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Effect of Two Controller Medications with Inhaled Corticosteroid in Mild to Moderate Persistent Asthma Patients

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Asthma is an inflammatory disease characterized by recurrent episodes of breathlessness and wheezing. Though inhaled corticosteroids play a vital role in the treatment of asthma, it alone or with long acting beta agonist cannot control asthma symptoms in most of the patients. The present study aims to assess the two controller medications in the form of oral tablets with inhaled corticosteroid combination in controlling forced expiratory volume in one second (FEV_1) in mild to moderate persistent asthma patients. A total of 108 patients with mild to moderate asthma were enrolled in this randomized controlled study from the pulmonary medicine department of a tertiary care hospital. Patients were randomized into two groups viz., Group 1 (n = 54) and Group 2 (n = 54). Group 1 patients received Montelukast and Group 2 patients received Doxofylline. Both the groups received Budesonide inhaler. Pulmonary function test was assessed at the baseline and on follow up days. No significant difference was observed with respect to socioeconomic and educational status of patients between the groups. Significant ($p<0.001$) improvement in percentage predicted FEV_1 after 120 days treatment was observed with both Montelukast and Doxofylline treated groups. There is no statistically significance between the groups. No major adverse events were found during the study period. The study concluded that both controller medications helped in improving lung function.

Key words: Asthma, montelukast, doxofylline, budesonide, FEV_1

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INTRODUCTION

Asthma is a common chronic lung disease affecting the airways that carry air in and out of the lungs. The inside wall of the bronchial airways are inflamed and swollen. This inflammation or swelling makes the airway more sensitive to irritants and cause the allergic reaction. Asthma is characterized mainly by wheezing, coughing, chest tightness and shortness of breath. The frequency and severity varies from person to person. (Antonicelli *et al*., 2004). According to World Health Organization (WHO) statistics, asthma affects 300 million people and its prevalence increases globally by 50% every decade (Leckie *et al*., 2000). Even though many classes of drugs are available for current approach for asthma treatment, there are no drugs that can reverse the disease process. All these drugs and combinations only can improve asthma conditions and reduce frequency of exacerbations and the need for rescue medications (Partridge and Hill, 2000).

The goals of asthma therapy are to achieve asthma control (i.e.,) near normal lung function, absence of asthma symptoms, no activity limitations and no episodes of worsening asthma. Twice daily doses of an Inhaled Corticosteroid (ICS) are main choice for nearly all types of asthma patients. Starting with an intermediate dose and then to diminish the dose (Step down therapy) when symptoms are controlled after 3 months is in general practice. If symptoms are not controlled, a Long Acting Beta Agonist (LABA) is added (Step up therapy), most suitably by switching to a combination inhaler (Pauwels *et al*., 2003). The dose of controller medications should be accustomed accordingly, as judged by the need for a rescue inhaler. ICS plus LABA combination become a gold standard combination for asthma patients and it is recommended by the Global Initiative for Asthma (GINA) guideline as a first line treatment regimen (Holgate and Polosa, 2006).

However many patients with persistent asthma cannot attain all the above treatment goals with this gold standard combination (Viswanathan *et al*., 1966). Therefore, finding a new combination regimen is always a welcome sign. The present study is aimed to assess effectiveness of two controller medications namely Montelukast and Doxofylline with an inhaled corticosteroid Budesonide in mild to moderate persistent asthmatic patients.

MATERIALS AND METHODS

Study protocol and recruitment: The study was approved by the Institutional Ethical Committee (298/IEC/2012) and it was undertaken at Pulmonary Medicine department in SRM Medical College hospital and research center, Kattankulathur, Tamil Nadu, India. This is a randomized open label study. A total of 108 patients completed the study. Patients were aged between 18 to 65 years, either sex, without co-morbidities and mild to moderate persistent condition were included in the study. Patient with history of cardiac disorders, COPD, pregnant women and lactating mothers, significant hepatic and renal dysfunction and voluntary withdrawal were excluded from the study. Written consent was obtained from all participants.

Sample size calculation: The sample size was calculated with an approximate 7.6% difference between two groups for a significant increase in pulmonary function with the standard deviation of 0.05. An alpha value of 0.05 and power of 0.8 were assumed for calculation using 1:1 ratio of independent sample t-test. 54 patients must complete the study in each group. Considering 20% dropout, 64 patients should be included in each group.

