International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Original Research Article

Montelukast versus Long Acting Beta-2 Agonists as Add on Therapy in Asthma

Shilpa Patrick[1*], Dinesh K. Badyal[2*], Navjot Singh[2**], Pradeep K Sharma[1#]

[1]Assistant Professor, [2]Professor,
[*]Dept. of Pharmacology, [**]Dept. of Medicine, [#]Dept. of Chest Medicine,
Christian Medical College & Hospital, Ludhiana, India

Corresponding Author: Shilpa Patrick

Received: 24/05/2015 *Revised: 20/06/2015* *Accepted: 29/06/2015*

ABSTRACT

Aims: This study was designed to evaluate the efficacy and safety of montelukast versus long acting β2-agonists as add on therapy in adult Indian patients with moderate asthma.
Methods: This prospective, randomized, comparative study was conducted in 120 patients, divided into 3 groups. Group A was prescribed montelukast plus inhaled corticosteroids (ICS), group B was prescribed inhaled salmeterol plus ICS and group C was prescribed inhaled formoterol plus ICS. Efficacy was measured on the basis of pulmonary function test (PFT), absolute eosinophil count and quality of life questionnaire. Safety profile of the drugs was evaluated using self-reported adverse effects by the patients.
Results: There was an increase in FEV1, FEV1: FVC and PEFR at the end of 3 months. In Group A, the mean increase in FEV1:FVC from baseline of 68.55 was 78.43, in Group B it was from 68.07 to 81.62 and in Group C it was from 68.52 to 82.03 ($p<0.05$). PEFR increased from 274.28 to 303.78 in Group A, from 284.40 to 333.82 in Group B and from 284.40 to 334 in Group C at the end of 3 months ($p<0.05$). In group A, B and C, mini asthma quality of life questionnaire (mini AQLQ) score increased from baseline to 3 months, ($p<0.05$). No serious adverse events reported.
Conclusion: The combination of ICS plus formoterol resulted in more improvement in both PFT & mini AQLQ. Formoterol add on therapy was associated with significantly improved lung function, quality of life and reduced airway inflammation with mild side effects.

Key words: Asthma, Montelukast, Formoterol, Salmeterol.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Inhaled corticosteroids are the mainstay of treatment for asthma.
- Inhaled corticosteroids/ long acting β2-agonists a fixed dose combination is being developed for asthma.
- An alternative approach is to add a leukotriene receptor antagonist (LTRA) to an inhaled corticosteroid. Montelukast is a LTRA that improves asthmatic inflammation and prevents bronchoconstriction.

WHAT THIS STUDY ADDS

- This study describes the effect of long acting β2-agonists (LABAs) and leukotriene receptor antagonist as add on therapy to inhaled corticosteroids (ICS)on pulmonary function tests and quality of life.
- The pattern of response seen is a prompt increase in pulmonary function on starting the leukotriene antagonist as add on to ICS, which is maintained for the course of the study.
- The result shows that combination of ICS plus formoterol resulted in more improvement in both pulmonary function test & mini asthma quality of life questionnaire (AQLQ).

INTRODUCTION

Asthma is the most common chronic lung disease in both the developed and developing countries. [1] It is a chronic inflammatory airway disease, characterized by bronchial hyper responsiveness and variable airway obstruction. [2] Approximately 300 million people worldwide are currently suffering from this trivial disease and 180,000 deaths are attributed each year. [3] The estimated burden in India is more than 15 million. [4]

Current treatment strategies advocate a stepwise approach to treatment, which depends on the severity of the disease. [5] Current guidelines recommend inhaled corticosteroids as mainstay of treatment for asthma. [6] Anti-inflammatory treatment with inhaled corticosteroids improves lung function, decreases symptoms & reduces asthma exacerbations. [1,7] However, patients who are sub optimally controlled on inhaled corticosteroids, there is an option of adding second line therapy with inhaled long acting Beta-2 (β_2) agonists (LABA) or oral leukotriene receptor antagonist, since both of these act on different parts of the inflammatory cascade.

