Original Article

Role of Montelukast on Vitamin D Levels in Asthma and Seasonal Allergic Rhinitis in Eastern India

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Abstract

Background: Allergic rhinitis and asthma are both chronic heterogeneous disorders, with an overlapping epidemiology of prevalence, health care and social costs in quality of life. Both are inflammatory disorders with a similar pathophysiology and vitamin D has a significant role in the pathogenesis of the disease.

Aims and Objective: The objective of this study was to evaluate the role of serum vitamin D in patients with symptomatic allergic rhinitis and active asthma during the allergy season and observe the effect of montelukast 10 mg daily as treatment.

Materials and methods: This study included 130 asthmatic and seasonal allergic rhinitis patients following a single-blind, placebo run-in period of 3 days–5 days, patients were randomized to oral montelukast 10 mg (n = 68) or placebo (n = 62) daily during the 2-week, double-blind, active-treatment period. The serum vitamin D was also evaluated in both the groups.

Results: The serum vitamin D levels were found to be higher in patients taking monteleukast compared to placebo after 2 weeks ($p < 0.001$). Montelukast reduced the Total Nasal symptoms score which includes Daytime nasal symptoms and Nighttime symptoms compared to placebo after 2 weeks ($p < 0.001$). **Conclusion:** Montelukast provides significant relief from symptoms of seasonal allergic rhinitis, while also conferring a benefit for asthma, in patients with both allergic rhinitis and asthma. Further, it has a beneficial role in improving vitamin D levels.

Keywords: Vitamin D, Asthma, Allergic Rhinitis, Montelukast, Leukotreine receptor antagonist

Introduction

Allergic rhinitis and asthma are both chronic heterogeneous disorders, with an overlapping epidemiology of prevalence, health care and social costs in quality of life. Allergic rhinitis (AR) is the most common type of chronic rhinitis, affecting 10-20% of the population, and evidence suggests that

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the prevalence of the disorder is increasing. Severe AR has been associated with significant impairments in quality of life, sleep and work performance.[1] On the other hand, Asthma is one of the most common chronic diseases worldwide and has been increasing in prevalence over the last few decades.[2, 3] Its exact cause remains unknown and likely has its origins in complex interactions among multiple genetic and environmental factors. Asthma and AR may both be clinical manifestations of a systemic inflammatory process within the respiratory tract. The link between these two airway disorders has been called the "integrated airway hypothesis."[4] Fewer epidemiological studies have shown an association between rhinitis and asthma where about 19-38% of patients with allergic rhinitis have coexistent asthma.[4, 5] The indications where data from clinical studies in patients with rhinitis and coexistent asthma have shown an improved control of nasal symptoms also frequently results in improved asthma symptom scores.[5]

Vitamin D has been shown to play a role in immunomodulation by interacting with T lymphocytes, dendritic cells, mast cells, monocytes and macrophages and some epidemiological studies have reported decreased vitamin D level in the blood of Asthma and allergic rhinitis patients.[6,7] Montelukast is a leukotreine receptor antagonist used for the maintenance treatment of asthma and seasonal allergic rhinitis. It acts by inhibiting physiological actions of LTC4, LTD4 and LTE4 at the Cystiene Leukotriene levels (Cys LT1 receptor).[8]

The role of montelukast on vitamin D in asthma and seasonal allergic rhinitis is still controversial. In India, vitamin D insufficiency/deficiency has been emerging in recent years. The treatment of montelukast on vitamin D deficiency could prevent asthma and seasonal AR upto some extent. None of the study has shown the effect of montelukast on vitamin D levels in AR as well as in asthma in eastern India. Thus the aim of our study was to study the role of serum vitamin D levels on asthma and allergic rhinitis subjects in Eastern India and observe if Montelukast treatment can lead to altered vitamin D levels in allergic rhinitis and asthma patients and develop its role in the diagnosis of disease.

Materials and Methods

The preliminary study included 130 asthmatic and seasonal allergic rhinitis patients following a single-blind, placebo run-in period of 3 days–5 days over a period of 6 months attending the Respiratory Medicine and ENT outpatient departments of ICARE Institute of Medical Sciences, Haldia, West Bengal which is a tertiary care hospital in the eastern part of India. Patients were randomized to oral montelukast 10 mg OD/ day (n = 70) or placebo (n = 60) daily during the 2-week, double-blind, active-treatment period. Informed consent was obtained from allergic rhinitis and bronchial asthma patients for the study. The inclusion criteria having a history of asthma or allergic rhinitis with eosinophilia on blood smear present. The study was approved by the Institutional Human Ethics Committee according to Helsinki guidelines. The exclusion criteria for the study were type 1 diabetes mellitus, protein energy malnutrition (PEM), taking drugs which interferes with vitamin-D metabolism like anti epileptic drugs or received vitamin D either oral / injection in last 6 months and subjects having any chronic liver, kidney or lung or neurological diseases. Total Nasal Symptoms score (TNSS) [out of 15] which includes daytime and nighttime symptoms were assessed between montelukast and placebo. Daily Rhinitis Symptoms score were also evaluated. 5 ml venous blood samples were obtained from the AR and/ or asthma patients in placebo and after 2 weeks followup taking oral montelukast. Non-fasting serum samples of asthma and AR subjects were analyzed for routine biochemical parameters immediately after collection while aliquots of the samples were also stored at -20^0 C for the assay of 25-hydroxyvitamin D. Serum vitamin D was measured as 25-hydroxyvitamin D is considered as the indicator of vitamin D. 25-hydroxyvitamin D was estimated by using commercially available ELISA kits (Calbiotech, USA). Anti-25-hydroxyvitamin D antibody (capture antibody) coated wells were incubated with standards (25-hydroxyvitamin D), samples and vitamin D-biotin conjugate at room temperature for 90 minutes. The binding of vitamin D-biotin conjugate to the wells by the capture antibody decreased by competition with 25-hydroxyvitamin D present in the standards or samples. Following a wash step, bound vitamin D-biotin was detected with streptavidin-horse radish

