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Efficacy of Seratrodast, a Thromboxane A_2 Receptor Inhibitor in a Double Blind Comparative Clinical Trial with Monteluklast

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Authors' contributions

This work was carried out in collaboration between all authors. Author BD designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors SN and DS managed the literature searches, coordination of the study, interpretation of data and analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To assess the comparative efficacy, safety and tolerability of seratrodast versus montelukast in controlling mild to moderate asthma in adult patients.
Study Design: Randomized, comparative, double blind, double dummy, multi-center, parallel group, non inferiority study.
Methods: Patients (n=205) with mild to moderate asthma continuing on the lowest dose of inhaled corticosteroid were recruited from 3 different centers across India. Patients were randomly assigned to receive either seratrodast 80 mg (n=103) or montelukast 10 mg (n=102) once daily for 28 days. The treatments were compared for improvement from the baseline values, as per the changes in asthma symptom score (wheezing, shortness of breath, expectoration, cough and chest tightness), lung function parameters (PEF, FVC and FEV_1), sputum and mucociliary parameters [fucose, eosinophil cationic protein (ECP) and albumin].
Results: Seratrodast and montelukast showed improvement in the clinical parameters of asthma

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as well as in the lung function tests and sputum parameters from baseline. Both the treatments significantly increased mean values of PEF, FVC and FEV_1 from the baseline after a 4 week treatment but seratrodast produced significantly greater improvement in PEF (0.416 L/s, *P*=.01). Moreover, there was significantly more reduction in expectoration score (*P*=.01), sputum concentrations of ECP (*P*<.001) and albumin (*P*<.001) in seratrodast group, signifying improvement in asthma condition. The two treatment groups had similar tolerability profiles. Mild increase in hepatic enzymes was seen in both the groups with no clinical significance. No serious adverse events were observed during the study.

Conclusions: Seratrodast, a Thromboxane A_2 receptor antagonist, was found to be better in the improvement of PEF, reduction in expectoration, ECP and albumin levels as compared to montelukast. Seratrodast can be recommended as a controller medication in mild to moderate asthma.

Keywords: Thromboxane A_2 receptor antagonist; asthma; seratrodast; montelukast; peak expiratory flow (PEF); eosinophil cationic protein (ECP); albumin.

ABBREVIATIONS

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CysLT1: Cysteinyl Leukotriene Receptor $_1$; ECP: Eosinophil Cationic Protein ; FEV_1: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; GINA: The Global Initiative for Asthma; ICS: Inhaled Corticosteroid; ITT: Intention to Treat; LTC_4: Leukotriene C_4; LTD_4: Leukotriene D_4; Monte: Montelukast; NCT: Nasal Clearance Time; PEF: Peak Expiratory Flow; PGD_2: Prostaglandin D_2; $PGF_{2\alpha}$: Prostaglandin $F_{2\alpha}$; SD: Standard Deviation; Sera: Seratrodast; SMCS: Sputum and Mucociliary Clearance Score; TXA_2: Thromboxane A_2 ; WBC: White Blood Cell.

DEFINITION

Prostanoid: Prostanoids are the cyclo-oxygenase metabolites of arachidonic acid and include prostaglandin (PG) D_2), PGE_2), $PGF_{2\alpha}$), PGI_2), and thromboxne A_2..

1. INTRODUCTION

Asthma is one of the most common chronic diseases, characterized by infiltration of various inflammatory cells including eosinophils, T lymphocytes and mast cells in airway smooth muscle [1]. Activation of these cells releases a number of inflammatory mediators which gives rise to bronchial hyperresponsiveness, bronchoconstriction, mucus secretion, increased vascular permeability and smooth muscle hypertrophy [2]. Studies have highlighted the role of arachidonic acid metabolites (leukotrienes, prostaglandins and thromboxane A_2) in the pathogenesis of asthma. Among these, thromboxane A_2 (TXA_2) has attracted attention as an important mediator in the pathophysiology of asthma because of its potent bronchoconstrictive activity and it is thought to be involved in both, airway hyperresponsiveness and late asthmatic response. Strategies for inhibition of TXA_2 include TXA_2 receptor antagonism and thromboxane synthase inhibition. There is an increasing evidence supporting usage of TXA_2 receptor antagonists, seratrodast and the thromboxane synthase inhibitor, ozagrel in the treatment of patients with asthma. Ramatroban, another thromboxane receptor antagonist, is currently under clinical evaluation for the treatment of asthma [3–7].

