

Randomized placebo-controlled trial comparing montelukast and cetirizine for treating perennial allergic rhinitis in children aged 2–6 yr

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Leukotriene receptor antagonists (LTRAs) were recently added to the method of treating allergic rhinitis (AR). However, in children under 6 yr old, there has been no study about its efficacy in treating AR. We aim to compare the clinical efficacy of montelukast, cetirizine and placebo in the treatment of children from 2 to 6 yr old with perennial allergic rhinitis (PAR), to see if there are any significant differences. Sixty children were selected and treated with montelukast, or cetirizine, or placebo once daily. The efficacy of the three agents was compared with the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) and Total Symptom Score (TSS) by diary. In addition, we also examined serum IgE, serum eosinophil cationic protein (ECP), blood eosinophil counts, nasal airway resistance (NAR) and eosinophil percentage in nasal smears. The results revealed that both montelukast and cetirizine were significantly efficacious compared with placebo in NAR, eosinophil percentage in nasal smears, PRQLQ, TSS and all symptom items except nasal itching, throat itching and tearing. For nasal itching, only cetirizine was significantly efficacious. On the other hand, for night sleep quality, montelukast was significantly superior to cetirizine.

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Allergic rhinitis (AR) is one of the most common allergic diseases and affects 5–50% of the world population (1). Histamine is the best-known mediator, shown to cause symptoms of AR (2). Non-sedating antihistamines have become the standard first-line therapy in treating AR (3). Among them cetirizine, a metabolite of hydroxyzine, is most often used in Taiwan. Intranasal corticosteroid, like antihistamine, is the cornerstone therapy for AR (4). However most parents in Taiwan do not like it and therefore the compliance is not good. Cysteinyl leukotrienes (CysLTs) are found in nasal airways of patients with AR (5, 6). Nasal challenge with exogenous CysLTs causes nasal symptoms (7, 8). CysLTs are important in the pathogenesis of AR (2, 9). These findings suggest that CysLTs receptor

blockade may reduce the symptoms of AR (10). Nonetheless its efficacy is still controversial. Although some studies have shown that leukotriene antagonists are efficacious in the treatment of AR (11–13), there are other studies showing that leukotriene antagonists are not efficacious (14–16). Recently montelukast, a CysLT receptor antagonist, has been approved by the United States Food and Drug Administration for treating AR (17). In contrast to cetirizine and intranasal corticosteroid, the compliance of montelukast is much better among young children because of its good taste.

The clinical experience of treating AR with leukotriene modifiers is limited. In children aged below 6 yr old, no study has ever been published. In this study, we aim to evaluate the clinical

efficacy of montelukast in children aged 2–6 yr old.

Materials and methods

Subjects

Of 102 patients screened, 60 patients aged from 2 to 6 yr old were selected. Patients were recruited based on a documented clinical history of perennial allergic rhinitis (PAR) of at least half a year, a positive prick-test for house dust-mite and a positive mite-specific IgE. Patients were excluded if they had taken the following drugs: corticosteroids or sodium cromoglycate within the past 4 wk, or H1-antagonist and/or decongestant within the past 7 days. The informed consent of all participating subjects was obtained. The study had also received approval by Chung Shan Medical University Hospital Institutional Review Board.

Study design

A randomized, double-blind, placebo-controlled, parallel-group study design was used. Patients were divided into three groups, 20 for each group, and received the following treatments: (i) Cetirizine (UCB FARCHIM S.A., Brussels, Belgium) 5 mg p.o. daily at bedtime, (ii) Montelukast (Merck & Co, Inc., Whitehouse Station, NJ, USA) 4 mg p.o. daily at bedtime, (iii) Placebo (glucose) 5 mg p.o. daily at bedtime. The patients were treated for 12 wk and returned to the clinic every 4 wk. At each visit, the subjects' preceding activity diaries were reviewed, a physical examination, a nasal airway resistance (NAR) test and a nasal smear were conducted. Also, at the baseline visit and the last visit, the serum total IgE level, serum eosinophil cationic protein (ECP) level and total peripheral blood eosinophil count were evaluated, and guardians were requested to complete Pediatric Rhinoconjunctivitis Quality of Life Questionnaires (PRQLQ).

