Montelukast therapy in asthmatic children with and without food allergy

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ABBREVIATIONS

FA: Food allergy

ICSs: Inhaled corticosteroids

LTRAs: Leukotriene receptor antagonists

FeNO: Fractional Exhaled Nitric Oxide

PGD2: Prostaglandin D2

CystLT: Cysteinyl Leukotriene

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Authors' Contributions

CS had primary responsibility for protocol development and analytic framework of the study, outcome assessment, and manuscript preparation. UMS and EAY participated in the development of the protocol and analytic framework of the study, had primary responsibility for review of the files, patient screening, enrollment, and data entry, and prepared the manuscript with CS. SF and SH had responsibility the statistical analysis. OS, OK and AC contributed to preparation and revision of the manuscript. All authors discussed the results and contributed to the final manuscript.

Keywords: Asthma, asthma control test, cysteinyl leukotrienes, exhaled breath condensate, FeNO, food allergy, methacholine, montelukast, prostaglandin D2.

To the editor

Asthma is a chronic airway disease with different endotypes. Recently, endotype-specific treatment modalities have been gradually increasing by the light of the advances of the asthma pathogenesis. As a component of the atopic march, children with food allergy (FA) are at increased risk for asthma.[1] Since leukotrienes are implicated in the pathogenesis of asthma and probably in food allergies, we hypothesized that asthmatic children with concomitant FA may respond favorably to anti-leukotriene treatment. To test this hypothesis, we conducted a randomized, double-blind, placebo-controlled, cross-over study in asthmatic children aged 6-18 years with and without FA. The protocol was approved by the research ethics committee. Parents and children provided written informed consent. The study is registered to Clinical trials NCT01618929. All participants have physician-diagnosed asthma based on spirometry or provocholine® tests. Food allergy was diagnosed by the current guideline.[2] Children with severe asthma, systemic or chronic lung disease, emergency room/hospital admission or systemic steroid usage within 3 months for asthma exacerbation were excluded. Of 149 patients who were invited, 113 included but 87 completed the study protocol between 2013 and 2015 (FigureS1). The baseline characteristics of the whole study population and per-protocol group were similar. The baseline characteristics of asthmatic children with and without FA were similar. Recruited children entered a run-in period of 2 to 6 weeks when all the drugs were discontinued except inhaled salbutamol as needed. Total IgE levels, eosinophil counts, spirometry tests (ZAN100 spirometry system, nSpire Health, Longmont, Colorado, USA), methacholine challenge test, childhood Asthma Control Tests (cACTs), Asthma Control Tests (ACTs), Fractional Exhaled Nitric Oxide (FeNO) measurements (portable analyzer (NIOX-MINO; Aerocrine, Stockholm, Sweden) and exhaled breath condensates (EBC) analysis were performed at the beginning of the run-in period and repeated 4 more times according to the protocol (Figure1). Cysteinyl leukotrienes (CysLT) and Prostaglandin D2 (PGD2) (Cayman Chemical Company, USA) and lipoxin A4 (Cusabio Biotech Co, China) levels were measured in the EBC by ELISA. The lipoxin levels did not include in the statistical analysis since they showed extreme variations. The primary outcome of the study was improvement in FEV1. A placebo-subtracted montelukast effect of 2% in FEV1% and a standard deviation of 5% [3, 4] with 80% power analysis and an alpha value of 0.05; the calculated sample size with a drop-out rate of 15% nearly 60 patients was initially planned to be included in each arm of the study. Twenty-six patients showed violations of the study protocol mainly of the timelines for drug and washout. All analyses were done both in the intention to treat (all patients) and per-protocol populations.

The baseline PGD2 and CysLT levels, eosinophil counts and total IgE levels of the asthma alone (AA) and food allergy and asthma (FAA) groups were significantly different from each other. (TableS1). The comparison of FEV1% did not show a statistically significant difference for within group analyses both in AA and FAA in cross-over montelukast and placebo phases (Table1 and 2). Comparison of montelukast and placebo effects in AA versus FAA groups showed a significant difference in favour of FAA group. However, this difference stemmed from the difference between AA and FAA groups at the beginning of the study and cannot be attributed to montelukast. PGD2, CysLT and FeNO measurements showed significant differences between AA and FAA groups. We compared for each phase the effect of montelukast/placebo for the two asthma groups. Significant differences were found; however, the presence of differences with respect to PGD2 and CysLT measurements at the beginning of the study prevents us to make a conclusion about the effect of montelukast between different groups. Both ACT scores and methacholine measurements did not show any difference with respect to either treatment and placebo groups in FAA and AA groups. We could not show a significant effect of montelukast compared to placebo both within groups and between the groups' comparisons. Initial measurements of PGD2 and CysLTs were significantly higher in the FAA group compared to AA group suggesting that the presence of FA in asthmatic children may represent a different phenotype which has distinct underlying pathophysiological mechanisms. There may be several reasons why the presence of FA had no effect on the montelukast in asthmatic children. All patients had mild asthma and normal FEV1%. Thus, the change in FEV1% conferred by the treatment may have been too small to detect a difference between montelukast and placebo. In two separate studies in mild asthmatics, Weiss et al.[5] failed to show the effect of montelukast compared to placebo with respect to days with worsening asthma. Montuschi et al.[6] showed a marginal effect of montelukast on FeNO levels when asthmatic children were not exposed to the responsible allergen. Knorr et al., showed montelukast has only modest effect on FEV1% but reduced acute exacerbations and improved the life-quality.[7] Spahn et al. showed improvements in lung function in asthmatic children by forced oscillometry and plethysmography without any change in FEV1% and FeNO levels.[8] More sensitive techniques may be required to detect a montelukast effect in children with mild asthma.

