Female	10	11
Male	5	4
Mean age (y)	42.46 (median, 41; range, 30-56)	43 (median, 44; range, 32-56)
Duration (mo)	15 (median, 13; range, 3-30)	16.2 (median, 15; range, 2-38)
Intolerance to NSAIDs	3	6
ASST positivity	6	5
Previous treatments		
Only H ₁ blockers	3	2
H ₁ and H ₂ blockers	1	1
H ₁ blockers, prednisolone	7	9
H ₁ blockers, terbutaline	1	2
H ₁ blockers, ketotifen, prednisolone	2	1
H ₁ blockers, cyclosporine	1	—

A single-blind, placebo-controlled, crossover clinical study was conducted to evaluate the efficacy and safety of montelukast in the management of refractory CIU.

METHODS

The study population consisted of 30 adult patients (21 women and 9 men) ranging in age from 30 to 56 years (mean $\pm$ SD, 42.76 $\pm$ 7.72 years) with a diagnosis of CIU defined as the presence of itchy wheals almost daily or at least 3 days per week for at least 6 consecutive weeks. All of the patients had refractory CIU that was poorly responsive to previous therapies with H₁ antihistamines alone or combined with other drugs (Table I). Patients with physical urticaria, pharmacologic urticaria, or urticaria induced by any other known cause and patients with a history of atopic diseases were excluded from the study. Pregnant and actively nursing women; patients with chronic infection, Hodgkin disease, and other malignancies; patients allergic to montelukast and cross-reacting medications; and patients given a diagnosis of hepatic, psychiatric, endocrine, or other major systemic diseases were also excluded.

After informed consent was obtained, the patients were randomized to 2 study groups to receive either 10 mg of montelukast or placebo once daily at bedtime and 10 mg/d of the same long-acting, nonsedating H₁ antihistamine, cetirizine, as needed. The patients were blind to therapy period. In period 1 the patients in group A received montelukast, and those in group B received placebo for 6 weeks. After a 2-week washout period, which is usually accepted as a sufficient washout time between treatments within crossover studies performed with montelukast,²⁰ each group was crossed over to the other treatment arm (period 2). Montelukast and matching placebo pills were given in weekly doses to the patients in the clinic by the investigator during the weekly evaluation times. All patients underwent an autologous serum skin test (ASST) before and after the therapies and after washout periods. Repeat tests were done with freshly drawn serum samples. A positive ASST result was accepted as a serum-induced erythematous wheal with a diameter of 1.5 mm or larger than the saline-induced response at 30 minutes, as previously described.²¹ A second test reading was also done at 60 minutes in all patients to determine the late or prolonged reactions according to the original description in the literature.²² For the safety analysis, routine blood chemistry and serologic tests were performed in all patients before and after each study period.

The patients were evaluated at baseline, weekly throughout, and at the end of each therapy period and after washout periods. The improvement was monitored by using the urticaria activity score (UAS), which was estimated daily by the patient, as previously

described.²³ The UAS consisted of the sum of the wheal number score and the itch severity score. The wheal numbers were graded from 0 to 3 as follows: 0, less than 10 small wheals (diameter, <3 cm); 1, 10 to 50 small wheals or less than 10 large wheals (diameter, >3 cm); 2, greater than 50 small wheals or 10 to 50 large wheals; and 3, almost covered. The severity of the itching was also graded daily from 0 to 3 (0, none; 1, mild; 2, moderate; and 3, severe). Thus UAS ranged from 0 to 42 per week for each patient. The patients also recorded the number of antihistamine tablets they took per week during each study period.

The changes in UASs and antihistamine counts during the 2 treatment periods were compared by using a 2-factor ANOVA with repeated measurements on one factor. A comparison of the baseline UASs and antihistamine numbers for period 2 was made with those for period 1 to detect changes that might be attributable to treatment carry-over from period 1 or a treatment-by-period interaction and the changes in the UAS. The Mann-Whitney *U* test was used for unpaired data, and the Wilcoxon signed-rank test was used for paired data. All statistical tests were 2-tailed, and a *P* value of less than .05 was considered to be statistically significant. An independent blind observer assisted data recording to minimize the potential influence of the investigator's knowledge of treatment condition.