Study design: Patients satisfying above study criteria were enrolled in the study. Enrolled patients were randomized by randomization chart generated by computer assisted random allocation procedure. Patients were divided into two groups namely Group 1 (n = 54) and Group 2 (n = 54). Clinical information relevant for the study was collected from the patients, healthcare professionals, necessary records and as well as from patient's bystanders in few cases. Antiasthmatic drugs prescribed till date were stopped and the patients were asked to take Salbutamol inhaler (i.e., Rescue medication) whenever necessary for a 7 day (run-in period) prior to the study. Patients were educated and counseled about the proper usage of inhalers. Patients who were in Group 1, received Budesonide 200 μg twice a day with an oral tablet of Montelukast 10 mg day^{-1} and Group 2 patients received Budesonide 200 μg twice a day (bid) plus tablet Doxofylline 400 mg for a period of four months. All patients could take short acting β-agonist in case of an asthmatic crisis. All the patient's pulmonary function test (FEV_1 by spirometry) and clinical symptoms were measured at the baseline and every follow up days i.e., Day 30, 60, 90 and 120. Each and every follow up, patient medication adherence and their inhaler usage technique were monitored.

Pulmonary function test: Pulmonary Function Test (PFT) was performed with spirometry. Spirometry is the measurement of flow of air into and out of the lungs. The patient's age, gender, race, height and weight were

measured before the procedure begins. The patient should not have eaten heavily within three hours of the test. Patients were instructed to wear loose-fitting clothing over the chest and abdominal area. The respiratory therapist or other testing personnel explained and demonstrated the breathing maneuvers to the patient. Spirometry test was performed with a spirometer, which consists of a mouthpiece and disposable tubing connected to a machine that records the results and displays them on a graph. The patient practiced breathing into the mouthpiece until he or she is able to duplicate the maneuvers successfully on two consecutive attempts. Nose clips were usually used to make sure air is only coming out of the mouth. Sometimes a test was repeated to get the best and maximum effort.

Statistical analysis: Data are expressed as Mean±SD. The probability value less than 0.05 was considered for statistical significance. Demographic characteristics like age and gender, baseline and final visit data were used to assess response rates by comparing usual care and intervention group. Student's t test was used for the comparisons within the groups. One-way ANOVA Bonferroni multiple comparison test was used for the comparisons between groups using GraphPad Software, Inc. (USA).

RESULTS

After designing the protocol, ethical clearance was obtained from the Human Institutional Ethics Committee. A formal sample size was calculated for the study with the consultation of biostatistician. A total of 141 patients attended the screening phase for mild to moderate asthma condition, out of which 128 patients met the study criteria. Thirteen patients were excluded from the study due to various reasons as mentioned in Fig. 1. The patients who got enrolled after giving informed consent was randomized into 2 groups. In the first group, out of 63 patients, 54 completed the study and in the second group, out of 65 patients, 54 patients completed the study. Reasons for drop out were mentioned in Fig. 1.

In group 1, out of 54 patients, 37 patients were male and 17 patients were female and their mean age was 55±8.1 years, mean BMI was 25.3±3.4. Out of 54 patients in group 2, 39 patients were male and 15 were female and their mean age was 54±8.0 years, mean BMI was 24.9±2.5. No significant difference was observed in age and BMI between the study groups (Table 1).

No patient was found less than one year of disease duration history. About 68.5% (n = 37) and 62.9% (n = 34) had a disease history of one to five years in group 1 and 2 respectively. Another 20.3% (n = 11) and 11.1% (n = 6) had 5-10 years and more than 10 years of disease duration

Table 1: Demographic data of the patients

Demographic variables	Group 1 (n = 54)	Group 2 (n = 54)
Age (in years) (Mean±SD)	55.17±8.1	54.35±8.0
BMI (Mean±SD)	25.3±3.4	24.9±2.5
Gender % (n)		
Male	68.5% (37)	72.2% (39)
Female	31.4% (17)	27.7% (15)
Duration of disease % (n)		
<1 year	0% (0)	0% (0)
1-5 years	68.5% (37)	62.9% (34)
5-10 years	20.3% (11)	24.0% (13)
>10 years	11.1 % (6)	12.9% (7)
Socioeconomic Status % (n)		
Coolie	24.0% (13)	29.6% (16)
Employed	22.2% (12)	20.3% (11)
Self Employed	27.7% (15)	22.2% (12)
Business	1.8% (1)	0% (0)
Professional	0% (0)	7.4% (4)
Others	24.0% (13)	20.3% (11)
Educational Status % (n)		
Illiterate	0% (0)	16.6% (9)
1 to 10	44.4% (24)	40.7% (22)
11 to degree	55.5% (30)	38.8% (21)
>degree	1.8% (1)	3.7% (2)