An important finding of our study was higher PGD2 and CystLTE4 levels in FAA compared to AA group. The role of leukotrienes in FA is not clear. PGD2 has two important receptors on mast cells called D prostanoid (DP) and CRTH2. Selective CRTH2 agonists was shown to induce asthma exacerbations and atopic dermatitis in mouse models.[9]Nakamura et al. showed exacerbation of food antigen induced mast cell hyperplasia at PGD2 deficiency.[10] A recent study showed a new egg-white protein called lipocalin-type PGD synthase which reacts with IgE antibodies in children with egg allergy.[11] According to the study investigated the effect of montelukast during oral immunotherapy, LTRAs may prevent food induced abdominal symptoms by inhibition of eosinophilic inflammation and degranulation of mast cells.[12] Lexmond et al.[13] showed an elevation in LTC4 synthase mRNA expression in eosinophilic esophagitis patients. All of these studies support our findings and suggest a possibly important role for leukotrienes in the disease process of FA. In a recent study synergistic effect of PGD2 with CystLT to stimulate the diverse functions of Th2 cells have been shown[14]. In our study, children with FAA had higher levels of both PGD2 and CystLT.

Our study has some limitations. First, we could not reach the aimed sample size because of the high protocol violations. Secondly, the difference in FEV1% between the groups at baseline made it difficult to evaluate the results. Most important strength of the study was the study design.

In conclusion, despite we could not find any difference in montelukast effect between FAA and AA groups, there is a significant difference between baseline PGD2 and CystLT levels between FAA and AA groups. This may be a different endotype of childhood asthma. Additionally, with a higher patient number and more severe disease phenotype this study could be repeated to see whether montelukast has any additional effect on asthmatic children with food allergy compared to only asthmatics.

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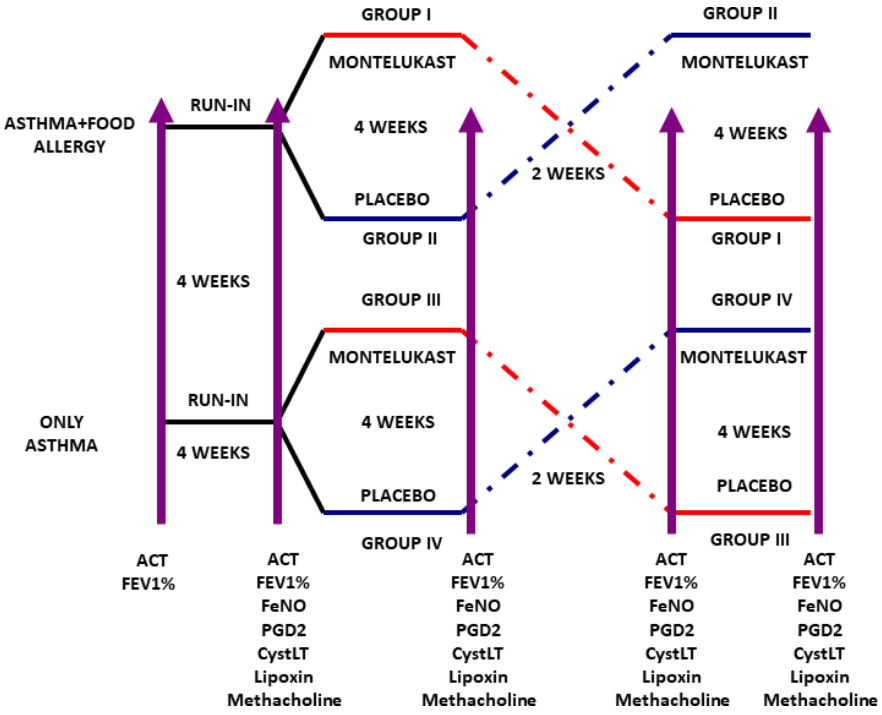
Figure 1. The study design



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