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The effectiveness of montelukast for the treatment of anti-histamine-resistant chronic urticaria

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Abstract Many patients with chronic idiopathic urticaria are not sufficiently controlled with histamine H₁-receptor antagonists. Leukotriene receptor antagonists have been reported to be effective for certain cases of urticaria, although their proper application remains to be established. To study the effectiveness of montelukast, a leukotriene receptor antagonist, for the treatment of chronic urticaria that was not controlled by histamine H₁-receptor antagonists. Twenty-five patients with chronic idiopathic urticaria were treated with 10 mg of montelukast for one week or more, without changing any precedent treatment that they were using before the study including histamine H₁-receptor antagonists. The effectiveness of montelukast for each patient was evaluated and compared with clinical features and/or backgrounds of the patients. Twelve patients, including six who had been treated with corticosteroids, were evaluated as “markedly improved” or “improved” following treatment with montelukast. There was no statistically significant relation of the effectiveness to the complications with non-steroidal anti-inflammatory drugs (NSAIDs) intolerance, mechanical urticaria, or reactions to autologous serum skin test. However, the patients for whom montelukast was effective were younger (33.2 ± 16.3 years, mean $\pm$ SD) ($P < 0.05$, Mann-Whitney test) and their duration of illness shorter (15.9 ± 18.3 months) ($P < 0.005$, Mann-Whitney test) than those of patients for whom montelukast was ineffective (45.9 ± 15.0 years, 89.6 ± 71.7 months). Montelukast may be worth trying for patients with

chronic idiopathic urticaria, when the condition is not sufficiently controlled with histamine H₁-receptor antagonists.

Keywords Chronic urticaria · Histamine H₁-receptor antagonist · Leukotriene receptor antagonist · Age · Treatment

Introduction

Urticaria is induced by the degranulation of skin mast cells in response to various stimuli. Chronic idiopathic urticaria, also simply termed as “chronic urticaria”, is defined as urticaria lasting for over six weeks without apparent cause or trigger for the symptoms [12]. The standard treatment for chronic urticaria is the oral administration of one or multiple histamine H₁-receptor antagonists [6]. However, many patients are not sufficiently controlled with such treatments [7]. Recently, several reports have shown that leukotriene receptor antagonists are effective for the treatment of urticaria, especially those with an autoimmune basis [1], those complicated with aspirin intolerance [11], or delayed pressure urticaria [9]. In contrast, by use of a randomized placebo-controlled trial, Lorenzo et al. [4] found montelukast, a leukotriene receptor antagonist, to be ineffective in chronic idiopathic urticaria. Moreover, Ohashi et al. [10] reported that a case of aspirin-sensitive urticaria was aggravated by pranlukast, another leukotriene receptor antagonist. Thus, leukotriene receptor antagonists may be effective for certain types of urticaria, but their proper application, particularly in relation to histamine H₁-receptor antagonists has not been established. In this study, we studied the effectiveness of montelukast in chronic idiopathic urticaria patients, who could not be sufficiently treated with histamine H₁-receptor antagonists with or without various clinical features including aspirin intolerance, mechanical urticaria and an autoimmune basis, and tried to clarify the factor related to the efficacy of this drug.

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Patients

Following informed consent, twenty-five chronic idiopathic urticaria patients who were not fully controlled with histamine H₁-receptor antagonists for more than 5 weeks were recruited. The age of the patients ranged from 4 to 72 years (39.8 ± 16.6 , mean $\pm$ SD) and the period of illness from 5 weeks to 20 years (54.3 ± 64.0 weeks, mean $\pm$ SD). Seven patients were complicated with an intolerance against NSAIDs, and 11 with mechanical urticaria, whereas none with deep pressure urticaria. Skin tests showed 7 out of 21 patients were positive for their own sera. Thirteen patients were treated with only histamine H₁-receptor antagonists and 12 patients were treated with histamine H₁-receptor antagonists and corticosteroids.

