

Efficacy of leukotriene receptor antagonist in chronic urticaria. A double-blind, placebo-controlled comparison of treatment with montelukast and cetirizine in patients with chronic urticaria with intolerance to food additive and/or acetylsalicylic acid

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Summary

Background The cause and pathogenesis of chronic urticaria are still poorly understood. IgE-independent reactions, are common in adult patients with chronic urticaria, who have daily spontaneous occurrence of weals. H₁-receptor antagonists (antihistamines) are the major class of therapeutic agents used in the management of urticaria and angioedema. Nevertheless, chronic urticaria is often difficult to treat and may not be controlled by antihistamines alone. It has been postulated that mediators other than histamine, such as kinins, prostaglandin and leukotrienes, may be responsible for some of the symptoms in urticaria which are not controlled by antihistamines. In this study, which was randomized double-blind, placebo-controlled, we compare the clinical efficacy and safety of montelukast (MT) 10 mg given once a day and cetirizine (CET) 10 mg given once a day with placebo (PLA), in the treatment of patients with chronic urticaria who have positive challenge to acetylsalicylic acid (ASA) and/or food additives.

Patients and methods A group of 51 patients, ranging in age from 15 to 71 years, with chronic urticaria and positive challenge to food additives and/or ASA, participated in this study for a period of 4 weeks, starting from a 3-day run-in. The assessment of the efficacy was based on scores of daily urticaria symptoms.

Results MT significantly increased the percentage of symptom-free days for hive and itch. Analysis of frequency distribution of urticaria scores for each symptom gave similar results (MT vs. CET and MT vs. PLA, $P < 0.001$). The interference with sleep due to their skin condition was also lower in the group treated with MT ($P < 0.001$). In addition, the median number of days without the rescue medication was significantly higher in the MT group (24 days) than both the CET and the PLA groups (18 days, $P < 0.001$, and 20 days, $P < 0.001$, respectively). Finally, a low incidence of adverse events was observed in this study.

Conclusion The results of this comparative study demonstrate that montelukast orally administered once a day is very effective for the treatment of cutaneous symptoms in patients with chronic urticaria due to food additives and/or ASA.

Keywords: ASA, chronic urticaria, food additives, double-blind, placebo-controlled challenge, leukotriene receptor antagonist, placebo.

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Introduction

In chronic continuous urticaria, characterized by daily spontaneous occurrence of hives for a duration of more than 6 weeks, non-allergic hypersensitivity reactions to food additives have been repeatedly reported [1–6]. The prevalence of acetylsalicylic acid (ASA) intolerance in patients with chronic urticaria ranges from 20% to 50% [4,7–9]. Patients who cannot tolerate ASA may also react to tartrazine, benzoate and other substances used as food preservatives or additives. Clinical manifestations of intolerance to these agents may appear 15 min to 20 h after ingestion, whereas the onset of urticaria may be delayed for up to 20 h [10].

The rational therapy of urticaria consists of the identification and avoidance of the causative agents. Nevertheless, these measures often fail to control the disease so that symptomatic treatment may be necessary [4,11,12]. H₁-receptor antagonists (antihistamines) are the major class of therapeutic agents used in the management of urticaria and angioedema [11,13]. Low-sedating antihistamines have become popular in the treatment of urticaria and angioedema because of the lack of both sedative and anticholinergic side-effects [10]. Cetirizine (CET) is one of most frequently used therapies and its recommended dose is 10 mg/day [10]. There are no restrictions on the ability to take this drug with other medications [14]. In double-blind, placebo-controlled studies CET has been found to be statistically superior to placebo in the treatment of rhinitis and chronic urticaria and angioedema [15]. Nevertheless, chronic urticaria is often difficult to treat and may not be controlled by antihistamines alone.

It has been postulated that mediators other than histamine, such as kinins, prostaglandin and leukotrienes, may be responsible for some of the symptoms in urticaria which are not controlled by antihistamines [16].

