

Discrepant clinical responses and blood chemokine profiles between two non-steroidal anti-inflammatory medications for children with mild persistent asthma

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In a randomized study, two oral medications, ketotifen and montelukast, were compared for children with mild persistent asthma. Montelukast revealed faster clinical responses than ketotifen, showing improved exhaled nitric oxide, peak expiratory flow, and asthma scores in 1 wk. After 8-wk of medication, both ketotifen and montelukast revealed improved clinical responses. However, 8 wk of ketotifen, but not montelukast, decreased plasma serum thymus and activation-regulated chemokine (317.854 ± 207.906 vs. 181.348 ± 167.109 , $p < 0.05$), macrophage-derived chemokine (355.11 ± 174.30 vs. 169.19 ± 62.42 , $p < 0.05$) levels. In conclusion, different oral non-steroidal anti-inflammatory drugs revealed faster or slower treatment responses due to different mechanisms.

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Asthma is a chronic inflammatory disorder (1). Evidences indicate that Th2 type immunoregulatory cytokines play a central role in the pathogenesis of airway inflammatory in asthma (2, 3), and chemokines are responsible for the trafficking of leukocytes to the inflammatory airways. Thymus and activation-regulated chemokine (TARC) and macrophage-derived chemokine (MDC) are Th2 chemokines involved in recruitment of receptor chemokine CC chemokine receptor (CCR)4-bearing Th2 cells toward allergen-challenged inflammation (4, 5).

Recent studies have demonstrated that CCR4 is preferentially expressed by Th2 cells (4, 5). This suggests that the CCR4-specific ligands such as TARC and MDC may be involved in the pathogenesis of bronchial asthma via recruitment of Th2 cells to inflammatory airways (6, 7). A study by Leung et al. (8) suggested TARC may be a useful inflammatory marker in assessing asthmatic exacerbation in children.

Currently, there has been a consensus protocol for early anti-inflammatory treatment to

childhood asthma, as recommended by the Global Initiative Asthma guideline (9). Montelukast, a specific leukotriene receptor antagonist, has been recommended for use in children with mild-to-moderate asthma (9). Ketotifen is another non-steroidal anti-inflammatory drug, useful in younger children with asthma (10). In this randomized study, we sought to investigate whether the montelukast and ketotifen therapy revealed different clinical responses and blood Th2 mediators as demonstrated by changes of exhaled nitric oxide (eNO), peak expiratory flow (PEF), asthma scores, TARC and MDC.

Methods

Patients and study design

The study was conducted in a double-blind, randomized design. The children recruited for this study fell into the category of mild persistent asthma as defined by the National Asthma

Education and Prevention Program (NAEPP), Expert Panel Report II, Guidelines for the Diagnosis and Management of Asthma, showing: symptoms >1 time a week, PEF > 80%, and PEF variability between 20 and 30% (9). Subjects who had acute febrile respiratory tract infection, or had been receiving corticosteroid, ketotifen or leukotriene receptor antagonist treatment within 4 wk before the study were excluded (11). Hospitalized patients were also excluded from the study. A total of 40 children with mild persistent asthma between the age of 6 and 14 yr were assigned to receive either montelukast or ketotifen in the outpatient clinic of our hospital. Informed consent was obtained from each parent.

The study protocol was approved by the Institution Review Board of Tri-Service General Hospital. Patients who were eligible for the study were randomly assigned to receive either ketotifen or montelukast for 8 wk at a 1:1 ratio using a computer-generated randomization code. To reach a double-blind design, ketotifen and montelukast were ground to powder and prepared in indistinguishable capsules containing 1 mg of ketotifen (Zaditen; Sandoz, Dorval, Canada) or 5 mg of montelukast (Singulair; Merck & Co, Cramlington, UK).

Assessment of treatment response

The asthma scores, modified from a previous study (11, 12), included coughing, wheezing, chest tightness and difficulty sleeping. In this scoring system, a score of 0–3 was assigned to each variable. The final scores range from 0 to 12 with the worst condition at 12. PEF was measured by a peak flow meter (Astech Co., Port Washington, NY, USA), and the eNO levels were measured by using a fast-response chemiluminescence analyzer (NOA 280; Seivers Instrument Inc., Boulder, CO, USA) with the validated, single-breath technique as previously described (11). While ambient NO concentration was >10 p.p.b., the study case was excluded for analysis (11). The plasma concentrations of TARC and MDC were determined by a commercially available ELISA assay systems (R&D system). Assays were performed using the protocols recommended by the manufacturer. Asthma scores, PEF, eNO, TARC and MDC were serially measured at 0, 1 and 8 wk after treatment.

Statistical analysis

Demographic data including age, sex and asthma scores were recorded and analyzed by using the

chi-square test and one-way analysis of variance. Changes in asthma scores, eNO levels, asthma scores (AS) and PEF between both groups before and after treatment were analyzed by using the Wilcoxon signed rank test. Changes in serum TARC and MDC before and after 1 and 8 wk of treatment were also analyzed by using the Wilcoxon signed rank test. Differences between montelukast and ketotifen groups were analyzed by using the Mann–Whitney test. A two-tailed p -value <0.05 was considered significant.