Table 2: Comparison of % FEV_1 between Day 0 and 120 among the study groups

	% Predicted FEV_1				
Groups	Day 0	Day 120	Mean difference	p-value	95% CI
Group 1	62.00±8.12	71.03±7.52	9.030	p<0.001	6.012 to 12.05
Group 2	62.24±3.04	73.03±7.41	10.790	p<0.001	7.772 to 13.81

Data expressed as Mean±SD, Paired t-test, GraphPad prism

in group 1. Whereas 24.0% (n = 13) and 12.9% (n = 7) patients in group 2 had the disease history of five to ten years and more than ten years, respectively.

In group 1, 24.0% (n = 13) and in group 2, 29.6% (n = 16) patients were found as coolies. In group 1 and 2, 22.2 and 20.3% patients were employed and 27.7 and 22.2% were self-employed, respectively. There was no patient in group 1 and 7.4% (n = 4) patients in group 2 were professional workers. Patients in others category included housewives in both groups.

The educational status of the patients was also shown in Table 1. No patient with usual care and 16.6% (n = 9) patients in intervention care group were illiterate. Twenty four and twenty two patients (44.4 and 22.0%) in usual and intervention care group finished first standard to tenth standard. 55.5% (n = 30) and 38.8% (n = 21) in usual and intervention care group patients had an eleventh standard to a degree education. No patient with usual care and 3.7% (n = 2) in the intervention group had post-graduation qualification.

The changes in the percentage FEV_1 values from baseline (Day 0) to end of the study (Day 120) in both groups are shown in Fig. 2. It is evident from the Fig. 2 that FEV_1 values are improved at every follow up. The percentage improvement in FEV_1 from baseline to end visit between the study groups were shown in Table 2. For the