Inhaled corticosteroids (ICS) are the most effective anti-inflammatory medication and are recommended as the initial controller treatment for asthma. However, for many patients with persistent asthma, ICS may fail to achieve adequate control and an add-on therapy is needed. Clinical guidelines recommend adding a long acting $beta_2$ agonist (LABA) to ICS therapy in patients with moderate to severe asthma. Adding a LABA to therapy is generally effective than increasing the ICS dose. But, controversy exists regarding LABA safety as significant proportion of patients using LABA add-on therapy may remain inadequately controlled and at high risk of exacerbation. Increasing the ICS dose may be useful in some cases but is associated with local and systemic side effects

[8,9]. Thus, addition of an alternative controller medications like prostanoid and leukotriene modifiers to ICS would be an appropriate option [10,11].

Previous reports show that, seratrodast, a selective TXA_2 receptor antagonist, improves airway inflammation and bronchial responsiveness along with improvement in mucociliary clearance in mild to moderate asthmatic patients [3,12]. It also significantly improves the asthma symptoms, peak expiratory flow (PEF) and diurnal variation in PEF along with a significant reduction in the number of activated eosinophils in the bronchial mucosa [3].

Several placebo-controlled clinical studies have shown the effectiveness of seratrodast and montelukast in the treatment of asthma [3,6,13,14]. However there is no direct comparison demonstrating the efficacy and safety of seratrodast and montelukast in adult asthmatic patients. Therefore, we planned a randomized, double blind, double dummy, multi-center, comparative clinical trial to evaluate the efficacy and safety of seratrodast 80 mg as compared to montelukast 10mg in the treatment of mild to moderate asthma.

2. MATERIALS AND METHODS

2.1 Study Design

This was a prospective, randomized, double blind, double dummy, multi-center, comparative, parallel group, non inferiority study, conducted at 3 centers across India. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and Indian regulatory guidelines for conducting clinical trials (Schedule Y). The study was approved by institutional ethics committee of Chatrapati Shahuji Maharaj Medical University, Lucknow and Central Ethics Forum, an independent ethics committee located in Sion, Mumbai. A written informed consent was obtained from each participant before enrollment in the study. The study was sponsored by Zuventus Healthcare Ltd. and conducted through a clinical research organization called Genelife Clinical Research.

2.1.1 Clinical Trial Registry of India (CTRI)

This study has been registered with the Clinical Trial Registry of India: CTRI/2013/03/003504 http://ctri.nic.in/Clinicaltrials/rmaindet.php?trialid=3253&EncHid=28792.92343&modid=1&compid=19

The primary objective of the study was to demonstrate efficacy of seratrodast as compared to montelukast in the improvement of clinical, pulmonary and mucociliary parameters in adult asthma patients. Secondary objectives of the study were to compare the two treatments for safety and patient compliance.

Primary end points of the study were to assess the improvement in the following parameters: 1) clinical: Asthma symptom score ; 2) pulmonary: peak expiratory flow (PEF), forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) and 3) sputum and mucociliary: visco-elasticity, sputum fucose, albumin and eosinophil cationic protein (ECP) level. Outcomes were measured as the mean changes from baseline in the various lung function parameters; mean changes from baseline in the sputum parameters; mean change from baseline in the mucociliary clearance; proportion of patients showing an improvement in the severity of the clinical symptoms of asthma at week 4 and proportion of patients with adverse events associated with the drug.

2.2 Inclusion and Exclusion Criteria

Two hundred and five (n=205) non-smoking [15] male or female patients (age range, 18 to 65 years) with active bronchial asthma of mild to moderate severity, defined by National Asthma Education and Prevention Program, were recruited from the outpatient department. Patients were maintained on the lowest dose of an inhaled corticosteroid as monotherapy with FEV_1 > 60% of predicted normal value or Morning PEF > 60% of predicted value. Patients expectorating sputum >20 g/d for at least 2 weeks prior to the study were eligible for inclusion.