RESULTS

Patient compliance was excellent, and all patients completed the study according to the protocol. Groups A and B were balanced with respect to baseline demographic data, including patient age and sex, duration of disease, intolerance to NSAIDs, ASST positivity, and prior therapies (Table I). Similarly, baseline UASs and the frequencies of antihistamine use for groups A and B were not significantly different (both *P* > .05). The study groups were also similar after the washout period because the differences between the baseline UASs and weekly antihistamine numbers for period 2 and those for period 1 showed no statistical significance, and the carry-over effect was excluded (both *P* > .05, Table II).

There were significant differences in UASs and weekly antihistamine counts per patient between the montelukast and placebo treatment periods (both *P* < .001, Figs 1 and 2). Although no patient showed complete clearance with placebo, a total of 18 patients became totally free of

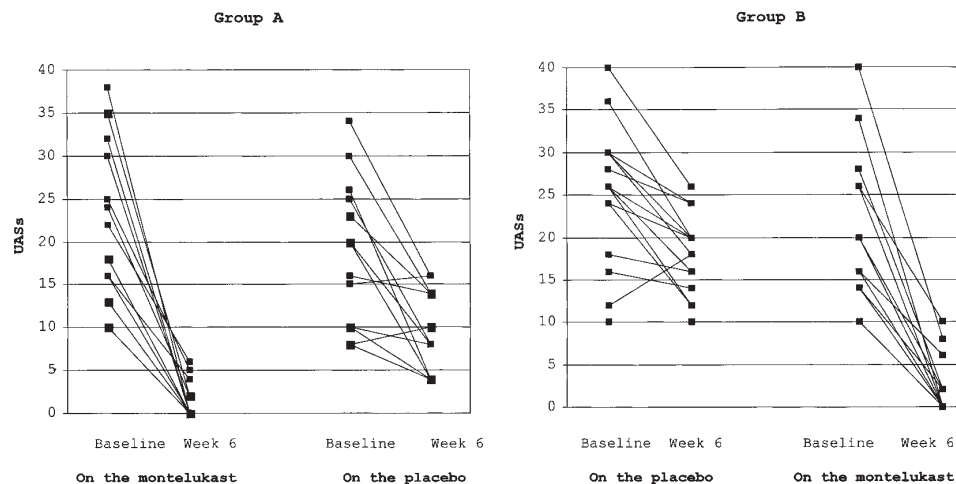


FIG 1. Individual UASs during periods 1 and 2.

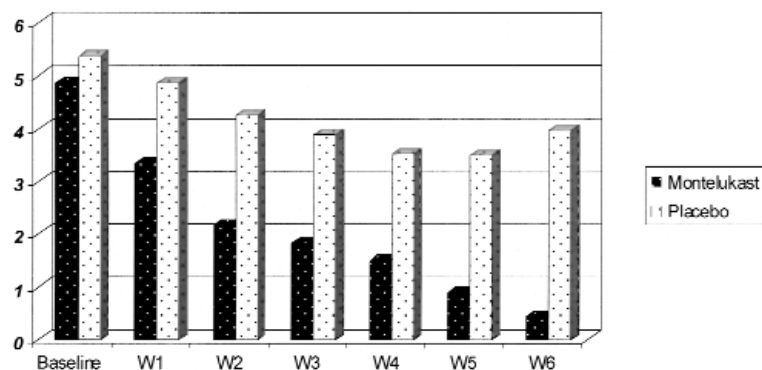


FIG 2. Mean number of weekly antihistamine tablets per patient during the montelukast and placebo periods.

TABLE II. Baseline values of mean UASs and mean antihistamine counts per patient used per week in the study groups in each study period

	Mean UASs			Mean antihistamine counts		
	Period 1	Period 2	P value*	Period 1	Period 2	P value*
Group A	23.93 (median, 24; range, 10-38)	17.66 (median, 16; range, 8-34)	>.05	5.06 (median, 5; range, 3-7)	4.93 (median, 5; range, 3-7)	>.05
Group B	20.8 (median, 20; range, 10-40)	21.2 (median, 20; range, 14-40)	>.05	5.8 (median, 6; range, 3-7)	4.66 (median, 4; range, 2-7)	>.05
P value†	>.05	>.05		>.05	>.05	

*Wilcoxon signed-rank test.

†Mann-Whitney U test.

urticaria and needed no antihistamine ingestion at the end of the 6-week therapy with montelukast. All of these complete responders were correctly able to identify the active medication after the completion of the whole trial and desired to continue the montelukast ingestion later.