Results

Demographic data of subjects

Forty patients were initially enrolled for this study and 37 completed this study. One asthma patient was excluded due to upper respiratory tract infection. Two other patients were excluded because of ambient NO concentration >10 ppb. There were no significant differences in age, gender, initial eNO, asthma scores, and PEF between the two study groups ($p > 0.05$).

Change in eNO level after treatment

As shown in Fig. 1, eNO levels were reduced significantly after montelukast treatment for 1 wk (26.00 ± 12.37 vs. 16.76 ± 8.82 ; $p < 0.01$). However, 1 wk treatment of ketotifen could not suppress eNO effectively (23.00 ± 14.66 vs. 23.32 ± 14.65 ; $p > 0.05$). eNO levels were reduced significantly after 8 wk treatment not only in the montelukast group (26.00 ± 12.37 vs. 16.65 ± 8.18 ; $p < 0.01$), but also in the ketotifen group (23.00 ± 14.66 vs. 18.16 ± 6.40 ; $p < 0.05$).

Change in PEF after treatment

A significant increase in PEF was found in the montelukast treatment for 1 wk (217.94 ± 107.43 vs. 257.35 ± 124.96 ; $p < 0.01$), and the improvement was also observed at 8 wk (217.94 ± 107.43 vs. 275.59 ± 125.70 ; $p < 0.001$). In contrast, treatment with ketotifen did not increase PEF at 1 wk (216.58 ± 91.80 vs. 231.05 ± 100.27 ; $p > 0.05$), although it significantly increased after the treatment at 8 wk (216.58 ± 91.80 vs. 250.26 ± 97.59 ; $p = 0.001$).

Change in asthma score after treatment

A significant improvement in asthma score was also found in the treatment with montelukast for 1 wk (2.53 ± 1.62 vs. 1.35 ± 0.70 ; $p < 0.05$).

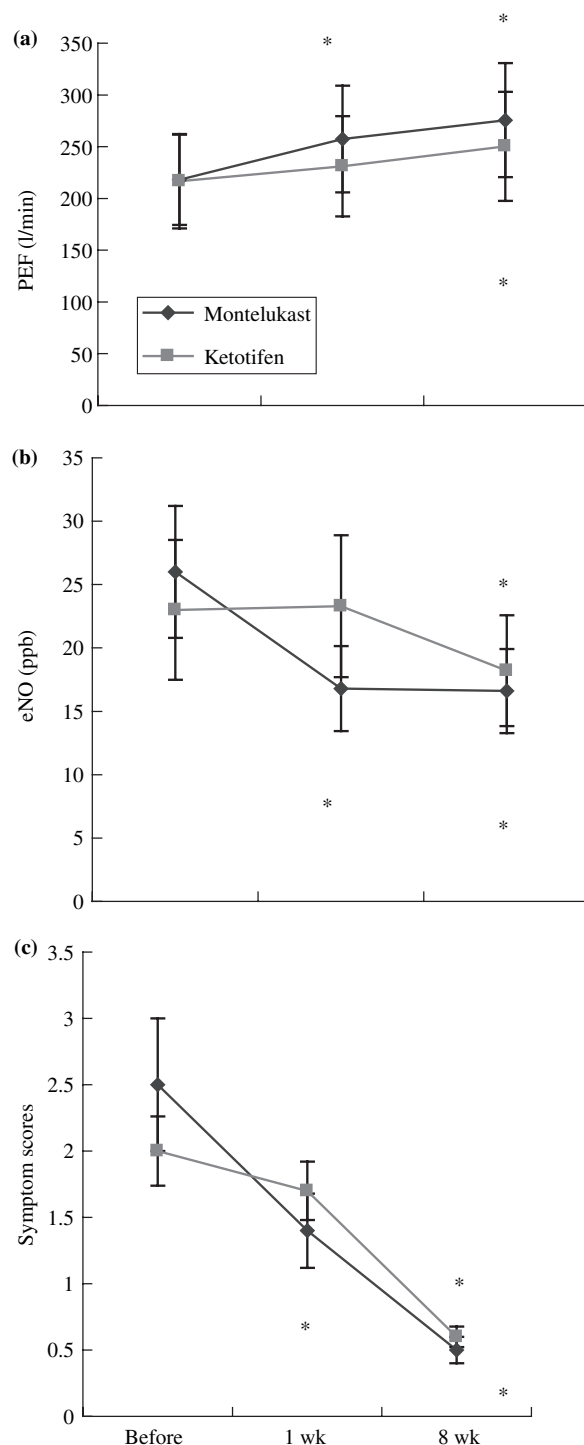


Fig. 1. Change in asthma scores, exhaled nitric oxide (eNO) and peak expiratory flow (PEF) before and after montelukast and ketotifen treatment for 1 and 8 wk (* < 0.05).