Among the exclusion criteria were: history of hypersensitivity to study medication; patients treated with a course of systemic or inhaled high dose corticosteroids or any other anti-inflammatory drugs, such as sodium cromoglycate or nedocromil sodium, during the previous 4 weeks; patients receiving either a short acting or long acting beta-2 agonists either as a monotherapy or in combination with a corticosteroids; patients receiving a course of antibiotics or mucolytic agents during the previous 4 weeks; patients showing evidences of pulmonary infection on chest radiograph and sputum bacteriology (bacteria > 107 /ml); pregnant and breastfeeding women, reproductive

age group women not using birth control measure; those with uncontrolled heart disease, thyroid disorders, coagulation disorders and hematologic problems.

2.3 Interventions and Randomization

Patients were randomized 1:1 to receive either montelukast 10 mg or seratrodast 80 mg for a period of 28 days along with placebo of the respective comparator drugs. Computer generated simple block randomization chart was used to randomize the eligible patients. Each patient was administered two tablets for 28 days; one tablet of either seratrodast 80 mg (Zuventus Healthcare Ltd, India) or montelukast 10 mg (MSN Laboratories, India) and a second tablet of placebo similar in appearance to the comparator in other arm. Patients were instructed to take both the tablets once daily in the evening after food in accordance with the prescribing information of the study medication. Patients were allowed to continue with their pre-randomization lowest dose inhaled corticosteroid therapy (budesonide 200 µg/ day; fluticasone 250 µg/ day) as per the dosage established under the supervision of the principal investigator. Study medications were labelled to ensure that both the patient and the investigator were blinded to the treatment allocation. Adherence to assigned regimen was assessed by recording the amount of returned investigational drug at the end of study. Treatment compliance was considered adequate, if patients have used at least 75% of scheduled doses. Use of analgesics, antibiotics, mucolytics and drugs acting on central nervous system was restricted during study period. Drugs like warfarin, theophylline, phenytion, bisphosphonates, itraconazole, diazepam, aminopyrine, corticosteroids and monoamine oxidase inhibitors were not permitted at any time during the study. Any other concomitant medications given to patients were recorded in the case report form.

2.4 Efficacy Assessments

The efficacy of both treatments was assessed based on the changes in the asthma symptom score, lung function parameters and sputum and mucociliary clearance score (SMCS) from the baseline. Asthma symptom score comprised of five parameters viz. wheezing score, shortness of breath score, expectoration score, cough score and chest tightness score on scale of 0-3 (0= No symptom; 1= mild - symptoms occurred > 2 days/week but not daily; 2= moderate - symptoms occurred daily, with minor limitation in normal activity; and 3= severe - symptoms occurred throughout the day, with extreme limitations in normal activity) thus total asthma symptom score ranged from 0 to 15 [16,17].

Pulmonary function tests were evaluated under three major categories viz. PEF, FEV_1 and FVC. Spirometry was performed at the baseline and at each follow up visit (week 2 and week 4). Each of these parameters was measured three times to ensure reproducibility. Best of the three readings was considered for evaluating the improvement in pulmonary function parameters.

To analyze sputum, at baseline and each follow up visit, the samples of sputum were collected and weighed and assessed for appearance and density. Its appearance was noted as 1= serous; 2= mucous; 3= mucopurulent; and 4= purulent and density as 1= fluid; 2= semi-fluid; 3= dense; and 4= very dense. The sputum was analyzed for biochemical parameters (ECP, fucose and albumin). At each visit the nasal clearance time (NCT) was determined in each patient using saccharin method. The time required to perceive a sweet taste, after placing a particle (1 mm in size) of saccharin 1 cm behind the anterior end of the inferior turbinate, was recorded. Same test was carried in other nostril after half an hour. Average of two readings was taken as nasal clearance time.

2.5 Safety and Tolerability Assessments

Adverse events were documented based on spontaneous reporting and investigator's assessment at each visit. Safety assessments included clinical or laboratory adverse events reported during the study period. Adverse events were coded using medical dictionary for regulatory activities (MedDRA) version 13.1. A need for hospitalization was considered to be serious adverse event and patient to be withdrawn from the study. The tolerability of the study medication was assessed based on the physician's and patient's opinion on a 4 point rating scale (1=excellent; 2=satisfactory; 3=good and 4=poor).