Before entering the study, 11 patients had a positive response to the ASST, and in 4 of them, the autologous serum-induced erythema and wheal response reached the maximum diameter by 60 minutes and continued for several hours. Nine of the patients with positive ASST

results, including the late responders, had negative test results at the end of the montelukast therapy period. Interestingly, the 4 patients who had expressed a late and prolonged test reactivity before montelukast were again reactive to the test, although to lesser degrees, after the washout period. All 9 patients with aspirin-sensitive urticaria were among the complete responders and had more favorable responses to montelukast than the remaining patients with CIU. All of the patients who were initially intolerant to aspirin and other NSAIDs

showed an increased tolerability to these drugs, even after the cessation of montelukast ingestion.

No severe adverse effect was observed with montelukast, and the tolerability profile of montelukast was similar to that of placebo. The most common adverse event was a transitory and mild headache that occurred in 5 female patients.

DISCUSSION

CIU can be difficult to treat in some patients whose symptoms cannot be controlled with conventional antihistamine therapy alone. The duration of the wheals in CIU is often longer than 12 hours, and H_1 and H_2 antagonists might only partially alleviate the clinical symptoms. Release of mast cell mediators causes inflammation and accumulation and activation of other cells, including eosinophils, neutrophils, and possibly basophils.^{1,2} Mediators other than histamine, such as newly generated eicosanoid lipid-derived mediators, predominantly PGD_2 and LTC_4 , and preformed mediators, including proteases and proteoglycans, have been suggested to be responsible for the late-phase reactions in the cases of CIU that cannot be treated with antihistamines alone.^{24,25}

The LTs are the metabolites of the arachidonic acid pathway involved in acute and chronic inflammatory processes and allergic inflammation.²⁶ LTs are generated by a number of cells, including mast cells, eosinophils, basophils, and neutrophils, that are present in the airways of patients with asthma and in the skin of patients with CIU as well. They mediate chemotaxis, vascular permeability, edema, eosinophil migration, airway constriction, and smooth muscle contraction.^{6,12,24-26} LTB_4 is an endogenous itch mediator.²⁷ On a molar basis, LTs are 100 times more potent than histamine, and intradermal LTD_4 injection causes a wheal-and-flare response that could be inhibited by an LTD_4 antagonist.²⁸ The patients with CIU had been found to have larger reactions to intradermal LT injections compared with healthy subjects.^{29,30}

LRAs are recommended and currently used in the treatment of mild-to-moderate asthma and allergic rhinitis.^{3,20} Montelukast sodium is a new selective receptor antagonist of LTD_4 , and its administration orally once a day was recently shown to be very effective in the treatment of cold urticaria¹⁵ and delayed pressure urticaria.¹⁶ Pacor et al¹² have found that montelukast was more effective than cetirizine and placebo in the treatment of CU related to food additives and aspirin. Nettis et al¹³ have also demonstrated that montelukast had better therapeutic effects compared with those of fexofenadine for CIU, and the majority of the patients with positive ASST results were unreactive after montelukast therapy of 30 days.

The present study results demonstrated that montelukast was more effective than placebo, and the need for rescue medication (cetirizine) was significantly lower in the montelukast period in the patients with CIU. Not all patients in the study population had severe CIU because UASs ranged from 10 to 40, and an average of

about 5 pills per week seemed to be sufficient to control symptoms. However, some patients thought that daily antihistamine pill ingestion was not beneficial to control of their diseases, and therefore they took such pills irregularly and possibly fewer than needed. Nevertheless, both patients with severe CIU and those with mild-to-moderate CIU had similar favorable responses to montelukast therapy, as seen in Fig 1. It was also very efficient in all patients who were initially intolerant to NSAIDs, and no significant side effects were observed during montelukast therapy. Another remarkable finding was that the majority of the patients (9/11) who had initially positive ASST results had negative test results at the end of the montelukast therapy. Although this effect was limited to the therapy period and test reactivity recurred after washout in 4 patients with initial late-prolonged reaction, it was permanent in the remaining patients. This observation suggests that sera from patients with positive ASST results might also induce de novo production of LTs in addition to histamine liberation, as previously demonstrated by Wedi et al,³¹ and some patients with autoimmune urticaria possibly require longer therapy periods with montelukast.

In conclusion, montelukast might be a safe and effective alternative therapeutic agent in the management of patients with CIU, including patients with autoimmune urticaria and those intolerant to NSAIDs. Further experimental research and long-term clinical studies are required to determine the role of LTs in the pathogenesis of CIU and autoimmune urticaria and to confirm the efficacy of montelukast and other LRAs in the treatment of CU, as well as to determine the optimal timing and dosing of the therapy.

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