This improvement lasted for 8 wk (2.53 ± 1.62 vs. 0.47 ± 0.62 ; $p < 0.05$). Treatment with ketotifen for 1 wk did not decrease AS (2.00 ± 0.75 vs. 1.74 ± 0.65 ; $p > 0.05$), but significantly increased after the treatment for 8 wk (2.00 ± 0.75 vs. 0.58 ± 0.77 ; $p < 0.05$).

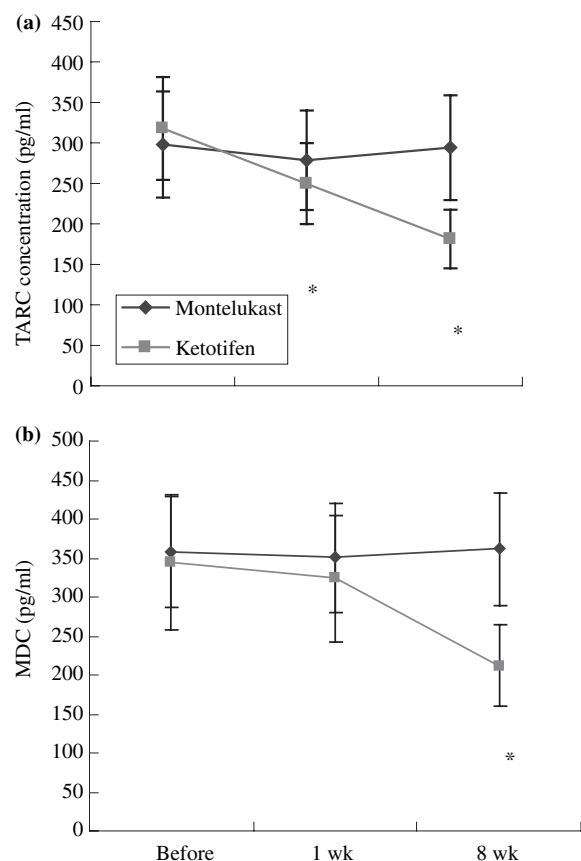


Fig. 2. Change in thymus and activation-regulated chemokine (TARC) and macrophage-derived chemokine (MDC) levels before and after montelukast and ketotifen treatment. Ketotifen treatment for 8 wk significantly decreased plasma TARC (a) and MDC (b). However, montelukast treatment did not decrease plasma TARC (a,b; * < 0.05).

Change in plasma TARC and MDC after treatment

Plasma TARC levels were significantly reduced after ketotifen treatment for 1 wk (317.85 ± 207.91 vs. 249.69 ± 171.22 ; $p < 0.015$) and that for 8 wk (317.85 ± 207.91 vs. 181.35 ± 167.11 ; $p < 0.009$) (Fig. 2a). In contrast, TARC levels were not reduced in patients with the montelukast treatment for 1 and 8 wk (298.69 ± 131.60 vs. 278.57 ± 116.88 ; $p > 0.05$; 298.69 ± 131.60 vs. 294.18 ± 173.04 ; $p > 0.05$) (Fig. 2a). Plasma MDC levels did not significantly decrease in the ketotifen treatment group until 8 wk of treatment (345.43 ± 111.01 vs. 212.17 ± 72.27 ; $p < 0.05$). There was no significant change in MDC levels during the whole course of montelukast treatment (Fig. 2b).

Discussion

Oral non-steroidal maintenance therapy for children with asthma include theophylline, leukotriene receptor antagonists and ketotifen (2, 13).

The routine use of theophylline as maintenance therapy is limited due to its side effects. Ketotifen, a slow-onset anti-histamine, has been effectively used to prevent the development of asthma from children who were at risk (10, 14). Ketotifen reduced the IL-5-induced increase in the eosinophil, neutrophil and epithelial cell populations and pulmonary inflammation, especially the desquamation of bronchial epithelial cells (15). Our data showed that ketotifen treatment for 8 wk did improve AS, PEF, eNO and plasma TARC. Plasma TARC concentrations increased in children with intermittent asthma when compared with normal subjects (8, 16). Recent studies showed that the bronchial epithelium in asthmatic patients expressed TARC and MDC, which are implicated in the recruitment of Th2 cells toward inflammatory airways (6). The prophylactic effect of ketotifen has been demonstrated in children with mild-to-moderate asthma between 5 and 15 yr after 14 wk of therapy (14). In the present study ketotifen treatment decreased TARC and MDC levels, suggesting that the prophylactic effect may result from inhibition of TARC expression and Th2 cell migration to airways.

The fact that montelukast treatment quickly reduced eNO levels and improved AS and PEF suggests that it did have anti-inflammatory effects of airways. Montelukast did not decrease TARC and MDC levels, suggesting a different mechanism. Montelukast, a leukotriene antagonist, may compete with the late-asthma mediator and cause a faster symptom release. Ketotifen, an anti-histamine with mast stabilization effect, may slowly modulate the Th2-related chemokine production for later improvement of asthma. Further studies are needed to determine whether a combination of early montelukast with late ketotifen administration can provide a better regimen for childhood asthma.

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