

# Montelukast *versus* Budesonide as a First Line Preventive Therapy in Mild Persistent Asthma in 2 to 18 y

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## Abstract

**Objectives** To compare the efficacy of oral Montelukast and inhaled Budesonide as a first line preventive therapy in mild persistent asthma in age group 2–18 y.

**Methods** This prospective randomized controlled clinical study was conducted for 12 wk. Sixty patients of mild persistent asthma aged 2 to 18 y were randomly allocated to either oral Montelukast ( $n=60$ ) or inhaled Budesonide ( $n=60$ ) group. Outcomes measured were improvement in peak expiratory flow rate (PEFR), forced expiratory volume 1 s/forced vital capacity (FEV1/FVC), day time and night time symptoms and frequency of exacerbations and need to change medications.

**Results** There was significant improvement in PEFR, FEV1/FVC, day time and night time symptoms and frequency of exacerbations in both groups. However, more significant improvement in FEV1/FVC (CI 95 %,  $p=0.029$ ) and day time symptoms (CI 95 %,  $p=0.002$ ) was seen in Budesonide group compared to Montelukast group.

**Conclusions** The present study suggests that oral Montelukast is not inferior to Budesonide in treatment of mild persistent asthma in 2 to 18 y children in terms of control of symptoms and improvement in pulmonary function tests over a 12 wk period. However, there was more significant improvement in day time symptoms, more significant increase in FEV1/FVC ratio and less exacerbation in patients receiving Budesonide compared to those receiving Montelukast. However, side effects due to long term use of steroids such as growth stunting and bone osteopenia should also be considered before recommending. Trial registered at CTRI no. REF/2012/09/004035

**Keywords** Childhood asthma · Montelukast · Budesonide · Mild persistent asthma

## Introduction

Asthma is the most common chronic illness of childhood, affecting approximately 10 % of children. Worldwide, the prevalence of childhood asthma and hospitalizations for it are increasing [1]. Incidence of asthma in India is also increasing [2] and childhood asthma has an impact on the social and emotional aspects of lives of the children and their families. In addition, there may be considerable financial burden on families. Asthma is one of the common reasons for children's absence from school, affecting child's academic performance [3]. It reduces the quality of life for children as it leads to growth retardation, inability to exercise, and nocturnal bouts of wheezing resulting in loss of sleep that may also impair daytime concentration at school [4].

All recent consensus statements on asthma now advocate aggressive treatment of airway inflammation. Current clinical practice guidelines recommend the use of anti-inflammatory controller therapy for the long-term treatment of persistent asthma [5, 6]. Inhaled corticosteroids (ICS) are recommended and are used widely as first-line controller agents, with leukotriene-modifying agents being recommended as alternative or add-on therapies. Inhaled corticosteroids have adverse effects such as growth stunting in children, suppression of the adrenal axis, and bone osteopenia on long term use [7]. Cysteinyl leukotriene plays a key role in mediating inflammatory process in asthma [8]. Antileukotriene agents such as Montelukast act by blocking the effects of the Cysteinyl leukotriene and have proved very effective in controlling symptoms of asthma among adults and in reducing markers of chronic inflammation among adults and children [9–12],

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which may have important glucocorticoids-sparing effects. Theoretically, Anti-leukotriene have the advantage of being administered orally in a single or twice daily dose and importantly, seem to lack the adverse effects on growth, bone mineralization and on the adrenal axis, associated with long-term systemic glucocorticoids therapy.

However, clinical trials among adults determined that Montelukast is similar to Beclomethasone in improving asthma control [13], it is similar to Triamcinolone in reducing bronchial hyperresponsiveness [14], and acts as an alternative to doubling the dose of inhaled budesonide, on the basis of multiple parameters of asthma control [15]; at present adequate studies in children are not available which clearly signify the efficacy of Montelukast as a preventive therapy in persistent asthma. Studies which include age group 2–18 y (pediatric age group including adolescence) have not been done. The purpose of this study is to review the efficacy of anti-leukotriene as monotherapy as compared to inhaled glucocorticoids.