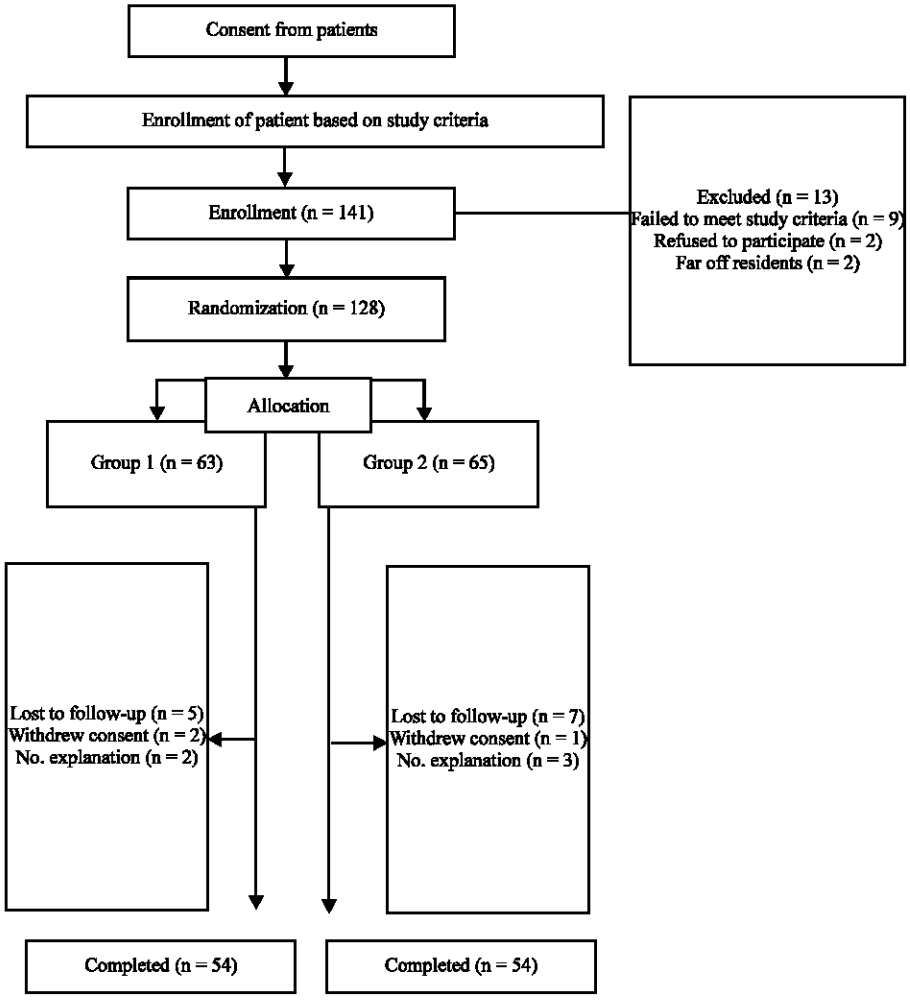

Fig. 1: Flow chart of patients recruitments and treatments

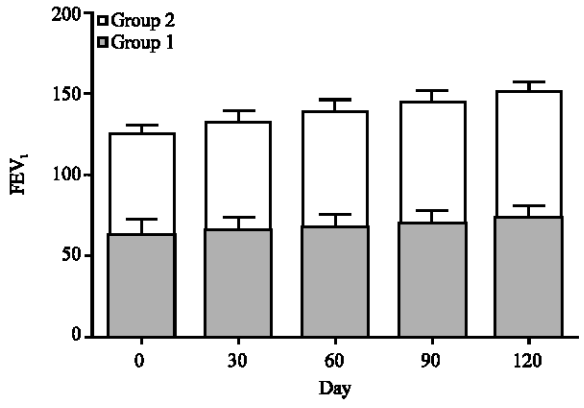

Fig. 2: Comparison of improvement in % Predicted FEV_1 between the study groups from baseline to end visit

FEV_1 between the study groups from baseline to end visit patients in group 1, the mean difference was 9.030 with the confidence interval of 6.012 to 12.05. In group 2 patients, the mean difference was 10.79 with the confidence interval of 7.772 to 13.81. Significant ($p<0.001$) improvement in FEV_1 after 120 days treatment was observed in both Montelukast and Doxofylline treated groups. There is no statistically significance were observed between the groups.

Physical examination including oropharyngeal inspection, heart rate and blood pressure were monitored for study patients. There were no significant changes in such assessments recorded in all the clinical visits compared to baseline values (Data are not shown). Asthma exacerbations which required hospitalization were considered as serious adverse events. There was no such critical situation faced by study patients of both groups.

DISCUSSION

Pharmacotherapy is essential for asthma management and is based on stepwise treatment for different levels of asthma severity: intermittent, mild persistent, moderate persistent and severe persistent. Antiasthma drugs are classified into the controller and preventive medications. Common antiasthma medications include corticosteroids (inhalation and oral), long acting-beta2 agonists (LABA), Cromolyn sodium or Nedocromil sodium, Methylxanthines and Leukotriene modifiers (Suissa *et al*., 2000).

Among the controller medications, Inhaled Corticosteroid (ICS) are the mainstay. Anti-inflammatory action of ICS in the lungs is well established and ICS has proven its efficacy in improving pulmonary function and reducing exacerbations of asthma. The use of ICS is considered as one of the best treatment options for patients with mild to moderate asthma condition (Jenkins *et al*., 2005). However, not all the patients achieve the asthma treatment goal with corticosteroid. Because, asthma is a multi factorial disease where inflammation alone is not playing the role. The pathophysiology of asthma is complicated. Leukotrienes and phosphodiesterase also play a major role in progression of asthma (Lin *et al*., 2004). Unfortunately, corticosteroids do not have any effect on either synthesis or release of cysteinyl leukotrienes in the lungs and on phosphodiesterase enzyme control.