2.6 Sample Size

Sample size selection was based on a published clinical trial data of seratrodast 80 mg versus zafirlukast 20 mg as an add-on with inhaled corticosteroid treatment [18]. In order to

determine the efficacy of Seratrodast as compared to Montelukast, a non inferiority equivalence criteria was considered for this study. With a two-sided test at significance level 0.05 and 100 patients per treatment group, the study was determined to have 80% power to detect a difference between the treatment groups of at least 10 % in response rate.

2.7 Statistical Analysis

The demographic data was analyzed descriptively by using frequency distribution tables. All values were expressed as mean±standard deviation (SD), unless stated otherwise. All outcome indicators were normally distributed and analyzed with respect to the change in value from the baseline by using paired Student's t test. Comparisons between treatment groups were analysed using unpaired Student's t test and the statistical significance was considered at P = .05. All efficacy analysis were performed on the intention-to-treat (ITT) population, which included all patients who were randomized to receive at least one dose of either of the study medication and had efficacy data post baseline.

3. RESULTS

Of 205 patients, 103 were assigned to seratrodast treatment group and 102 to montelukast. During the treatment period, two patients had withdrawn their consent for continuation in the study; one from each group. These patients were considered as ITT population for efficacy analysis and were excluded from safety analysis (Fig. 1).