Cysteinyl leukotrienes are found in the airways of asthmatics, indicating that the addition of an leukotriene receptor antagonists (LTRAs) e.g. montelukast may provide more complete attenuation of the inflammatory process. [8] Add on therapy with β_2 agonists (LABA) e.g. formoterol and salmeterol to an inhaled corticosteroids is more effective in improving lung function and reducing asthma symptoms and exacerbations. Salmeterol is a partial agonist and has a slower onset of action, whereas formoterol is a full agonist and demonstrates a quicker onset of bronchodilation. [9] Combination treatment is therefore recommended in current guidelines to achieve additional control. [10]

The addition of a long acting β_2-agonists or a leukotriene receptor antagonist to inhaled corticosteroids has been shown to prevent exacerbations and improve quality of life. [11] Addition of LTRAs reduces the need of ICS among patients requiring moderate to high dosage of corticosteroids to maintain asthma control. Currently available ICS plus LABA combination require twice daily administration whereas LTRAs are given once daily orally as add on to ICS. Once-daily treatment helps to improve patient's compliance and, therefore, disease management of this chronic condition. Inhaled LABAs have been associated with class related systemic side effects such as the potential to raise heart rate and cause ventricular arrhythmias.

Considerable debate has emerged concerning the long term use of β2-agonists in asthma. A comparative study between montelukast and salmeterol as add on to ICS, concluded good overall control in asthma symptoms. However, very few studies are available comparing the long term use of these agents. Hence, we planned this study to evaluate the efficacy and safety of montelukast versus long acting β2-

agonists as add on therapy in adult Indian patients with moderate asthma.

MATERIALS AND METHODS

Subjects

Patients of either gender aged 18 yrs to 70 yrs, diagnosed to have moderate asthma (according to GINA 2008)[1], with FEV_1 or PEFR <80% predicted, having persistent asthma symptoms (day or night), who required at least two puffs per day of reliever therapy with their usual short-acting β_2-agonist were included in the study. Patients with tuberculosis, respiratory tract infections or acute asthma exacerbation(requiring emergency treatment or hospitalization within last 4weeks), pregnancy and lactation, on oral corticosteroids within last 4 weeks, pre-bronchodilator FEV1 of <60% of predicted value, any known allergy to the study drug or refusal to give informed consent were excluded from the study.

Study design

This prospective, randomized, comparative clinical study was conducted in 120 patients. All patients with a diagnosis of moderate asthma were enrolled in the study if they fulfilled the inclusion criteria. Patients were continued on their usual maintenance dose of inhaled corticosteroid throughout the study. The study was approved by institute research committee and all patients signed a written informed consent before enrolment in the study. Patients were randomly divided into three groups of 40 patients each, according to computer generated random number table. Group A (n=40) were given montelukast 10mg tab orally once a day as add on to inhaled corticosteroids. Group B (n=40) were given inhaled salmeterol 50-100µg twice a day as add on to inhaled corticosteroids. Group C (n=40) were given inhaled formoterol 12-24µg twice a day as add on to inhaled corticosteroids.

Assessments of pulmonary function tests and evaluation of mini AQLQ

Each patient underwent a base line evaluation (1^{st}visit) which included complete medical history and pulmonary function tests. All patients received treatment for a period of 90 days. Patients were evaluated again after 30 days (2^{nd} visit) and 90 days (3^{rd} visit). Compliance was ensured by interviewing patient and by pill count method at every visit. Efficacy evaluation was based on below mentioned pulmonary function parameters: FVC (Forced vital capacity), FEV_1 (Forced expiratory volume in first second), ratio of FEV_1/ FVC, PEFR (Peak expiratory flow rate). All these measurements were measured with spirometer (Medical international research company: Italy). Each spirometry were performed and interpreted in accordance with the reproducibility and acceptability criteria of the European thoracic society. Disposable one valve mouth piece was used to reduce the risk of cross infection. Patients were instructed to sit upright and to breathe in maximally and hold the mouth piece between the teeth to secure airtight seal. Then to breath out as hard and as fast as possible until the lungs are empty. Three satisfactory blows were performed and best values were taken as interpretation.

Mini asthma quality of life questionnaire (Mini AQLQ), medical research council (MRC) dyspnea scale and absolute eosinophils count was used to measure secondary efficacy parameters.

Safety profile was evaluated on the basis of spontaneously reported adverse effects and subjective assessment which was performed on visits 1, 2 and 3.