## Material and Methods

After informed written consent from parents this prospective randomized open label controlled clinical study (CTRI no. REF/2012/09/004035) was carried out in 60 pediatric patients aged 2 to 18 y having newly diagnosed as mild persistent asthma that attended OPD or admitted in the wards of department of Pediatrics or Department of Tuberculosis and Respiratory Diseases, Sir Takhtsinhji General Hospital, Bhavnagar, Gujarat over duration of 6 mo (February through July 2012). Institutional review board approval (no. 248/2012) was obtained. Patients with age < 2 y, having history of status asthmaticus in past 4 wk, who had taken long acting beta agonists, steroids, chromolyn sodium, nedocromil sodium or theophylline in past 4 wk or having tuberculosis, pneumonia, foreign body aspiration, congenital heart diseases and congenital anomalies of respiratory tract, *i.e.*, laryngomalacia were excluded from the study.

Child was considered to have asthma if he had three or more episodes of wheezing/fast breathing/coughing in the past year that lasted more than 1 d and affected sleep with

- (1) one of the following: parental history of asthma, a physician diagnosis of atopic dermatitis, evidence of sensitization to aeroallergens or h/o quick resolution/convincing improvement in signs and symptoms with administration of short acting beta agonists or short course of oral corticosteroids; OR
- (2) two of the following: evidence of sensitization to foods,  $\geq 4\%$  peripheral blood eosinophilia, wheezing apart from colds or allergic rhinitis.

Patients were categorized into mild persistent asthma based on revised CDC guidelines mentioned in Nelson textbook of Pediatrics.

On first visit, detailed history (including perinatal history, family history and allergen history) and anthropometry were taken. Baseline investigations [Absolute Eosinophil Count, Peak Expiratory Flow Rate (PEFR) and Forced Expiratory Volume 1 s (FEV1)/Forced Vital Capacity (FVC) for patients > 6 y] were done.

Patients were randomized using computer generated random number sequence into two groups of 30 each (Table 1) and accordingly medications were prescribed.

Group A: Patients were given Montelukast 4 mg tablet (up to 5 y) and 5 mg (> 5 y) as once daily night time dosage for 12 wk.

Group B: Patients were given metered dose inhaler (MDI) Budesonide (with spacer) 100 microgram/puff as 2 puffs twice a day (400 microgram/d) for 12 wk. Dose of Budesonide was same for all age groups.

Parents were instructed about how to use MDI and spacer and also about the dose, frequency and route of administration of medications. Parents were advised to keep diary [100 page notebook in which columns were made including day time symptoms, night time awakening, and difficulty in carrying out day to day activities and use of short acting beta agonists (SABA) or oral steroids] at home. During the course of the study, exacerbations were treated with levosalbutamol nebulisation (SABA) and/or oral prednisolone, depending upon the severity.

**Table 1** Patient characteristics

| Patient characteristics | Group A<br>(n=30) | Group B<br>(n=30) |
|-------------------------|-------------------|-------------------|
| Age (y)*                | 5.70 $\pm$ 0.66   | 5.27 $\pm$ 0.62   |
| 2 to 5 y                | 16                | 18                |
| >5 y                    | 14                | 12                |
| Sex (M/F)               | 23/7              | 19/11             |
| Weight (kg)*            | 15.36 $\pm$ 1.22  | 15.01 $\pm$ 1.11  |
| Allergen history (+/-)  | 21/9              | 19/11             |
| Family history (+/-)    | 12/18             | 7/23              |
| Perinatal history (+/-) | 7/23              | 8/22              |
| AEC $\geq$ 400 (+/-)    | 13/17             | 18/12             |
| PEFR*                   | 207.9 $\pm$ 8.90  | 200.0 $\pm$ 7.49  |
| FEV1/FVC*               | 68.57 $\pm$ 1.43  | 69.00 $\pm$ 1.24  |

AEC Absolute eosinophilic count; SD Standard deviation; PEFR Peak expiratory flow rate; FEV1 Forced expiratory volume 1 s; FVC Forced vital capacity

$p > 0.05$

\*(Mean  $\pm$  SD)

Follow up of the patients were taken after 1<sup>st</sup> wk, 2<sup>nd</sup> wk, 4<sup>th</sup> wk, 6<sup>th</sup> wk, 8<sup>th</sup> wk and 12<sup>th</sup> wk. On each follow up, inquiry was made about occurrence of symptoms in daytime, nocturnal awakening due to symptoms, limitation of day to day activity, exacerbations requiring use of rescue medications (SABA/steroids) or occurrence of side effects, if any. PEFR and FEV<sub>1</sub>/FVC (> 6 y) was measured at each visit. Primary outcome variables were daytime symptoms, nocturnal awakenings, PEFR and FEV<sub>1</sub>/FVC (> 6 y), while exacerbations requiring use of rescue medication and occurrence of side effects were secondary outcome variables. PEFR was done using “mini-Wright peak flow meter and FEV<sub>1</sub>/FVC measured using RMS-Helios spirometer”.