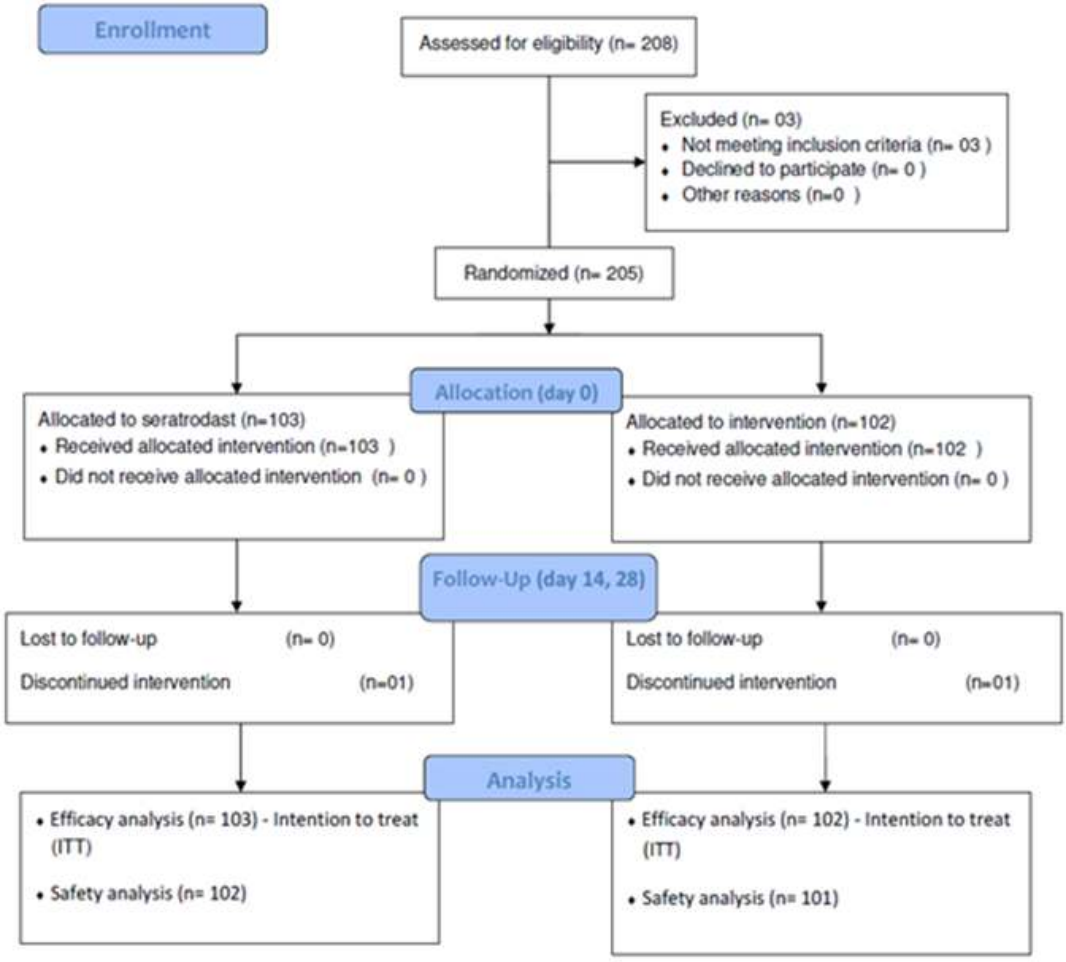

Fig. 1. Participant flow diagram
(The Consort chart representing the randomized comparative clinical trial)

3.1 Baseline Demographics and Characteristics

The baseline demographics and lung function characteristics of patients in both the groups were similar (Table 1). The mean age of the patients enrolled in the study was 44.71±12.89 and 42.47±12.2 years in montelukast and seratrodast treatment groups, respectively. All the enrolled patients were being maintained on low dose inhaled corticosteroid therapy (budesonide 200 µg/ day/ fluticasone 250 µg/ day), demonstrated FEV_1 > 60% and PEF > 60% of predicted values, as described in the inclusion criteria. The ICS use during the study period was recorded. In Montelukast group (n=102), 55 patients were maintained on budesonide 200 µg/ day and 47 were on fluticasone 250 µg/ day; similarly, in seratrodast group (n=103), 59 patients were maintained on budesonide 200 µg/ day and 44 were on fluticasone 250 µg/ day throughout the study period.

3.2 Efficacy Assessment

During the 4 week study period, patients were assessed for improvement in the clinical symptoms of asthma, lung function parameters, sputum and mucociliary clearance on day 0, day 14 and day 28.

3.2.1 Proportion of patients demonstrating improvement in asthma

Both, seratrodast and montelukast showed similar improvement in asthma symptoms after 4 weeks of therapy (Table 2). When evaluated on the basis of 'at least one parameter showing improvement', seratrodast demonstrated an efficacy of 99.03% as compared to 98.04% of montelukast, and the percentage of patients with improved asthma score was higher in seratrodast group as compared to montelukast (72.82% vs 66.66%; *P* = .05).The percentage of patients with improved PEF was significantly higher in seratrodast group as compared to montelukast (80.58% vs. 74.51%, *P* value= .01).

3.2.2 Clinical symptoms assessment

Although, both the treatments significantly improved the symptom score for all five major symptoms (wheezing, shortness of breath, expectoration, cough and chest tightness) from the baseline after a 4 week treatment period (*P*<.001), the improvement in expectoration score was found to be statistically significant in seratrodast group as compared to the montelukast treated patients (*P*=.01).

There was no significant difference between the groups in the reduction of total asthma score (*P* =.6*).* The changes in the mean symptom scores at baseline, day 14 and day 28 is given in Table 3.

3.2.3 Lung function tests

The effect of seratrodast and montelukast on lung function tests is shown in Table 4. Both the treatments significantly increased the mean values of FVC, FEV_1 and PEF from the baseline after a 4 week treatment period (*P*<.001). The difference in mean changes of FVC and FEV_1 was -0.004 Liters (L) (95% CI:-0.065 to 0.073, *P* = .91) and 0.029 L (95% CI: -0.106 to 0.048, *P* = .46) respectively. Seratrodast improved PEF better than montelukast, where the mean difference between the two groups was 0.416 L/s (Liters per second) (95% CI: 0.150 to 0.682; *P* = .01).

Table 1. Baseline characteristics and lung function tests of study patients

Characteristics	Montelukast 10 mg (n=102)	Seratrodast 80 mg (n=103)	*P*-value
No. of patients			
Male, n (%)	64 (62.7)	56 (54.4)	.25*
Female, n (%)	38 (37.3)	47 (45.6)	
Age, years (Mean±SD)	44.71±12.89	42.47±12.2	.22#
Body weight, Kg (Mean±SD)	61.52±14.60	60.10±14.33	.48#
BMI, kg/m^2 (mean±SD)	24.40±8.54	23.87±5.59	.13#
Lung function tests			
FVC (Liters)	2.580±0.552	2.463±0.608	.15#
FEV_1 (Liters)	1.994±0.365	2.008±0.494	.81#
PEF (Liters/second)	4.358±1.281	4.124±1.333	.78#