Leukotrienes, released from dermal mast cells, have been identified as an important contributory factor in the clinical manifestations of chronic urticaria. Sulphidopeptide leukotrienes enhance venular permeability and constrict intestinal and bronchial smooth muscle [17–19]. An important role for these molecules in asthma, based on their bronchospastic activities, has been postulated [19]. Anti-leukotrienes have demonstrated effectiveness in blocking some of the adverse effects of leukotrienes in asthmatic subjects [20].

Montelukast, a potent and selective leukotriene receptor antagonist (LTRA) has been shown to attenuate the effects of sulphidopeptide leukotrienes in bronchial asthma [20]. However, little is known regarding what effect, if any, leukotriene antagonists have on control of chronic urticaria [21–24]. Since leukotrienes are continuously produced from

plasma-membrane arachidonate of inflammatory cells via the lipoxygenase pathway, we hypothesized that montelukast might be beneficial in the management of chronic urticaria to food preservatives or additives, because of the possibility of blocking the receptors of sulphidopeptide leukotrienes.

In this study, which was randomized double-blind placebo-controlled, we compare the clinical efficacy and safety of montelukast (MT) 10 mg given once a day and CET 10 mg given once a day with placebo (PLA), in the treatment of patients with chronic urticaria who have positive challenge to food additives and/or ASA.

Methods

Patients

A total of 51 patients were enrolled at the Policlinico G.B. Rossi, Verona, Italy. Their age ranged from 15 to 71 years. Patients were recruited on the basis of a clinical history of chronic urticaria and the presence of positive challenge to food additives and/or ASA. Pregnant or lactating women and patients taking any drugs for any concomitant pathology were excluded. The protocol was approved by the local ethics committee of the hospital and patients gave informed written consent to participate in the study.

Experimental protocol

A randomized, double-blind, placebo-controlled, parallel-group study design was used. Seventeen patients of each group received the following treatments: MT 10 mg given once a day or CET 10 mg given once a day or placebo (PLA). The treatments prepared by the hospital pharmacy were not distinguishable from each other. The patients were selected by file from the Department of Clinical and Experimental Medicine of Verona, Section of Internal Medicine. All patients have an intolerance to food additives and/or ASA (see 'Challenge to food additives and ASA'). The period of treatment started after a 3-day run-in. Patients were treated for 4 weeks. Each patient was subject to five different visits. At each visit urticaria symptoms (hives, itch and angioedema) were assessed by patients through a questionnaire, and the patients received a daily record diary for urticaria symptoms. Only the patients with a total symptom score > 3 (sum of the values of symptoms considered) during the run-in period were enrolled (see below 'Assessment of symptoms'). After 14 days a follow-up visit was planned for all patients.

Assessment of symptoms

Patients were instructed to record their symptoms daily on a

Table 1. Doses used for double-blind, placebo-controlled challenges

Substances under investigation	First dose (mg)	Second dose (mg)	Third dose (mg)	Lowest dose (mg)	Higher dose (mg)
Tartrazine (E102)	10	10	20	10	40
Erythrosine (E127)	50	50	100	50	200
Sodium benzoate (E211)	50	50	100	50	200
P-hydroxybenzoate (E215)	50	50	100	50	200
Sodium metabisulfite (E223)	5	5	10	5	20
Monosodium glutamate (E620)	100	100	200	100	400
ASA	10	10	20	10	40

diary card. Urticaria symptoms included hives, itch and angioedema and the interference with sleep due to the skin condition. The hives were scored as follows: 0, no hives; 1, one to six hives; 2, seven to 12 hives; and 3, > 12 hives. The itch was scored as follows: 0, no itch; 1, mild itch; 2, moderate itch; and 3, severe itch. The angioedema was scored as follows: 0, no angioedema; 1, angioedema located in one part of the body; 2, angioedema located in two parts of the body; 3, angioedema located in three parts of the body or diffuse.

The final value of urticaria symptoms for each patient is given by the sum of the scores of the three symptoms considered.

Similarly the patients reported the extent of interference with sleep due to their skin condition on a scale of 0–3: 0, none; 1, mild; 2, moderate; and 3, severe.