Diary

A diary was given to each subject since 7 days before the start of the treatment. Guardians were instructed to record the subject's daily symptoms. Symptoms included four nasal symptoms (nasal itching, sneezing, rhinorrhea and nasal congestion) and four non-nasal symptoms (throat itching, conjunctival itching, conjunctival hyperemia and eye tearing). Symptoms were scored as follows: 0, none, not noticeable; 1, mild, noticeable but not bothersome; 2, moder-

ate, noticeable and bothersome some of the time; 3, severe, bothersome most of the time and/or very bothersome some of the time. The Total Symptom Score (TSS) was the mean of eight symptoms, ranged from 0 to 3. The baseline TSS was calculated as the mean of the daily during the baseline study period of 7 days. Subsequently TSS was based on the scores for the previous 28 days at 4, 8, and 12 wk after treatment. Besides this, we also incorporated the item of night sleep quality in the diary, in which symptoms were scored as follows: 0, slept well and did not wake up; 1, did not sleep too well or woke up once; 2, slept poorly or woke up two to three times; 3, slept very poorly or woke up more than three times.

PRQLQ

The PRQLQ features 23 items corresponding to five separate survey domains (nose symptoms, eye symptoms, practical problems, other symptoms, and activities) (18). Questionnaire respondents provided their response according to a seven-point scale.

Nasal airway resistance

The NAR was assessed using a Micro Medical MicroRint airways resistance meter, which used the interrupter method (19). This method requires minimal subject cooperation. It is therefore useful for measuring NAR in very young children.

Nasal smear

The underside of the patient's inferior turbinate was rubbed with a cotton swab, and the collected cells were smeared onto a glass slide. The slides were stained with Leu stain and examined with a light microscope. Counting a minimum of 100 leukocytes and expressed the eosinophil count as a percentage of the total number of leukocytes.

Safety and tolerability

Safety and tolerability for the treatment groups were assessed at each visit by adverse event reporting and by the observation of any changes in vital signs.

Statistical analysis

A standard PC with SPSS 11.0 software was used. All collected data were expressed as a mean $\pm$ s.d. One-way analysis of variance and

Tukey method were used to compare the demographics and baseline characteristic data between the three groups. $p < 0.05$ was regarded as significant.

Results

Of 102 patients screened, 60 patients met the inclusion criteria and all of these completed the whole study. The baseline characteristics are shown in Table 1. There were no clinically meaningful differences among the three groups.

Changes from baseline were shown in Table 2. For TSS, cetirizine was significantly superior to montelukast at week 12 (Fig. 1). For PRQLQ, both cetirizine and montelukast significantly reduced the values after 12 wk of treatment. For serum IgE, ECP, and blood eosinophil counts, both cetirizine and montelukast did not significantly reduce the values. For NAR, both cetirizine and montelukast significantly reduced the values at week 8 and week 12. For eosinophil percentage in nasal smear, both cetirizine and montelukast significantly reduced the percentage.

Changes from baseline of individual symptom items were shown in Table 3. For nasal itching, cetirizine was significantly superior to montelukast at week 12 (Fig. 2). For night sleep quality, montelukast was significantly superior to cetirizine at week 8 and week 12 (Fig. 3). No serious adverse events were observed. Only mild medication-induced sedation was noted in two of the patients treated with cetirizine.

Discussion

In one of our previous studies, published in 2002, we compared the efficacy of cetirizine, oxatamide, ketotifen and placebo for children aged

Table 1. Baseline characteristics

	Cetirizine (n = 20)	Montelukast (n = 20)	Placebo (n = 20)
Male/female ratio	12/8	11/9	9/11
Age (yr)	4.53 ± 0.91	4.49 ± 1.09	4.36 ± 0.87
Height (cm)	109.08 ± 8.88	105.05 ± 9.21	103.45 ± 8.13
Body Weight (kg)	18.43 ± 2.74	17.69 ± 3.38	17.34 ± 3.15
TSS	1.38 ± 0.41	1.27 ± 0.44	1.29 ± 0.39
Night sleep quality	1.22 ± 0.41	1.31 ± 0.36	1.26 ± 0.35
PRQLQ	76.15 ± 16.25	67.40 ± 17.11	71.20 ± 17.40
Total IgE titer (IU/ml)	451.55 ± 432.50	341.70 ± 326.22	395.50 ± 355.08
ECP level (ng/l)	21.45 ± 14.62	20.90 ± 20.54	20.85 ± 19.10
Blood eosinophil counts (per μ l)	466.50 ± 372.63	431.00 ± 292.03	437.60 ± 289.02
NAR (Kpa/l/s)	1.86 ± 0.14	1.93 ± 0.22	1.91 ± 0.21
Eosinophil % in nasal smears	64.80 ± 29.89	53.20 ± 27.71	56.15 ± 26.39