The data was represented as mean ± standard error (SE). Data was analysed using ANOVA (Analysis of variance) with post hoc Bonferroni test, for comparing three different groups and a paired 't-test'

for comparison within the group. Chi-square test was used for non-parametric data. p value <0.05 was considered as statistically significant.

RESULTS

Table 1 shows the baseline characteristics of all the patients in the three groups. The mean age was comparable in the three groups. There was a slight female predominance in all the three groups. There was no statistical significant difference in the FVC, FEV_1, FEV_1: FVC and PEFR of the patients done at baseline. However, statistically significant differences were observed in mean FVC, FEV_1, FEV_1:FVC and PEFR values between Montelukast add on to ICS (group A), Salmeterol plus ICS (group B) and Formoterol plus ICS (group C) as compared to the baseline ($p<0.05$). PFT changes at different time intervals in the three groups are shown in table 1.

There was an increase in FVC in patients treated with Group A, B and C and it was statistically significant ($p<0.05$). The mean increase in FVC at the end of 3 months in group C (WMD 0.19) was more than group B (WMD 0.18) and group A (0.06). Although there was increase in mean FVC in all the groups but on intergroup comparison it was not statistically significant.

At each visit there was a statistically significant ($p<0.05$) increase in mean FEV_1 as compared to baseline in all three groups. Significant improvement was observed in FEV_1 at 1 month and 3 months as compared to baseline, with a mean difference of WMD 0.19 in Group A, 0.28 in Group B and 0.30 in Group C and was statistically significant ($p<0.05$). The mean increase in FEV_1 in between the groups was found to be statistically significant only at the end of the study (3 months). On intergroup comparison, It was observed that the mean increase in group B (WMD 0.09) and group C (WMD 0.11) were comparable and were greater than group A.

There was an increase in FEV_1:FVC from baseline to 3 months with mean difference of 9.88 in Group A, 13.50 in Group B and 13.51 in Group C which was statistically significant ($p<0.05$). On intergroup analysis it was seen that when group A was compared with group B (WMD 3.62) and group C (WMD 3.63), the results were statistically significant ($p<0.05$). However, when group B was compared with group C the values were not statistically significant (Figure 1).

An increase in PEFR was observed at 1 month and 3 months as compared to baseline with a mean difference of 49.42 and was statistically significant (Figure 1and 2). The PEFR increased at 1 month and 3 month (WMD 50.15), which was statistically significant (Figure 1 and 2). There was an increase in PEFR from baseline at 1 and 3 months in all the three groups. Although there was an increase in PEFR at 1 month and 3 month but it was statistically significant only at 3 months (Figure 2). It was also observed that statistically significant improvement was there in group B (WMD 19.92) and C (WMD 20.65) when compared to group A ($p<0.05$). There was no statistically significant difference between group B and group C.

The mini AQLQ score was comparable at baseline in the three groups. In group A, B and C, mini AQLQ score increased from baseline to 3 months and was statistically significant ($p<0.05$) in all groups. There was significant improvement in quality of life of patients in group C at 1 month as compared to group A and group B. At 3 months it was observed that there was significant improvement in group B and group C as compared to group A ($p<0.05$). The mini AQLQ score was comparable in group A and B up till 1 month. Figure 3

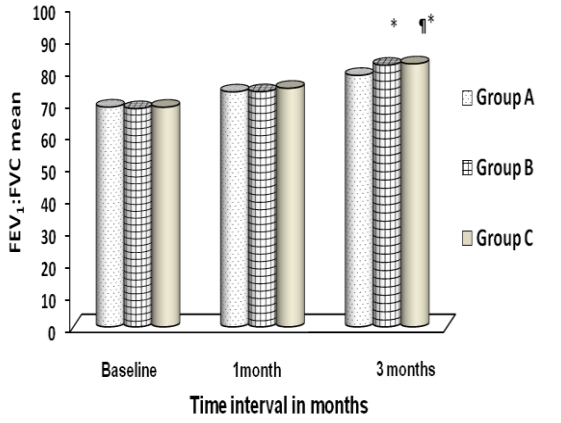

Figure 1: Changes in FEV_1: FVC at different time intervals in different groups.
* p<0.05 as compared to group A
¶ p>0.05 as compared to group B