Rescue medication was CET 10 mg (cetirizine, Zirtec®). No other medication was permitted during the trial.

Challenge to food additives and ASA

All patients enrolled in this study have an intolerance to food additives and/or ASA. In order to identify the main eliciting agents, all patients were exposed to food additives and acetylsalicylic acid (ASA) by double-blind, placebo-controlled challenges (DBPC). For the DBPC we used the following additives: tartrazine (E102), erythrosine (E127), sodium benzoate (E211), p-hydroxybenzoate (E215), sodium metabisulfite (E223), monosodium glutamate (E620), and finally ASA. The food additive, ASA and placebo were in gelatin capsule (LoFarma, Milan, Italy) [25]. Only one DBPC per day was performed. Each substance under investigation was challenged with at least a 1-week interval.

None of the patients presented urticaria symptoms at the time of testing. Antihistamines had been interrupted 3 days before the challenges. An informed consent was obtained from all the subjects. Challenges were administered using a

double-blind placebo-controlled procedure during the morning hours. Before each DBPC, patients received a sham-challenge with placebo (talc). When no urticaria symptoms were noted after placebo, 1 h later DBPC was performed using the substance under investigation. Substances and placebo were given in a randomized sequence. Three placebo capsules and three doses of substance under investigation were given at the dosages reported in Table 1. Each dose was given after 1 h, if no symptoms had developed with the previous administration. Only the appearance of unequivocal worsening of urticaria (defined as pruritic and erythematous areas raised over normal skin) and/or the appearance of angioedema (defined as swelling of the skin and/or external mucosa) were considered as a positive response.

The results of DBPC and the doses that induced urticaria and angioedema are reported in Table 2.

Statistical analysis

The primary assessment of the efficacy of these drugs was based on the analysis of the percentages of symptom-free days during the 4 weeks of treatment. Moreover, a median score was obtained for each patient for each symptom. The treatments were compared with the Kruskal–Wallis test. A separate comparison of MT with placebo and with CET was carried out with the Wilcoxon rank-sum test. All statistical tests were two-tailed and used a 5% level of significance.

Results

All patients completed the study. The characteristics of the patients are shown in Table 2. In Table 2 we also report the results of DBPCs, previously performed, the substance(s) under investigation that were positive, and the doses that induced urticaria symptoms.

Table 2. Patients' characteristics

	Montelukast (<i>n</i> = 17)	Cetirizine (<i>n</i> = 17)	Placebo (<i>n</i> = 17)
Male to female ratio	5/12	7/10	10/7
Mean age (years)	34.5	40.1	36.2
Age range (years)	15–65	21–65	21–71
Mean duration of urticaria (months)	15.1	15.5	17.3
Duration urticaria range (months)	7–36	2–36	6–38
Food additive and/or ASA	Yes	Yes	Yes
Adverse events	4	5	7
Lack of efficacy	0	8	13
<i>Food additive and/or ASA positiveness*</i>			
Patient number			
1	ASA (20 mg), E102 (40 mg)	ASA (20 mg), E215 (100 mg), E620 (200 mg)	E211 (100 mg)
2	ASA (20 mg)	E211 (100 mg), E223 (10 mg)	ASA (20 mg)
3	E127 (100 mg)	ASA (20 mg), E102 (20 mg), E211 (100 mg), E127 (100 mg)	E211(100 mg), E215 219 (100 mg)
4	E223 (10 mg)	ASA (20 mg), E223 (10 mg)	E215 (100 mg)
5	E102 (20 mg)	ASA (20 mg)	ASA (20 mg)
6	ASA (20 mg), E620 (200 mg)	E127 (100 mg), E223 (10 mg), E620 (200 mg)	E127 (100 mg)
7	ASA (20 mg)	E223 (20 mg), E620 (200 mg)	ASA (20 mg)
8	E102 (20 mg), E223 (20 mg)	E215 (100 mg)	E620 (200 mg), E223 (10 mg)
9	ASA (20 mg)	ASA (20 mg), E102 (20 mg), E223 (10 mg)	ASA (20 mg), E102 (20 mg), E211 (100 mg), E127 (100 mg)
10	E102 (20 mg)	ASA (20 mg), E102 (20 mg), E211 (100 mg), E127 (100 mg)	E211 (100 mg)
11	E223 (10 mg)	E127 (100 mg)	ASA (20 mg)
12	ASA (20 mg)	ASA (10 mg), E102 (20 mg), E211 (100 mg)	ASA (20 mg)
13	E215 (100 mg)	E 127 (100 mg)	ASA (20 mg)
14	ASA (20 mg)	E 127 (100 mg)	ASA (20 mg), E215 (100 mg)
15	ASA (20 mg)	ASA (20 mg), E223 (10 mg), E215 (100 mg), E620 (200 mg)	ASA (20 mg)
16	E211 (100 mg)	ASA (20 mg), E223 (10 mg), E215 (100 mg)	E211 (100 mg)
17	ASA (20 mg), E211 (100 mg)	ASA (20 mg), E223 (10 mg)	ASA (20 mg)