Two controller medications namely Montelukast and Doxofylline were chosen in the study. Montelukast is a leukotriene receptor antagonist. The cysteinyl leukotrienes especially LTC_4, LTD_4 and LTE_4 induce many pathological changes in lungs including airflow obstruction, mucus secretion and inflammatory cell infiltration (Rosenwasser and Boyce 2003; Robinson, 2004; Gelfand and Dakhama, 2006). Thus, anti-leukotriene agents have a beneficial action on controlling asthma. Doxofylline is a xanthine derivative drug. It has antitussive and bronchodilator activity by inhibiting phosphodiesterase activity (Leff, 2001; Akbari *et al*., 2006; Patel *et al*., 2010). Thus, it produces neutrophil migration inhibition, inhibition of lymphocyte, neutrophil, activation of monocyte and inhibition of inflammatory mediators.

Effect of Montelukast and Doxofylline on controlling asthma was studied in many studies (Leckie *et al*., 2000; Reiss *et al*., 1998; Patel *et al*., 2010). But the study not only included inhaled corticosteroid but also added long acting beta agonist as second controller medication. RADAR and MONICA trials (Keith *et al*., 2009; Virchow *et al*., 2010) studied the effectiveness of Montelukast but the study added Montelukast as a second controller medication to the inhaled corticosteroid and long acting beta agonist combination. There is no clinical study reported in comparing the Montelukast and Doxofylline with inhaled corticosteroid Budesonide alone as combination on mild to moderate persistent asthma patients and especially no study reported on south Indian population.

The combination of high dose inhaled corticosteroid, short acting β_2 agonists with a leukotrine receptor antagonist (zafirlukast) was studied by Virchow *et al*. (2000) and Patel *et al*. (2010). The study was conducted for a period of six weeks and they reported a significant improvement in the lung function and reduced exacerbations.

Dupont *et al*. (2005) observed an improvement in pulmonary function and asthma symptoms with add-on leukotrine receptor antagonist therapy, for a period of two months in an open labeled study with insufficiently controlled asthma patients with inhaled corticosteroid and long-acting β_2 agonists as fixed dose combination. (Shah *et al*., 2006; Korn *et al*., 2009; Keith *et al*., 2009) studied the effectiveness of controller medications as add on therapy to inhaled corticosteroid, in improving lung functions and asthma symptoms. All these studies were carried out for a period of eight weeks. With this background, a period of 120 days study duration in the present study was relatively considered to be sufficient to identify the effectiveness of study medications. However, this may be the limitation of this study and another potential weakness of the study is that there is no standard group for comparison of the study groups.

Inhaled corticosteroid and long acting beta agonist is a gold standard combination for mild to moderate persistent asthma. It would be better if the study added this combination as one of the study group. Future studies may address this issue.

The finding of this study suggests that the addition of Montelukast (10 mg day^{-1}) and Doxofylline (400 mg day^{-1}) to the inhaled corticosteroid Budesonide (200 μg twice a day) combination helps in improving FEV_1 without any adverse effects. No statistically significant difference was observed among the two tested groups in the extent of improvement in FEV_1. This suggests that Montelukast and Doxofylline are well tolerated when added as a controller medication to inhaled corticosteroid.

CONCLUSION

Controller medications in the form of Montelukast and Doxofylline as an add on therapy to inhaled corticosteroid are effective in the improvement of FEV_1. This kind of study in Indian population would help the health care professionals in choosing the appropriate treatment regimens to control asthma. However, considering an open label design, future studies are warranted with blinding techniques and long duration to substantiate the current findings.

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REFERENCES

Akbari, O., J.L Faul, E.G. Hoyte, G.J. Berry and J. Wahlstrom *e al*., 2006. CD4+ invariant T-cell-receptor+natural killer T cells in bronchial asthma. N. Engl. J. Med., 354: 1117-1129.

Antonicelli, L., C. Bucca, M. Neri, F. De Benedetto and P. Sabbatani *e al*., 2004. Asthma severity and medical resource utilization. Eur. Respir J., 23: 723-729.

Dupont, L., E. Potvin, D. Korn, A. Lachman and M. Dramaix *et al*., 2005. Improving asthma control in patients sub optimally controlled on inhaled steroids and long-acting b_2-agonists: Addition of montelukast in an open-label pilot study. Curr. Med. Res. Opin., 21: 863-869.

Gelfand, E.W. and A. Dakhama, 2006. $CD8^+$ T lymphocytes and leukotriene B_4: Novel interactions in the persistence and progression of asthma. J. Aller. Clin. Immunol., 117: 577-582.