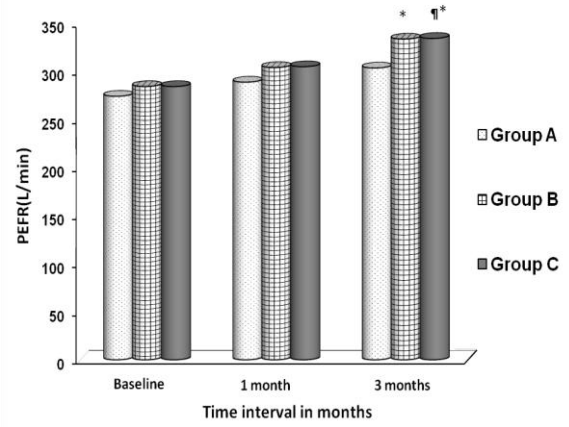

Figure 2: Changes in PEFR at different time intervals in different groups.
* p<0.05 as compared to group A
¶ p>0.05 as compared to group B

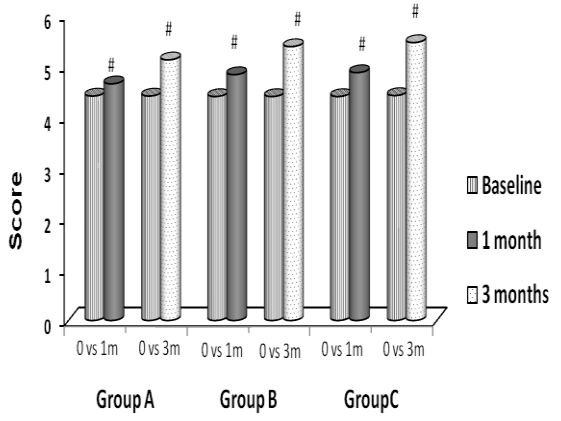

Figure 3: Mini asthma Quality of life Questionnaire (Mini AQLQ) score at different time intervals
# P<0.05 as compared to baseline

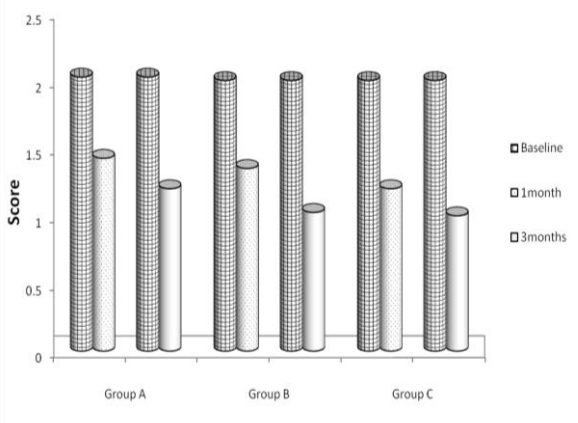

Figure 4: MRC score (Mean ± SE) at different time intervals in different groups

The mean AEC in group A, B and C decreased from baseline to 3 months and the difference was statistically significant in the 3 groups (p<0.05). Inter-group comparison of AEC was done at baseline, 1 month and 3 month. It was observed that there was reduction in AEC in group A, group B and group C. However no statistically significant difference was found in the three groups. The AEC was comparable at baseline and up till 1 month.

The MRC score in group A, B and C decreased from baseline and at 3 months and the difference was statistically significant in the 3 groups (p<0.05). Inter-group comparison of AEC was done at baseline, 1 month and 3 month. It was observed that there was reduction in AEC in group A, group B and group C. However no statistically significant difference was found in the three groups. The AEC was comparable at baseline and up till 1 month.

In our study, there were no serious adverse events reported. Most of the adverse events reported were mild. The mild adverse events reported in the 3 groups were headache, dizziness, palpitations, nausea, tiredness and tremors. Table 2

The use of rescue medication was observed to be more among patients in group A (15%) and group B (12%) as compared to group C (5%).