** Chi-square test; # unpaired Student's t test; BMI: Body mass index; FVC= Forced vital capacity; FEV_1 = forced expiratory volume in 1 second; PEF= Peak expiratory flow*

Table 2. Proportion of patients in seratrodast and montelukast treatment groups demonstrating improvement in asthma at week 4

Parameter (at 4 week)	Montelukast 10 mg (n=102)	Seratrodast 80 mg (n=103)	*P*-value
Patients with decreased asthma score, % (n)	66.66 (68)	72.82 (75)	.07
Patients with increased FVC, % (n)	82.35 (84)	79.61 (82)	.5
Patients with increased FEV_1, % (n)	82.35 (84)	82.52 (85)	.2
Patients with increased PEF, % (n)	74.51 (76)	80.58 (83)	.01
Patients with decreased nasociliary clearance score, % (n)	38.23 (39)	39.80 (41)	.2
Patients with improvement in all asthma parameters, % (n)	19.61 (20)	22.33 (23)	.1
Patients with improvement in at least one asthma parameter, % (n)	98.04 (100)	99.03 (102)	.2

FVC= Forced vital capacity; FEV_1 = forced expiratory volume in 1 second; PEF= Peak expiratory flow

3.2.4 Sputum analysis and mucociliary clearance

After a 28 days of treatment, the mean change in nasal clearance time from baseline was found to be -2.506 min (95% CI: -3.31 to -1.70) and -2.12 min (95% CI: -2.920 to -1.32) in montelukast and seratrodast group, respectively. Both the groups showed similar improvement in the nasal clearance time and sputum characteristics and there was no statistical difference (*P*=.4). Sputum laboratory tests showed better improvement in seratrodast group for ECP (*P* <.001) and albumin (*P* <.001) from the baseline values (Table 5).

'Investigator's global assessment' for drug efficacy having 4 categories showed 'excellent efficacy' in 18.6% and 19.41%, 'good efficacy' in 33.34% and 34.9%, 'satisfactory efficacy' in 46.07% and 44.66%, 'poor efficacy' in 1.9% and 0.9% of patients in montelukast and seratrodast groups respectively. No difference was observed in the overall drug compliance (99.02% for montelukast vs 98.06% for seratrodast).

3.3 Safety and Tolerability

Safety assessments were made at the end of week 2 and 4 after the start of treatment (n=203). Adverse events were reported in 39 subjects (38.23%) and 44 subjects (42.71%) in montelukast and seratrodast groups respectively. There was no statistically significant difference (*P*=.26) in the number of adverse events reported between the groups. The summary of the adverse events observed during the study is listed in Table 6.

All these adverse events were mild and resolved without any clinical intervention. The patients were followed up regularly until adverse events were completely resolved. No serious adverse events were reported during the study.

4. DISCUSSION

This was a multi-center, double blind, double dummy, randomized, comparative study with non inferiority design, to evaluate the efficacy and safety of seratrodast and montelukast in adult asthmatic patients. We found that treatment with either seratrodast or montelukast as an 'add on therapy' to inhaled corticosteroid (ICS), showed significant improvement in all major clinical symptoms of asthma, lung function tests, sputum and mucociliary clearance from baseline (*P* <.001). However, seratrodast was associated with greater improvement in PEF (*P* =.01) (Table 4) and a greater reduction in expectoration score (*P* =.01), ECP (*P* <.001) and sputum albumin levels (*P* <.001) as compared to montelukast (Tables 3, 5).

Clinical symptoms of asthma include wheezing, shortness of breath, expectoration, cough, and chest tightness. There was a significant improvement in these symptoms with both the drugs from the baseline, at day 14 and day 28 (*P* <.001). There was no significant difference between the treatment groups in the reduction of total asthma score (*P* =.6*)* (Table 3). Similar results were observed by Xin Li et al. [19]. However, the reduction in expectoration was found to be significantly better in seratrodast group (*P*=.01) and this observation is in line with the findings of Ishiura et al where a 4 week clinical trial showed better improvement in cough threshold with seratrodast as compared to pranlukast [20]. The superior efficacy of

seratrodast as compared to leukotriene antagonists in reducing expectoration might be attributed to the inhibitory action on TXA_2 but not on CysLTs receptor mediated sputum production [20].