Sample size was calculated using alpha and beta variables with the help of assistant professor of PSM. Statistical analysis was done using Graphpad Prism 6.0 software. Unpaired *t* test for quantitative data and chi-square test for qualitative data was used.

## Results

Sixty patients were enrolled in the study. There were no clinical significant differences in two treatment groups in their baseline characteristics (Fig. 1).

PEFR was measured on enrolment and then at 1, 2, 4, 8, 12 wk (at each visit). Improvement was measured at each visit compared to the previous visit. Increase in PEFR was evident from 1<sup>st</sup> wk of treatment in both the groups (Table 2). Mean increase in PEFR at the end of 12 wk in Montelukast group was  $32.86 \pm 3.04$  L/min (CI 95 %, 20.4 to 60.3,  $p = 0.025$ ) and in Budesonide group was  $40 \pm 2.27$  L/min (CI 95 %, 20.6 to 61.1,  $p = 0.0004$ ); difference was not statistically significant ( $p = 0.07$ ).

FEV<sub>1</sub>/FVC ratio was measured on enrolling and then at each visit at 1, 2, 4, 8, 12 wk. Mean increase in ratio was measured at each visit compared to the baseline. Mean increase in FEV<sub>1</sub>/FVC ratio was  $16.36 \pm 1.35$  % in Montelukast group (CI 95 %, 11.28 to 18.15,  $p < 0.0001$ ) and  $22.69 \pm 1.04$  % in Budesonide group (CI 95 %, 19.13 to 26.21,  $p < 0.0001$ ). Increase in FEV<sub>1</sub>/FVC ratio was clinically evident from 1<sup>st</sup> wk of treatment in both the groups. However, improvement was statistically significant in Budesonide group compared to Montelukast group. (CI 95 %, 5.2 to 10.7,  $p < 0.01$ ) (Fig. 2).

There was significant improvement in day time symptoms in both the groups starting as early as 2<sup>nd</sup> wk of therapy. Mean days with symptoms in Montelukast group in 1<sup>st</sup> wk were  $2 \pm 0.16$  and in 12 wk were  $0.33 \pm 0.08$  (CI 95 %,  $-2.0$  to  $-1.2$ ,  $p < 0.0001$ ). In Budesonide group, mean days with symptoms in 1<sup>st</sup> wk were  $1.7 \pm 0.18$  and in 12 wk were  $0.03 \pm 0.03$  (CI 95 %,  $-2.1$  to  $-1.3$ ,  $p < 0.0001$ ). Improvement in day time