Study protocol

All patients received 10 mg montelukast once a day for 1 week or more in addition to histamine H₁-receptor antagonists and other medication that they had been taking.

The number and the duration of wheals and the degree of itching was assessed at the study outset and at the second visit of the patients to the clinic 1 or 2 weeks later by the same dermatologist, using the scoring system for urticaria proposed by Grattan et al. [5] with a slight modification. Namely, the number of wheals was scored as 0 for the condition without any wheal; 0.5 for 1–9 small (diameter <3 cm) wheals; 1 for 10–50 small or <10 large (>3 cm) wheals; 2 for >50 small or 10–50 large wheals; 3 for the condition where almost all the body surface was covered with wheals. The duration of wheals was scored as 0, when wheals did not appear or disappear within 1 h; 1, when wheals lasted for no less than 1 h and disappeared in less than 2 h; 2, when wheals lasted for no less than 2 h and disappeared in less than 12 h; 3, when wheals lasted for 12 h or more. The severity of itch was scored as 0, none; 1, mild; 2, moderate; 3, severe. The maximal daily score of the urticaria symptoms therefore, ranged from 0 to 9. Montelukast effectiveness was classified as follows: “Markedly improved”, if all the symptoms disappeared or the average score of the urticaria symptoms in the preceding 4 to 7 days decreased by 3 or more; “improved”, if the decrease was not less than 2 but less than 3; “slightly improved”, if the decrease was not less than 1 but less than 2; “No change”, if the change of the score was within 1; and “worse”, if the score decreased by 1 or more.

Results

Table 1 shows the demographic and clinical characteristics of the patients and the efficacy of montelukast in each subject. Among 25 patients who completed the

study, 8 were classified as having “markedly improved”, 4 as having “improved”, 3 into “slightly improved”, 7 into “no change” and 3 into “worse”. One patient (patient No. 21) who was classified into “no change” had complained of sleeplessness and aphtha during the period of montelukast treatment, but these disappeared upon cessation of montelukast treatment and no further adverse reactions were reported. Six out of 12 patients who had been treated with corticosteroids responded well to montelukast and were classified as having “markedly improved” or “improved”. Moreover, two of them (patient No. 1 and 6) were able to stop their use of corticosteroids, and another two (patient No. 3 and 10) were able to stop their use of corticosteroids and no longer had symptoms of urticaria.

Table 2 summarizes the clinical characteristics in relation to the effectiveness of montelukast. Montelukast was effective for 4 out of 7 patients who showed positive reactions to their autologous sera, 3 out of 9 patients who were intolerant to NSAIDs, and 5 out of 12 patients whose condition was complicated with mechanical urticaria. A statistically significant relation between any of these clinical features and the effectiveness of montelukast ($P > 0.05$, Fisher’s exact test) was not found. However, with respect to age and period of illness, patients for whom montelukast was effective were younger (33.2 ± 16.3 years, mean $\pm$ SD) ($P < 0.05$, Mann-Whitney test) and exhibited a shorter period of illness (15.9 ± 18.3 months, mean $\pm$ SD) ($P < 0.005$, Mann-Whitney test) than for those whom montelukast was ineffective (45.9 ± 15.0 years, 89.6 ± 71.7 months, mean $\pm$ SD) (Fig. 1).

Discussion

We have demonstrated that montelukast was effective for 12 out of 25 patients with chronic urticaria, for whom treatment with histamine H₁-receptor antagonists had proved ineffective. Other authors have reported that patients who showed positive skin reactions to autologous sera and/or those with aspirin intolerance were more sensitive to montelukast treatment [1, 11]. However, we found no significant difference in such conditions between patients who responded to montelukast and those who did not. In addition, our study revealed a difference with respect to age and duration of illness between those who responded to montelukast and those who did not; namely, those who responded to montelukast tended to be younger and had experienced a shorter duration of illness.