Table 2. Changes from baseline

Change from baseline (wk)	Cetirizine (mean ± s.d.)	Montelukast (mean ± s.d.)	Placebo (mean ± s.d.)
TSS			
0-4	-0.22 ± 0.19 ($p = 0.047$)	-0.19 ± 0.20	-0.09 ± 0.09
0-8	-0.40 ± 0.24 ($p < 0.001$)	-0.36 ± 0.20 ($p < 0.001$)	-0.11 ± 0.10
0-12	-0.60 ± 0.25 ($p < 0.001$)	-0.43 ± 0.23 ($p < 0.001$)	-0.11 ± 0.12
Night sleeping quality			
0-4	-0.16 ± 0.09 ($p < 0.001$)	-0.20 ± 0.07 ($p < 0.001$)	-0.04 ± 0.04
0-8	-0.26 ± 0.13 ($p < 0.001$)	-0.34 ± 0.12 ($p < 0.001$)	-0.05 ± 0.03
0-12	-0.32 ± 0.15 ($p < 0.001$)	-0.45 ± 0.17 ($p < 0.001$)	-0.08 ± 0.05
PRQLQ, 0-12	-31.15 ± 23.36 ($p < 0.001$)	-19.15 ± 20.71 ($p = 0.028$)	-3.85 ± 5.56
Total IgE, 0-12	-71.50 ± 196.24	-37.15 ± 123.59	10.60 ± 41.93
ECP, 0-12	-2.35 ± 11.03	-1.75 ± 24.40	0.15 ± 3.61
Blood eosinophil counts			
0-12	-60.65 ± 384.19	-67.50 ± 291.04	2.95 ± 51.97
NAR, 0-4	-0.10 ± 0.06	-0.10 ± 0.07	-0.05 ± 0.10
0-8	-0.15 ± 0.14 ($p = 0.026$)	-0.16 ± 0.13 ($p = 0.007$)	-0.05 ± 0.04
0-12	-0.16 ± 0.11 ($p = 0.013$)	-0.17 ± 0.15 ($p = 0.007$)	-0.05 ± 0.05
Eosinophil % in nasal smears			
0-4	-7.35 ± 14.53	-5.55 ± 14.63	-2.05 ± 11.01
0-8	-16.90 ± 27.46 ($p = 0.028$)	-14.65 ± 22.28	0.75 ± 9.37
0-12	-20.05 ± 22.06 ($p = 0.004$)	-15.15 ± 16.49 ($p = 0.045$)	-2.15 ± 9.16

p-value is for the comparison with placebo.

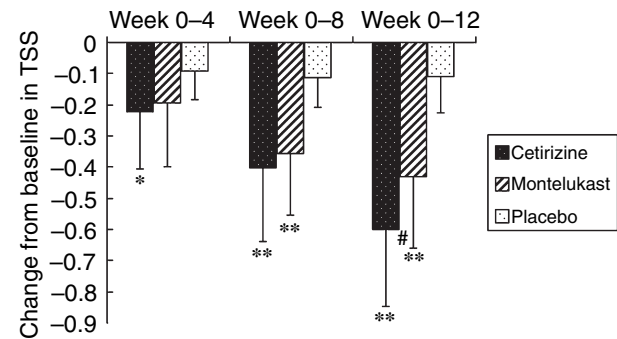


Fig. 1. Change from baseline in TSS. Significant change compared with placebo (* $p < 0.05$, ** $p < 0.001$), cetirizine compared with montelukast (# $p < 0.05$).

6-12 yr old with PAR. Cetirizine was shown to be more efficacious in treating PAR (20). Comparing the result to our present study in children aged 2-6 yr old, improvements via cetirizine treatment were almost the same in these two different age groups.