Holgate, S.T. and R. Polosa, 2006. The mechanisms, diagnosis and management of severe asthma in adults. Lancet, 368: 780-793.

Jenkins, C.R., F.C. Thien, J.R. Wheatley and H.K. Reddel, 2005. Traditional and patient-centered outcomes with three classes of asthma medication. Eur. Respir J., 26: 36-44.

Keith, P.K., C. Koch, M. Djandji, J. Bouchard and E. Psaradellis *et al*., 2009. Montelukast as add-on therapy with inhaled corticosteroids or inhaled corticosteroids and long-acting b-2-agonists in the management of patients diagnosed with asthma and concurrent allergic rhinitis (The RADAR Trial). Can. Respir J., 16: 17-31.

Korn, D., B.P. Vanden, E. Potvin, M. Dramaix, E. Herbots and R. Peche, 2009. Efficacy of add-on montelukast in patients with non-controlled asthma: A Belgian open-label study. Curr. Med. Res. Opin., 25: 489-497.

Leckie, M.J., A. Ten Brinke, J. Khan, Z. Diamant and B.J O'Connor *et al*., 2000. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness and the late asthmatic response. Lancet, 356: 2144-2148.

Leff, A.R., 2001. Regulation of leukotrienes in the management of asthma: Biology and clinical therapy. Ann. Rev. Med., 52: 1-14.

Lin, H., K.M. Boesel, D.T. Griffith, C. Prussin and B. Foster *et al*., 2004. Omalizumab rapidly decreases nasal allergic response and FcåRI on basophils. J. Aller. Clin. Immunol., 113: 297-302.

Partridge, M.R. and S.R. Hill, 2000. Enhancing care for people with asthma: the role of communication, education, training and self-management: 1998 World Asthma Meeting Education and Delivery of Care Working Group. Eur. Respir. J., 16: 333-348.

Patel, Y.A., P. Patel, H. Bavadia, J. Dave and C.B. Tripathi, 2010. A randomized, open labeled, comparative study to assess the efficacy and safety of controller medications as add on to inhaled corticosteroid and long-acting β2 agonist in the treatment of moderate-to-severe persistent asthma. J. Postgr. Med., 56: 270-274.

Pauwels, R.A., S. Pedersen, W.W. Busse, W.C. Tan and Y.Z. Chen *et al*., 2003. Early intervention with budesonide in mild persistent asthma: A randomised, double-blind trial. Lancet, 361: 1071-1076.

Reiss, T.F., P. Chervinsky, R.J. Dockhorn, S. Shingo, B. Seidenberg and T.B. Edwards, 1998. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: A multicenter, randomized, double-blind trial. Arch. Intern Med., 158: 1213-1220.

Robinson, D.S., 2004. The role of the mast cell in asthma: Induction of airway hyperresponsiveness by interaction with smooth muscle? J. Allergy Clin. Immunol., 114: 58-65.

Rosenwasser, L.J. and J.A. Boyce, 2003. Mast cells: beyond IgE. J. Aller. Clin. Immunol., 111: 24-32.

Shah, A.R., L.D. Sharples, R.N. Solanki and K.V. Shah, 2006. Double-blind, randomised, controlled trial assessing controller medications in asthma. Respiration, 73: 449-456.

Suissa, S., P. Ernst, S. Benayoun, M. Baltzan and B. Cai, 2000. Low-dose inhaled corticosteroids and the prevention of death from asthma. New Engl. J. Med., 343: 332-336.

Virchow, J.C., A. Prasse, I. Naya, L. Summerton and A. Harris, 2000. Zafirlukast improves asthma control in patients receiving high-dose inhaled corticosteroids. Am. J. Respir. Crit. Care Med., 162: 578-585.

Virchow, J.C., A. Mehta, L. Ljungblad and H. Mitfessel, 2010. Add-on montelukast in inadequately controlled asthma patients in a 6-month open-label study: The MONtelukast in Chronic Asthma (MONICA) study. Respir. Med., 104: 644-651.

Viswanathan, R., M. Prasad, A.K. Thakur, S.P. Sinha and N. Prakash *et al*., 1966. Epidemiology of asthma in an urban population. A random morbidity survey. J. Indian Med. Assoc., 46: 480-483.