Several immunosuppressive treatments, such as high dose corticosteroids (≥ 30 mg prednisolon daily), cyclosporine, plasmapheresis and intravenous infusion of immunoglobulins (IVIG), have been reported to be effective for patients who are not well controlled by histamine H₁-receptor antagonists, especially when the patients show a positive reaction in autologous serum

Table 1 Demographic and clinical characteristics of the patients and the effect of montelukast

Patient	Sex	Age	Period of illness (month)	ASST ^a	Complication		Preceding medications (dosage in mg)	Effect of montelukast
					NSAIDs intolerance	Mechanical urticaria		
1	F	27	7	—	—	—	Olopatadine (10), betamethasone (0.5)	Markedly improved
2	M	26	60	—	—	—	Cetirizine (20), mequitazine (6)	Markedly improved
3	M	36	18	—	+	—	Fexofenadine (120), mequitazine (6), hydroxyzine (75), betamethasone (0.75)	Markedly improved
4	M	32	1.3	—	+	—	Ebastine (20), homochlorcyclizine (40), betamethasone (1.0)	Markedly improved
5	F	45	2	+	—	+	Cetirizine (20), chlorpheniramine (12), betamethasone (1.0)	Markedly improved
6	F	23	18	+	—	—	Ebastine (10), mequitazine (6), loratadine (10), betamethasone (0.25)	Markedly improved
7	F	60	24	—	—	+	Ebastine (20)	Markedly improved
8	M	30	1.5	—	+	—	Olopatadine (20), ebastine (10), hydroxyzine (75)	Markedly improved
9	F	29	6	+	—	+	Ebastine (10)	Improved
10	M	63	7	+	—	+	Ebastine (20), betamethasone (0.5)	Improved
11	M	4	42	ND ^b	—	—	Oxatomide (5)	Improved
12	F	23	5	ND ^b	—	+	Olopatadine (20), mequitazine (6), homochlorcyclizine (40)	Improved
13	M	35	2	—	—	—	Loratadine (20), betamethasone (1.0)	Slightly improved
14	F	37	120	+	—	—	Ebastine (10), betamethasone (0.5)	Slightly improved
15	F	34	14	—	+	+	Olopatadine (20)	Slightly improved
16	F	29	36	—	—	+	Fexofenadine (180), betamethasone (0.5)	No change
17	M	55	192	+	+	+	Ebastine (10)	No change
18	F	61	132	—	—	+	Homochlorcyclizine (30), hydroxyzine (50)	No change
19	M	69	42	ND ^b	—	+	Olopatadine (20), betamethasone (0.5)	No change
20	F	47	240	—	—	+	Cetirizine (10)	No change
21	F	38	72	+	—	—	Ebastine (10)	No change
22	M	72	80	—	+	—	Loratadine (10), ebastine (10)	No change
23	F	24	21	ND ^b	+	—	Ebastine (10), azelastine (1)	Worse
24	M	49	72	—	—	+	Olopatadine (20), betamethasone (0.25)	Worse
25	F	47	132	—	—	—	Ebastine (10), betamethasone (0.5)	Worse

^a autologous serum skin test^b not done

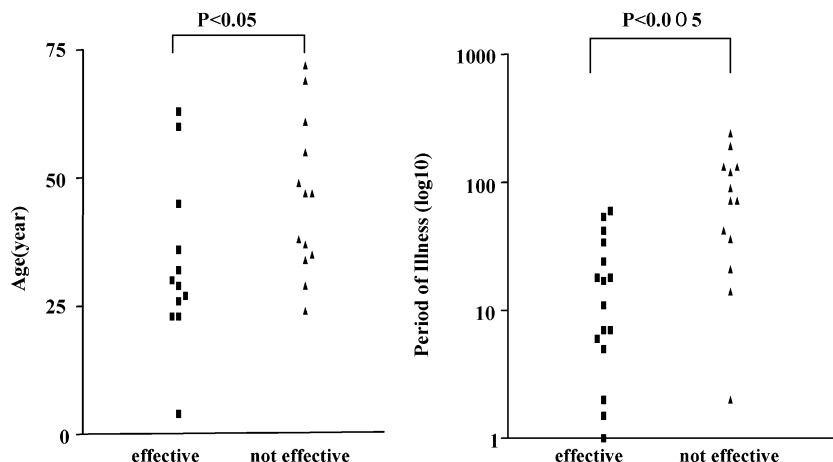
Table 2 The analysis of clinical characteristics versus the effectiveness of montelukast in patients with chronic urticaria