Fig. 1 Flow chart

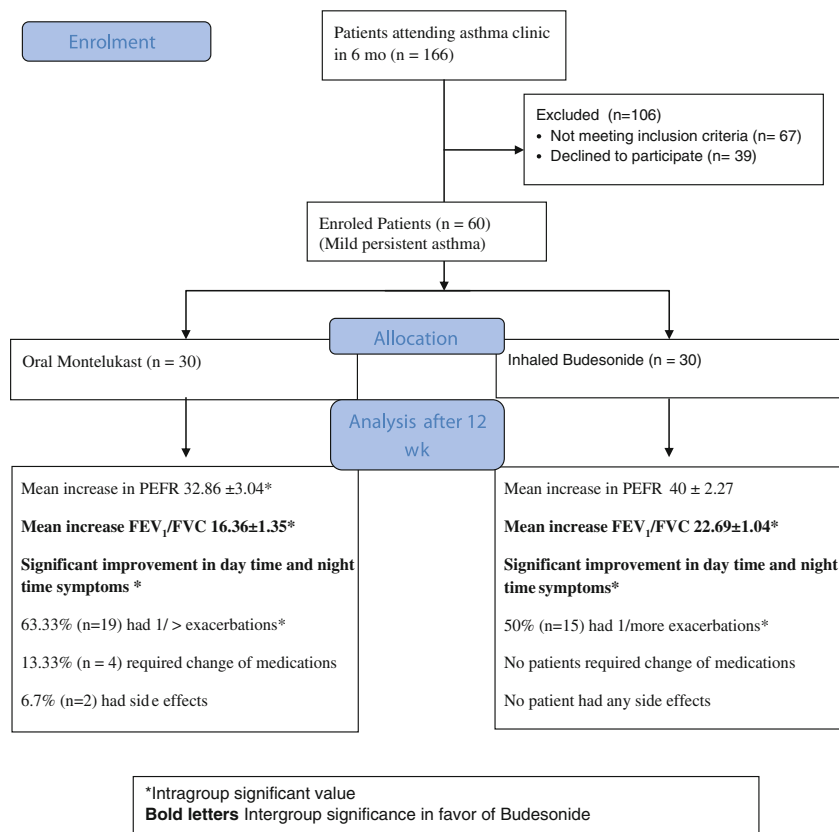


**Table 2** Results

|                                        | Group A (Oral Montelukast) | Group B (Inhaled Budesonide) |
|----------------------------------------|----------------------------|------------------------------|
| Primary variables                      |                            |                              |
| Mean increase in PEFR                  | 32.86±3.04*                | 40±2.27*                     |
| <b>Mean increase FEV1/FVC</b>          | <b>16.36±1.35*</b>         | <b>22.69±1.04*</b>           |
| <b>Mean days/week with symptoms*</b>   |                            |                              |
| At start                               | 2.00±0.16                  | 1.82±0.18                    |
| At end of 12 wk                        | 0.33±0.08                  | 0.03±0.03                    |
| <b>Mean nights/week with symptoms*</b> |                            |                              |
| At start                               | 1.03±0.15                  | 1.00±0.17                    |
| At end of 12 wk                        | ±0.06                      | 0                            |
| Secondary variables                    |                            |                              |
| 1/> exacerbations*                     | 63 %                       | 50 %                         |
| Change of medications                  | 13.33 % (n=4)              | 0                            |
| Side effects                           | 6.07 % (n=2)               | 0                            |

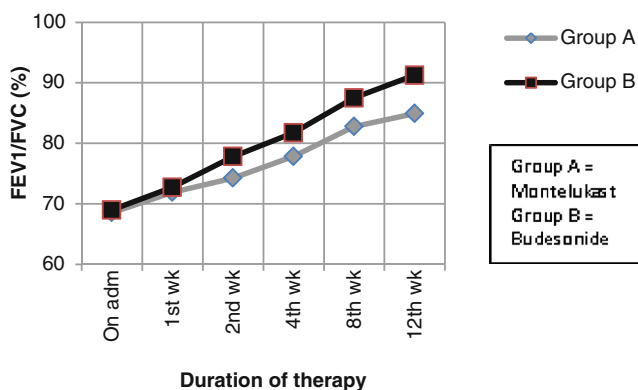
\*Intragroup significant value

**Bold letters** Intergroup significance in favor of Budesonide

symptoms was significant in Budesonide group compared to Montelukast group (CI 95 %, −0.48 to −0.11,  $p = 0.03$ ).

There was significant improvement in night time symptoms in both groups; from  $1.03 \pm 0.15$  nights/wk to  $0.13 \pm 0.06$  nights/wk in Montelukast group (CI 95 %, −1.2 to −0.6,  $p < 0.0001$ ) and from  $1.0 \pm 0.17$  nights/wk to 0 nights/wk in Budesonide group (CI 95 %, −1.2 to −0.6,  $p < 0.0001$ ). Difference in decline in night time symptoms between two groups was not statistically significant ( $p > 0.05$ ).

In the present study, 63.33 % (19/30) patients in Montelukast group and 50 % (15/30) patients in Budesonide group experienced one or more exacerbations requiring use of rescue medications. 13.33 % (4/30) in Montelukast group required change of medications due to poor control of symptoms. No patient in Budesonide group required change of medications. The difference was not statistically significant ( $p > 0.05$ ).