Table 1: Demographic Profile and Pulmonary function tests of patients at different time intervals

	Group A(n = 40) Mean ± SE	Group B(n = 40) Mean ± SE	Group C(n = 40) Mean ± SE
Number of patients	40	40	40
Age (in years) (Mean ± SE)	40.22±2.54	42.88±2.02	41.82±2.04
Sex (M:F)	17:23	18:22	17:23
Weight (Kg)	61.87±1.45	63.5±1.75	62.35±1.59
Height (cm)	163.38±1.23	163.12±1.40	162.40±1.36
Baseline	1.61±0.06	1.60±0.03	1.63±0.05
2 visit	1.64±0.06#	1.68±0.03#	1.71±0.04#¶
3 visit	1.67±0.06#	1.79±0.03#	1.83±0.04#¶
FEV_1 Baseline	1.10±0.04	1.14 ±0.02	1.16±0.03
2 visit	1.19±0.04#	1.22 ±0.02#	1.24±0.05#¶
3 visit	1.30±0.04#	1.43±0.02#*	1.46±0.04#*¶
FEV_1:FVC Baseline	68.55±0.83	68.07±0.80	68.52±0.88
2 Visit	73.28±0.86#	73.01±0.78#	74.43±0.90#¶
3 Visit	78.43±0.83#	81.62±0.81#*	82.03±0.98#*¶
PEFR Baseline	274.28±8.40	284.40±8.36	284.40±8.84
2 Visit	288.95±8.80#	304.18±8.48#	305.05±8.91#¶
3 Visit	303.78±8.46#	333.82±8.45#*	334±8.94#*¶

# p<0.05 as compared to baseline, * p<0.05 as compared to group A, ¶ p>0.05 as compared to B.
FVC=Forced vital capacity; FEV_1= Forced expiratory volume in one second.
PEFR= Peak expiratory flow rate

Table 2: Adverse drug reaction in different groups

	Group A (n=40)	Group B (n=40)	Group C (n=40)
Headache	9	8	6
Drowsiness	2	1	1
Restlessness	4	6	5
Oral candidiasis	1	2	1
Nausea/vomiting	2	4	1
Palpitations	0	8	5
Tiredness	4	2	3
Dizziness	11	0	1
Tremors	0	1	2

No significant difference was observed between Groups.

DISCUSSION

In our study, it was seen that there was a significant increase in FEV_1 in all the three groups as early as one month and maximum improvement was seen at 3 months as compared to baseline. Since all the study groups were receiving standard treatment in addition to add on therapy, we expected an increase in FEV_1. The FEV_1 improved in all the three subgroups although the maximum improvement was seen with formoterol. The mean increase in FEV_1 is in accordance with one of the previous study which has compared the efficacy of formoterol (9 µg) and montelukast (10 mg) as add-on to low dose budesonide 400 µg daily. More significant increase in the FEV_1 was seen in the group treated with formoterol add on as compared to montelukast add on group. The average difference in the improvement from baseline in FEV_1 between LABAs and montelukast was similar to our study. [12]

As change of 200ml or more in FEV_1 is considered to be a clinically important difference. [13] The mean improvement in FEV_1 observed with group A was 190 ml, in group B 280 ml and in group C it was 290 ml. Many studies have demonstrated that FEV_1: FVC reversibility of ≥ 12% can lead to clinically significant improvement in asthma symptoms. [14] In our study reversibility was more with formoterol (13.51%) and salmeterol (13.50%) as compared to montelukast (9.8%).

An increase in PEFR was observed in montelukast and salmeterol add on groups however, greater increase in PEFR was observed in formoterol add on group. The mean difference of 20.5 L/min was observed between montelukast and formoterol. These results were also consistent with meta-

analysis comparing LABAs with antileukotrienes as add on to ICS.

The lung functions showed more improvement with formoterol and salmeterol add on group as compared to montelukast add on group. This is possibly because of the synergistic effect of LABA + ICS. LABAs enhance intracellular binding of corticosteroids and potentiate the anti-inflammatory action of corticosteroids. Moreover, corticosteroids protect against down-regulation of β_2 receptors with LABA therapy. On the other hand, inhibition of cys-LT-induced bronchial smooth muscle contraction is likely to be involved in the therapeutic effects of LTRA to improve lung functions. LTRA and LABAs affect different points in the inflammatory cascade that results ultimately in bronchoconstriction and bronchial hyper responsiveness. Long-acting β_2-agonists act predominantly at the bottom of this cascade at the site of smooth muscle, as bronchodilatory agents, although it has been suggested they may also possess weak anti-inflammatory properties. Leukotriene receptor antagonists attenuate the proinflammatory effects of leukotrienes, such as increased microvascular permeability, eosinophil chemotaxis, mucus secretion, as well as blocking leukotriene-induced smooth muscle constriction and proliferation. Hence, better control of asthma symptoms and improvement in lung function favors use of formoterol as add on to ICS as compared to salmeterol or montelukast add on to ICS.