Clinical features	Montelukast		
	Effective	Not effective	Total
Autologous serum skin test ($P=0.66$)			
Positive	4	3	7
Negative	6	8	14
Total	10	11	21
Intolerance against NSAIDs ($P=1.00$)			
Yes	3	4	7
No	9	9	18
Total	12	13	25
Complication with mechanical urticaria ($P=0.69$)			
Yes	5	7	12
No	7	6	13
Total	12	13	25

skin tests [6]. However, the applications of these treatments are limited, because of the high potential of side effects and/or the high expenditure involved in providing them. Increasing the doses of histamine H₁-receptor antagonists, addition of a histamine H₂-receptor antagonist, or addition of other immunomodulative drugs, such as 4,4-diaminodiphenylsulfone (DDS) may be

effective for a certain population of the patients [15]. However, clinical evaluations of such treatments are controversial. For instance, Bleehe et al. [2] reported the effectiveness of cimetidine, a histamine H₂-receptor antagonist through a randomized double-blind study, whereas Simons et al. [3] reported that cimetidine was ineffective.

Fig. 1 The relation of montelukast effectiveness to the age and the period of illness of the patients. The age and the period of illness of the patients who responded well to montelukast were younger and shorter than those of the patients who did not



Leukotrienes are synthesized by the arachidonic acid metabolic pathway in inflammation, including allergy. Amongst leukotrienes, leukotriene (LT) B₄, LTC₄, and LTD₄ have particularly potent effects. LTB₄ is involved in the migration of granulocytes into tissues. LTC₄ evokes a wheal-and-flare reaction, when intradermally injected [13]. LTC₄, LTD₄ and LTE₄, collectively known as cysteinyl-leukotrienes, act on two types of receptors: a cysteinyl leukotriene 1 (CysLT1) receptor and CysLT2 receptor. Montelukast competes with cysteinyl-leukotrienes for binding to CysLT1 receptors.

In patients with aspirin intolerance, leukotriene synthesis may be enhanced by aspirin, through halting of the prostaglandin synthesis pathway by the inhibition of cyclooxygenase. The leukotrienes produced may then induce vascular permeability and smooth muscle contraction [14]. Thus, LT receptor antagonists are of potential use in overcoming the condition of aspirin intolerance. In type 1 hypersensitivity, as large amounts of LTs are synthesized and released from mast cells, this suggests that LT receptor antagonists may be effective for urticaria, as well as of use in overcoming the condition of aspirin intolerance.

It remains unclear why montelukast was more effective for patients who were younger in age and for those who had a shorter history of urticaria. Nevertheless, this study suggests that montelukast, or possibly other CysLT1 receptor antagonists, may prove of value for such patients, when treatments with histamine H₁-receptor antagonists are ineffective. CysLT1 receptor antagonists are reportedly less effective than low doses of inhaled corticosteroids for the treatment of bronchial asthma. Therefore, they are evaluated as potentially useful add-on therapy for corticosteroids in asthma treatment according to the Global Initiative for Asthma (GINA) [8]. However, our results suggested that CysLT1 receptor antagonists may be even more effective than low doses of corticosteroids for chronic urticaria treatment when administered with histamine H₁-receptor antagonists, because four patients were able to stop their use of corticosteroids by taking montelukast. Further studies with patients, more clearly categorized in terms of their

age and duration of their illness, with adequate controls should elucidate the usefulness of montelukast for urticaria.

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