peroxidase (SA-HRP) using tetramethylbenzidine (TMB) as the substrate. For drawing the calibration curve from the measured absorbance readings, a 4- parametric logistic (4-PL) curve was used.

Statistical analysis of different biochemical parameters was performed by Students' *t*-test. All variables were expressed as mean ± SD (standard deviation). Means obtained from two normally distributed sample groups were compared by Student's unpaired two-tailed "*t*"-test and for nonparametric Mann-Whitney *U* "*t*" test. All statistical analyses were performed by using Graph Pad prism software (version 5, 2007, San Diego, California, USA). Statistical analysis for sex distributions was evaluated by chi-square test by using statistical software STATA (version 8, Copyright 1984–2003, Stata Corporation, Texas, USA).

Results

The demographic profile as well as biochemical profile of the bronchial asthma and/or allergic rhinitis subjects is depicted in Table 1. There was no significant difference in age, sex distribution or BMI in either of the two groups between placebo and oral montelukast subjects (Table 1). Moreover, TNSS were lower in subjects taking oral montelukast as compared to placebo and were statistically significant (2.92 ± 1.20 versus 9.78 ± 2.39; $P < 0.001$) (Figure 1). However, serum 25 OH vitamin D levels were higher in oral montelukast taking cases as compared to placebo and were statistically significant (22.10 ± 4.84 versus 16.34 ± 3.29 ng/ml; $P < 0.001$) (Figure 2).

Table 1 Demographic and biochemical profile of subjects.

Demographic and Biochemical profile of AR and/or Asthma patients		
	Placebo (n=62)	**Oral Montelukast (n=68)**
Age (in years)	31.75 ± 15.71	32.42 ± 23.05
Sex (M/F)	31/29	38/32
BMI (kg/m^2)	24.20 ± 1.39	25.69 ± 1.98
TNSS	9.78 ± 2.39	2.92± 1.20 *
FPG (mg/dl)	87.62 ± 11.29	89.18 ± 10.90
Total Chol. (mg/dl)	175.40 ± 17.38	189.20 ± 23.41

TNSS, Total Nasal Symptoms Score; FPG, fasting plasma glucose. Age, BMI, and serum levels of biochemical parameters were expressed as the means ± SD. Statistically significant, * p < 0.001 vs Placebo.

TNSS were determined as described in methods for placebo and AR and/or asthma subjects. Values expressed as the means ± SD. Statistically significant, * p < 0.0001, vs Bronchial asthma.

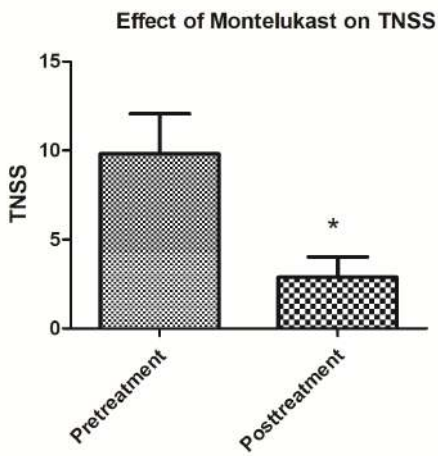

Fig. 1 TNSS score in placebo and oral montelukast intake in AR and asthma subjects.

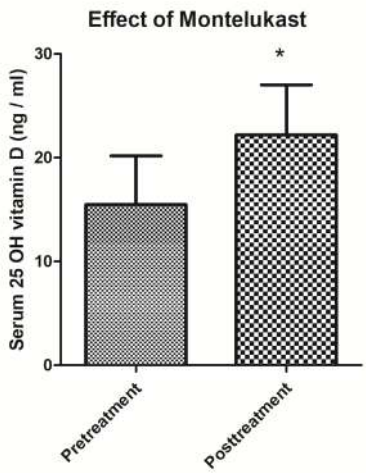

Fig. 2 Serum levels of vitamin D in placebo and oral montelukast intake in AR and asthma subjects.