*ASA and/or food additive positiveness, within parenthesis the doses that induced urticaria and angioedema during DBPC.

Assessment of efficacy

During the treatment with MT, the median percentage of symptom-free days for hive, itch and agioedema was always significantly higher than the one in the PLA group ($P < 0.001$) (Fig. 1). In addition, MT provided a significantly better protection than CET in terms of the percentage of days without hive, itch and agioedema. The analysis of frequency distribution of urticaria scores for each symptom gave similar results; MT vs. CET and MT vs. PLA, $P < 0.001$ (Fig. 2).

Similarly, the interference with sleep due to the skin condition was lower in the group treated with MT ($P < 0.001$) (Fig. 3).

Finally, the median number of days without the rescue medication was significantly higher in the MT group (24 days) than in either the CET or PLA group (18 days, $P < 0.001$, and 20 days, $P < 0.001$, respectively).

Safety

A low incidence of adverse events was observed in this

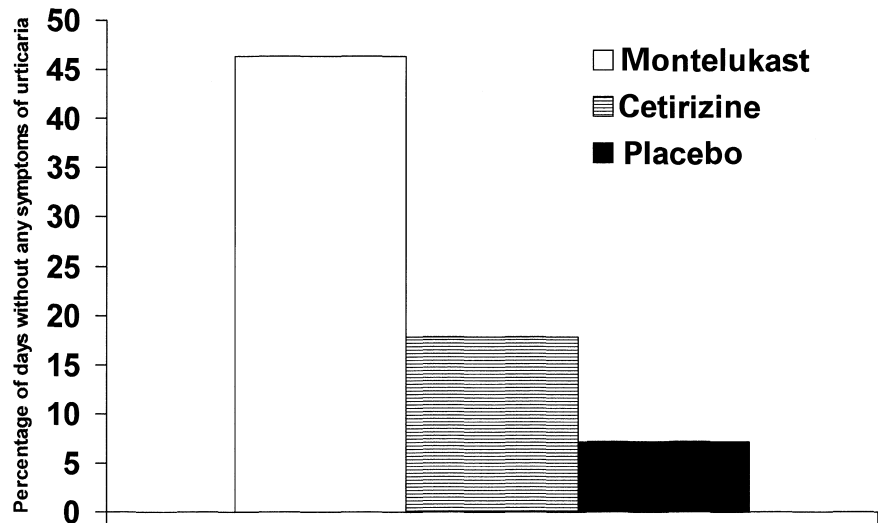


Fig. 1. Median of the percentages of symptom-free days during the 4 weeks of treatment with montelukast 10 mg once daily, or cetirizine 10 mg one daily, or placebo.

study. All adverse events were rated as mild. Drowsiness was reported by four patients in the MT group, by five patients in the CET group and by seven patients in the PLA group.

Discussion

This is the first placebo-controlled study comparing the clinical effects of MT and oral antihistamine in chronic

urticaria. The results of this comparative study demonstrate that MT administered orally once a day is more effective for the treatment of cutaneous symptoms in patients with chronic urticaria with intolerance to ASA and/or food additives than placebo or CET.