Improvement in quality of life was observed in all the 3 groups. Although, there was an increase in Mini AQLQ score in the three add on groups A, B and C (montelukast, salmeterol and formoterol), it was observed to be more with formoterol (group C) add on.

Our study shows that the combination of ICS plus formoterol resulted in more improvement in both FEV_1, FEV_1: FVC and PEFR than ICS plus montelukast. Lung functions improved with all the study drugs although the maximum efficacy was seen with formoterol and the least with montelukast. Mini AQLQ and MRC also support this fact.

In conclusion, better asthma control was observed with formoterol add on, which was consistent with the improvement in PFT. Formoterol + ICS were found to bring significant decrease in symptoms of asthma and improve quality of life as compared with salmeterol + ICS and montelukast + ICS. Slightly, greater improvement in PFT measures, symptom control and quality of life was observed in formoterol add on group as compared to salmeterol group. Although few adverse effects were noted in the formoterol group but the benefits outweighs the risk of adverse effect. Table 2

Both montelukast and formoterol led to improvement in asthma but formoterol was associated with significantly improved lung function, quality of life, asthma symptoms and reduced airway inflammation. Hence, in asthmatic patients, who are inadequately controlled on ICS alone addition of formoterol can be a better treatment option compared to montelukast and salmeterol.

REFERENCES

1. Hansbro P, Kaiko G, Foster P. Cytokine/anticytokine therapy-novel treatment for Asthma. Br J Pharmacol 2011; 163: 81-95.
2. Schmidt DT, Rabe KF. Pharmacological treatment of asthma today. Eur Respir J 2001; 18: Suppl. 34, 34s–40s.
3. *Masoli M, Fabian D, Holt S. Global Initiative for Asthma (GINA) program: the global burden of asthma: executive summary of the GINA Dissemination Committee report.* Allergy2004*; 59,* 469-*478.*
4. Rai SP, Patil AP, Vardhan V, Marwah V, Pethe M, Pandey IM.Best Treatment

Guidelines For Bronchial Asthma. MJAFI 2007; 63: 264-268.
5. Global strategy for asthma management and prevention. Global Initiative for Asthma (GINA), 2008.Available from www.ginasthma.org (accessed on 30 October, 2009).
6. Udem BJ. Pharmacotherapy of asthma. In: Bruton LL, Lazo JS, Parker KL, editors. The pharmacological basis of therapeutics.11th ed. Mc Graw Hill: New York 2009; 717-736.
7. Ducharme FM, Lasserson TJ, Cates CJ. Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review). The Cochrane Library2009, Issue 3.
8. Ceylan E, Gencer M, Aksoy S. Addition of formoterol or montelukast to low dose budesonide: An efficacy comparison in short and long term asthma control. Respiration 2004; 71:594-601.
9. Barnes PJ. Clinical outcome of adding long-acting beta-agonists to inhaled corticosteroids. Respir Med 2001; 95: S12-6.
10. O'sullivan S, Akveld M, Burke CM, Poulter LW. Effect of the Addition of Montelukast to Inhaled Fluticasone Propionate on Airway Inflammation. *Am J Respir Crit Care Med* 2003; 167: 745-750.
11. Rodrigo J, Hall J. Acute asthma in adults. Chest 2004; 125: 1081-1102.
12. Ceylan E, Gencer M, Aksoy S. Addition of formoterol or montelukast to low dose budesonide: An efficacy comparison in short and long term asthma control. Respir 2004;71:594-601.
13. Ducharme F, Lasserson T, Cates C. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. Cochrane Database Syt Rev. 2011; (5): CD003137. Available from www. Cochraine library (assessed on 10 October, 2011).
14. Rodrigo J, Hall J. Acute asthma in adults. Chest 2004; 125: 1081-1102.

How to cite this article: Patrick S, Badyal DK, Singh N et. al. Montelukast versus long acting beta-2 agonists as add on therapy in asthma. Int J Health Sci Res. 2015; 5(7):178-185.

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