In 2004, we compared the therapies of montelukast and cetirizine in children aged 6-12 yr old with PAR. Both were shown to be signifi-

Table 3. Changes from baseline of individual symptom items

Change from baseline	Cetirizine (mean $\pm$ s.d.)	Montelukast (mean $\pm$ s.d.)	Placebo (mean $\pm$ s.d.)
Nasal itching (wk)			
0–4	-0.46 ± 0.40 ($p = 0.047$)	-0.20 ± 0.49	-0.17 ± 0.17
0–8	-0.71 ± 0.80 ($p = 0.033$)	-0.40 ± 0.50	-0.25 ± 0.28
0–12	-1.07 ± 0.74 ($p < 0.001$)	-0.48 ± 0.60	-0.20 ± 0.17
Sneezing (wk)			
0–4	-0.19 ± 0.48	-0.10 ± 0.50	-0.12 ± 0.33
0–8	-0.34 ± 0.50	-0.41 ± 0.48	-0.09 ± 0.31
0–12	-0.72 ± 0.57 ($p = 0.001$)	-0.56 ± 0.59 ($p = 0.013$)	-0.08 ± 0.36
Rhinorrhea (wk)			
0–4	-0.15 ± 0.69	-0.10 ± 0.52	-0.09 ± 0.34
0–8	-0.29 ± 0.42	-0.35 ± 0.45	-0.16 ± 0.27
0–12	-0.56 ± 0.40 ($p = 0.005$)	-0.49 ± 0.58 ($p = 0.022$)	-0.10 ± 0.35
Nasal congestion (wk)			
0–4	-0.29 ± 0.40	-0.27 ± 0.40	-0.02 ± 0.27
0–8	-0.40 ± 0.44	-0.49 ± 0.42 ($p = 0.017$)	-0.14 ± 0.27
0–12	-0.63 ± 0.40 ($p = 0.001$)	-0.57 ± 0.43 ($p = 0.003$)	-0.17 ± 0.24
Throat itching (wk)			
0–4	-0.12 ± 0.35	-0.23 ± 0.39	-0.09 ± 0.09
0–8	-0.28 ± 0.28	-0.25 ± 0.50	-0.07 ± 0.25
0–12	-0.26 ± 0.45	-0.20 ± 0.47	-0.05 ± 0.19
Conjunctiva itching (wk)			
0–4	-0.28 ± 0.46	-0.39 ± 0.36 ($p = 0.009$)	-0.03 ± 0.24
0–8	-0.58 ± 0.54 ($p < 0.001$)	-0.51 ± 0.41 ($p = 0.001$)	-0.02 ± 0.25
0–12	-0.76 ± 0.49 ($p < 0.001$)	-0.47 ± 0.57 ($p = 0.027$)	-0.08 ± 0.29
Conjunctiva hyperemia (wk)			
0–4	-0.18 ± 0.24	-0.19 ± 0.44	-0.10 ± 0.28
0–8	-0.43 ± 0.33 ($p = 0.007$)	-0.29 ± 0.44	-0.08 ± 0.26
0–12	-0.53 ± 0.41 ($p = 0.006$)	-0.45 ± 0.54 ($p = 0.031$)	-0.11 ± 0.26
Tearing (wk)			
0–4	-0.09 ± 0.11	-0.08 ± 0.19	-0.08 ± 0.12
0–8	-0.18 ± 0.17	-0.17 ± 0.17	-0.10 ± 0.15
0–12	-0.26 ± 0.28	-0.22 ± 0.29	-0.10 ± 0.14

p-value is for the comparison with placebo.

cantly efficacious in lowering the values and scores of nasal peak expiratory flow rate (nPEFR), eosinophil percentage in nasal smears, PRQLQ, TSS and all symptom items except throat itching and tearing (21). Comparing this result to our present study in children aged 2–6 yr old, most items were almost the same except three areas: (i) montelukast significantly reduced the blood eosinophil count in children aged 6–12 yr old ($p = 0.023$), but in children aged 2–6 yr old montelukast was unable to show a statistical significance ($p = 0.707$), (ii) montelukast significantly reduced the score of nasal

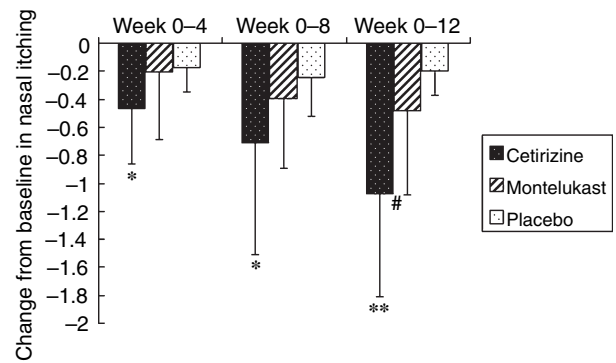


Fig. 2. Change from baseline in nasal itching. Significant change compared with placebo (* $p < 0.05$, ** $p < 0.001$), cetirizine compared with montelukast (# $p < 0.05$).