Serum levels of 25 OH vitamin D were determined as described in methods for placebo and AR and/or asthma subjects. Values expressed as the means ± SD. Statistically significant, * $p < 0.0001$, vs Bronchial asthma.

Discussion

The deficiency of vitamin D tends to increase in all the age groups which is promising to be a global health problem worldwide due to sedentary lifestyle, poor dietary intake, limited exposure to sunshine, sunscreen use, increased time spent indoors and intrinsic factors such as the skin melanin content and increased cutaneous destruction of vitamin D_3. Vitamin D plays an important role in the regulation of immune system, lymphocyte function, T cell antigen receptor signalling or activation, cytokine production and acts as an immuno-modulator in allergic rhinitis as well as in asthma.[9, 10,11]

On the otherhand, Montelukast sodium (Singulair®, Merck) is a selective and orally-active leukotriene-receptor antagonist (LTRA) that inhibits the cysteinyl leukotriene 1 (CysLT1) receptor. Montelukast mediates the bronchoconstrictor and proinflammatory actions of the CysLTs and acts as an effective and well-tolerated preventative treatment for asthma and allergic rhinitis in adults and children. In addition, montelukast has anti-inflammatory, mainly anti-eosinophil, properties.[8, 12]

Several studies have concluded randomly the lower levels of vitamin D which is associated with an increased incidence of asthma and other allergic symptoms.[13] Some studies have also established vitamin D deficiency as the strongest predictor of asthma or serum IgE levels and familial history of vitamin D deficiency also being a predictor of asthma.[14] One of the study by Li *et al.* in 435 asthma patients older than 18 years reported lower concentration of 25(OH) vitamin D which is similar to our study in the pretreatment group or placebo.[15]

Moreover, another study from Shaaban and Hashem also estimated serum vitamin D level in 75 adults with asthma and 75 healthy controls older than 18 years and reported that vitamin D level is lowered in the subjects which is in verification with our study in the pretreatment group.[16] This may be due to reduced serum vitamin D levels may be related with increased expression of tumor necrosis factor-α which is mediated by enhanced expression of this proinflammatory cytokine through which lower vitamin D levels could exert a proinflammatory effect in asthma.[17] Another study performed by Moradzadeh et al. in which the vitamin D level was analysed in 5,329 normal Iranian individuals showed that 27.2% suffered mild vitamin D deficiency, 42.8% moderate and 5.1% had a severe deficiency.[18] A study by Arshi et al reported the prevalence of severe vitamin D deficiency was significantly greater in patients with allergic rhinitis than the normal population (30% vs. 5.1%; p= 0.03) demonstrating that there is an association between serum vitamin D levels and allergic rhinitis subjects.[19] Our previous study also observed the severity of serum vitamin D levels which upon supplementation of vitamin D led to increase in serum vitamin D levels in asthmatic and allergic rhinitis subjects.[20]

A study from Philip G et al., observed a marked improvement in nasal and ocular symptoms after the two weeks treatment with montelukast 10 mg and reported that this significant reduction in the symptoms of allergic rhinitis has a positive impact on asthma-related problems in association with both the disorders.[21] Further, montelukast plays a pivotal role and has a beneficial impact on cough and associated disorders.[22] Our study also established this which is similar to this study and further it also indicates that the serum vitamin D level is improved in the posttreatment subjects taking montelukast. Moreover, TNSS is also lowered in patients taking montelukast suggestive of its beneficial role in asthmatic and allergic rhinitis subjects. This may be due to the fact that montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity due to which bronchoconstriction is inhibited with decreased airway and blood eosinophils leading to improved control over asthma and allergic rhinitis.[23] Moreover, leukotrienes are inflammatory mediators which mediiates the slow-reacting substance of anaphylaxis produced by a number of cell types including eosinophils, mast cells, basophils, macrophages and monocytes. The cleavage of arachidonic acid in cell membranes which exert biological effects by binding and activating specific receptors results in the synthesis of these

mediators. These series of events occurring leads to contraction of the human airway smooth muscle, chemotaxis and increased vascular permeability.[24] These effects have led to their significant role in the pathogenesis of asthma and allergic rhinitis.

Our study have revealed that serum vitamin D has been significantly improved as well as TNSS have also enhanced in patients taking montelukast in AR and asthma subjects but nevertheless few limitations were there in our study which needs to be mentioned. The sample size of the study was less. Secondly, all of the patients included in this study were adults and no paediatric children were involved. Moreover, few of the patients were taking some other drugs such as antihistamines, topical corticosteroids which might interfere with serum vitamin D levels. Despite these limitations it has been observed that serum vitamin D levels were significantly improved in patients suffering from AR and asthma. However, supplementation of monteukast may be beneficial in the prevention of the pathogenesis of AR and asthma. Moreover, a large longitudinal study needs to be done to conclude the fact. Montelukast has been found to offer defence against severe asthma attacks and AR in adults and also in the improvement of serum vitamin D levels. Further trials focusing on children and adults who experience frequent severe asthma attacks and AR are needed before definitive clinical recommendations can be made.

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