Our study shows that MT remarkably reduces hives, itch and angioedema and reduces the interference with sleep due to urticaria. Its clinical efficacy with regard to the symptoms was greater than that of CET. Finally, the safety

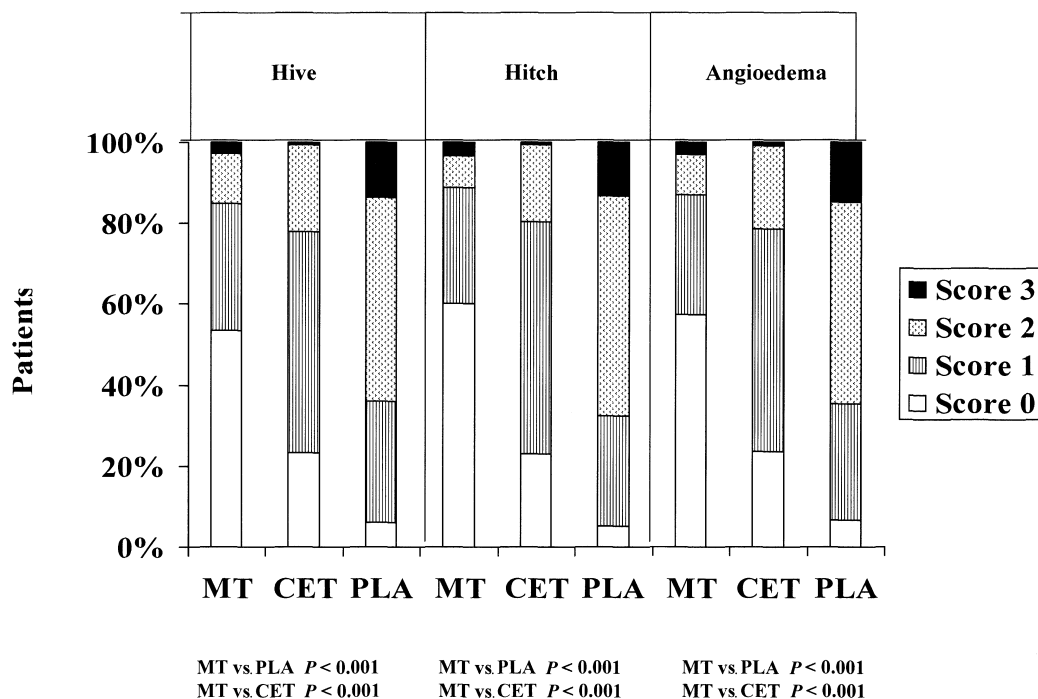


Fig. 2. Frequency distribution of median symptom scores recorded by patients receiving montelukast (MT) 10 mg once daily, cetirizine (CET) 10 mg once daily, or placebo (PLA).

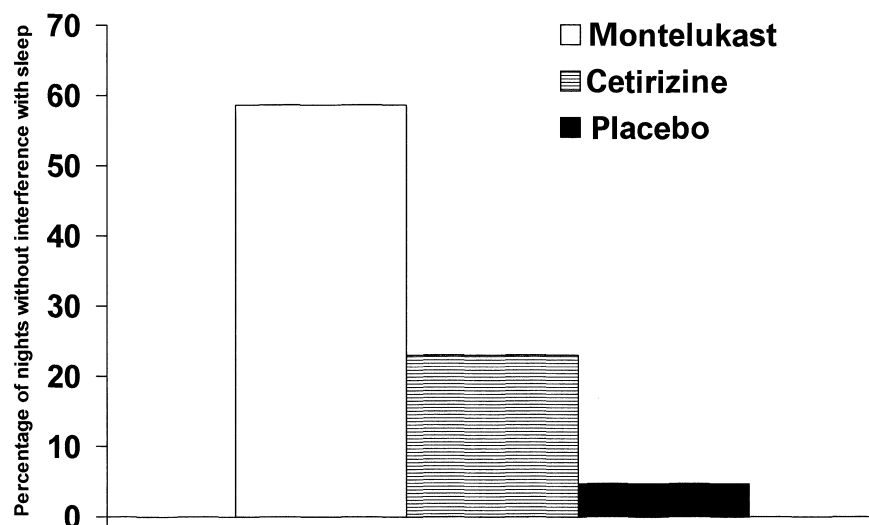


Fig. 3. Median number of nights without interference with sleep due to the skin condition during treatments with montelukast 10 mg once daily, or cetirizine 10 mg once daily, or placebo.