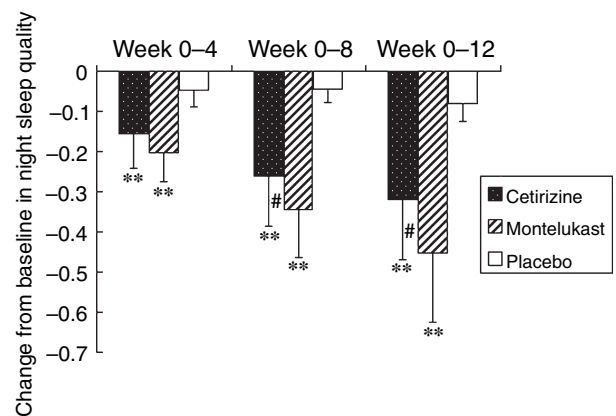


Fig. 3. Change from baseline in night sleep quality. Significant change compared with placebo (* $p < 0.05$, ** $p < 0.001$), cetirizine compared with montelukast (# $p < 0.05$).

itching in children aged 6–12 yr old ($p < 0.01$), but in children aged 2–6 yr old montelukast was unable to show a statistical significance ($p = 0.262$) and (iii) in children aged 2–6 yr old, montelukast significantly reduced the score ($p < 0.001$) and was also significantly superior to cetirizine for night sleep quality which was not included in children aged 6–12 yr old.

Concerning blood eosinophil count, recently three studies showed that montelukast significantly reduced the count in patients with AR aged 15–85 yr old (11–13). However in our present study, montelukast was unable to significantly reduce the count in children aged 2–6 yr old, although in our last study montelukast did significantly reduce the count in children aged 6–12 yr old. Whether the very young age of the subject will affect this result needs further investigation. On the other hand, one study showed that cetirizine was likely to significantly drop the level of circulating eosinophil (22). However our

studies showed that cetirizine did not significantly reduce the count.

Regarding nasal itching, montelukast was usually not supposed to have much efficacy for this. Some studies had shown that nasal challenge with exogenous leukotrienes had very limited effects on nasal itching (7, 8). Also, very young children may be unable to communicate that they have nasal itching. These factors may account for the discrepancy between the results of our two studies.

As for night sleep quality, the recent AR and its impact on asthma classification include sleep disturbance as a criterion that differentiates mild AR from moderate-to-severe disease (23). In the three studies mentioned above, montelukast was shown to significantly improve nighttime symptoms in patients aged 15–85 yr old (11–13). Our present study also showed this for children aged 2–6 yr old.

Eosinophil percentage in nasal smears have been widely used to assist diagnosing the AR (24, 25). There are inconsistent opinions regarding whether or not cetirizine and montelukast could decrease the eosinophil influx into nasal mucosa (15, 26–28). However in our studies, both montelukast and cetirizine did significantly decrease the percentage. Concerning nasal congestion, cetirizine was significantly better than montelukast in our last study. However, in our present study montelukast was slightly better than cetirizine at week 8.

Recently one review article mentioned two viewpoints (29): First, whereas leukotriene receptor antagonists (LTRAs) are predicted, on the basis of their mechanism of action, to improve nasal congestion significantly, clinical studies reveal LTRAs to be no better than antihistamines at improving nasal congestion. Second, LTRAs would not be expected to significantly improve nasal itching, sneezing, and rhinorrhea, based on their putative mechanism. However some studies showed improvement in these symptoms during treatment with LTRAs. Our recent studies are able to extrapolate these viewpoints to very young children aged below 6 yr old.

In conclusion, we believe our study to be the first study comparing the clinical efficacy of montelukast with cetirizine in children aged 2–6 yr old with AR. Our result showed that cetirizine did has better efficacy in treating most of the symptoms of PAR, but montelukast was also significantly efficacious, particularly for night sleep quality. Furthermore, at least 60% of asthmatic patients are likely to experience nasal symptoms and 20–30% of patients with

AR also have asthma (1). Therefore, when taking this into account montelukast may play a supplementary role in treating young children with AR.

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