**Fig. 2** Comparison in increase in FEV1/FVC ratio among two groups

Only 6.7 % (2) patients in Montelukast group experienced side effects (nausea/vomiting), while no patient in Budesonide group had any side effects.

## Discussion

The results of the present study demonstrated that both Budesonide and Montelukast were efficacious and well tolerated as first line preventive therapy in mild persistent asthma in age group 2 to 18 y. However, there was statistically significant difference in improvement of FEV1/FVC ratio and decline in day time symptoms in favor of Budesonide group compared to Montelukast group, whereas there was no statistically significant difference in improvement of PEFR, decline in night time symptoms and incidence of exacerbations requiring use of rescue medications or change of primary medications. Relatively high incidence of exacerbations in both groups was probably because of the study period which was in winter. Incidence of side effects was noted only in Montelukast group which was low and mild and self-limiting.

The results of the present study are consistent with those reported by Garcia Garcia et al. [16]. They showed no significant differences in percentage of asthma medication-free days at 52 wk in children age 6 to 14 y with mild persistent asthma. They also showed significantly better results with fluticasone compared with Montelukast on other measures including changes in mean percentage predicted FEV1, short acting beta agonist/systemic corticosteroid use, asthma control based on Pediatric Asthma Therapy Assessment Questionnaire, rate of mild/severe asthma exacerbations and morning-evening PEFR. Taken together, the results of study by Garcia Garcia et al. [16] and those of the current study, suggest more favorable results with inhaled corticosteroids than with Montelukast in subjects with mild persistent asthma.

Szeffler et al. [17], who did 52 wk study in children 2–8 y with mild persistent asthma to compare long term efficacy and safety of Budesonide and Montelukast showed no significant difference in time to first additional asthma medication in both the groups. However in that study better outcome were observed for Budesonide vs. Montelukast on the rate of asthma exacerbations requiring additional asthma medication and changes from baseline in morning and evening PEFR values. Similar results were obtained in both the groups in terms of rescue medication use, Spirometry variables and Child Health Status Domain. The present study showed significant improvement in FEV1/FVC and decline in day time symptoms in favor of Budesonide compared to Montelukast, while no significant differences noted in other parameters.

Karman et al. [18] performed randomized 14 wk prospective parallel group study in 63 children aged 8 to 14 y with mild persistent asthma. The study showed that Montelukast produced improvement in airway obstruction, daily symptom

scores, total daily beta agonist use, nocturnal awakenings, percentage of days and percentage of patients with asthma exacerbations and urinary leukotriene  $E_4$  levels which were similar to that produced by inhaled corticosteroids.

The differences in the results of the aforementioned studies and present study may be due to difference in the age group. Present study includes age group that ranges from preschool to school age to adolescence.

## Conclusions

The present study suggests that over a 12 wk period in 2–18 y children, oral Montelukast is not inferior to Budesonide in treatment of mild persistent asthma in terms of control of symptoms and improvement in PEFR. There was more significant improvement in day time symptoms, more significant increase in FEV1/FVC ratio and fewer exacerbations in patients receiving Budesonide compared to those receiving Montelukast.

Taken together, the results of the current study and other comparative trials of inhaled steroids vs. leukotriene receptor antagonists suggest that both groups are effective in controlling symptoms in preschool and school age children with mild persistent asthma. However, more significant improvements in Spirometry variables and symptom control were observed with inhaled steroids like Budesonide compared to Montelukast.

But, this should be weighed against the difficulty of inhaled route in small children, and definite side effects like voice change, decrease height velocity, osteopenia and hypothalamus pituitary axis suppression associated with long term use of (inhaled) corticosteroids, as well as occasional side effects of Montelukast like Churg-Strauss syndrome (hypereosinophilia) and neuropsychiatric manifestations [19, 20]

The present study has certain limitations. Blinding was not done as mode of administration of two drugs was different. Sample size was small. Study was conducted over 6 mo period. Patients were followed up for 12 wk. So long term side effects of any of the drug could not be assessed.

**Contributions** MBS: Did principle investigation; JG: Guided, gathered knowledge and collected the data; SK: Did data collection; JD: Did spirometry exercise and interpretation. Dr. Jayendra Gohil will act as guarantor for this paper.

**Conflict of Interest** None.

**Role of Funding Source** None.

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