evaluation confirmed that both MT and CET are well tolerated. Little is known regarding what effect, if any, leukotriene antagonists have on the control of chronic urticaria [21–24].

It has been previously shown that MT 10 mg once a day is effective in patients with asthma. In patients with asthma MT provides beneficial effects on the clinical symptoms and lung function that are additive to the bronchodilation obtained with inhaled β_2 -agonists [20]. Moreover, this drug has been shown to protect against the challenge with cold dry air-induced bronchoconstriction [26], ASA [27] and allergen [28]. We have now demonstrated that MT is effective also in patients with chronic urticaria to food additives and/or ASA.

In addition to the consistent control of chronic urticaria symptoms, MT has better effects than CET in decreasing the use of rescue medication. However, it should be noted that most patients included in the placebo group refrained from taking CET. This phenomenon has been previously noted in other clinical studies [29,30].

Leukotrienes comprise a group of bioactive mediators that derive from continuous oxidative metabolism of arachidonic acid of inflammatory cells through the 5'-lipoxygenase pathway. Therefore, their actions appear and last while inflammatory cells are present in the site of reaction. Previously referred to as slow-reacting substance of anaphylaxis [16–19], leukotrienes are believed to play an important role in immediate hypersensitivity reactions, notably in asthma. Leukotrienes have potent local effects on cutaneous vasculature [31]. Some previous studies have demonstrated that LTD₄ causes a weal and erythema response in the human skin [21,31]. In animals and human beings, skin studies with leukotriene antagonists have demonstrated suppression of vascular leakage caused by an

intradermal injection of LTD₄ [32–34]. Other studies have reported a remarkable heterogeneity of LTD₄ cutaneous vascular response in non-atopic and atopic subjects [21,35]. It is believed that leukotrienes may participate in the pathogenesis of urticaria and of other cutaneous diseases [36–38]. The activation of bioactive mediators in addition to histamine released from cutaneous mast cells is believed to participate in the pathogenesis of urticaria and angioedema observed both in non-atopic and atopic subjects [36]. This observation is supported by the fact that H₁ antagonist often, but not invariably, reduces the symptoms of urticaria [10,16]. This is particularly important because a significant number of patients with chronic urticaria have continued disease activity despite maximally tolerated antihistamines and have sometimes required systemic corticosteroid therapy [10]. This study suggests that H₁ antagonist may not be sufficient as a monotherapy in chronic urticaria to food additives and/or ASA.

The results of this study support the possible role of leukotrienes in the pathogenesis of chronic urticaria with intolerance to food additives and ASA. The mechanisms of additive intolerance remain largely unknown. ASA intolerance suggests a mechanism dependent on cyclooxygenase inhibition, with increased leukotriene production through the 5'-lipoxygenase pathway [39]. On the other hand, the possibility that cyclooxygenase blockade plays a pivotal role in the pathogenesis of aspirin-induced asthma has been suggested by the observation that leukotriene antagonists may prevent asthma following ASA challenge [26]. It is likely that the food additive intolerance, which characterizes a subset of patients with chronic urticaria, may have pathogenetic mechanism(s) similar to those hypothesized for ASA intolerance [40].

In conclusion, our positive results with antileukotriene

MT support the possible role of leukotrienes in the pathogenesis of chronic urticaria with intolerance to ASA and food additives and demonstrate that MT may be a useful drug in this condition. A strong advantage of MT is the pharmacokinetic profile: a single oral dose may provide protection for 24 h [41]. Additional studies are required to characterize further optimal conditions for the use of MT in chronic urticaria.

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