TXA_2 is a biologically potent arachidonic acid metabolite derived from the cyclo-oxygenase pathway [7]. It is a strong bronchial smooth muscle spasmogen and it is implicated in airway inflammation, impairment of mucociliary clearance, increased microvascular leakage, smooth muscle proliferation and in the genesis of bronchial hyperresponsiveness [6]. Seratrodast is a competitive, long acting TXA_2 receptor antagonist developed and marketed as an effective anti-asthmatic agent in Japan since 1997 [11]. Japanese Guideline for Adult Asthma recommends the use of seratrodast as a controller medication [21]. Several randomized clinical trials in asthma patients demonstrated a reliable efficacy of seratrodast in improving clinical symptoms and airway hyper-responsiveness by reducing airway inflammation [3,4,6,7].

It is known that eosinophilic airway inflammation is a hallmark characteristic of bronchial asthma [22]. Infiltrating eosinophils release various chemical mediators and cytotoxic proteins like ECP which are found to be responsible for bronchoconstriction, mucus hypersecretion, bronchial edema, epithelial damage and airway hyperreactivity. Airway inflammation can be directly assessed by measuring the ECP level in sputum [23]. TXA_2 was found to increase the eosinophil degranulation resulting in greater ECP release [24]. Moreover, activation of prostanoid TP (Thromboxane) receptors exacerbates the inflammation of the airways by synthesis and release of eosinophilic chemokines [25]. This suggests that TXA_2 is an important mediator in the regulation of eosinophil degranulation, and might prove to be a beneficial target in the treatment of bronchial asthma. ECP levels in sputum are significantly increased in asthmatic patients and directly correlated to the severity of asthma. Studies also report that high sputum ECP levels are associated with deterioration of previously well controlled asthma [26]. In addition, ECP levels were found to be significantly correlated with the parameters of airway obstruction such as PEF, FVC, FEV_1, airway responsiveness, number of inhaler puffs needed and patient's symptom scores [24].

Fukuoka et al. demonstrated a significant reduction in ECP concentration with seratrodast treatment and its withdrawal resulted in increased ECP levels [27]. Consistent with other published reports on the effect of seratrodast in reducing airway inflammation via ECP inhibition [3,27], the current study also showed reduced sputum ECP concentration with seratrodast therapy (P <.001) (Table 5). These results suggest that seratrodast is useful as an anti-inflammatory agent in the management of bronchial asthma.

Measurement of PEF is important in identifying airflow limitation. The correlation between airflow and symptoms is variable, some patients being poor perceivers of changes in airway patency, whereas others quickly perceive small changes. Recording PEF is therefore, of value in clinical practice where it can be helpful in monitoring the progress of airflow limitation, assessing its severity and the effects of treatment [28]. We observed the improvements in PEF after 28 days in both seratrodast and montelukast group, where the improvement was significantly more in seratrodast group. (0.614 L/sec Vs. 0.199 L/sec; P=.01) (Table 4). This improvement in PEF is in line with the previous findings, which shows that the addition of seratrodast to the ICS therapy significantly improved PEF [3,26,27].

In present study, significant PEF improvement seen in seratrodast group is not accompanied by increase in FEV_1 or FVC. Literature review of published data reveals that relationship between PEF & FEV_1 is not established and it is not possible to predict FEV_1 from PEF or vice versa [29–31]. Across the spectrum of the severity of airflow obstruction there is considerable variability between measurements of FEV_1 and PEF when expressed as % predicted, such that the FEV_1 may be as much as 35% lower or up to 15% higher than the PEF for patients with obstructive lung diseases [30]. Evidence indicates that significant changes in PEF without being accompanied by significant changes in FEV_1 (and vice-versa) are not uncommon in asthmatic subjects [32].

Table 3. Changes in the mean symptom scores from baseline, on day 14 and day 28 in both study groups

Seratrodast study group	**Wheezing**	**Shortness of breath**	**Expectoration**	**Cough**	**Chest tightness**	**Total asthma score**
Baseline (mean±SD)	1.4±0.8	1.5 ±0.8	1.5±0.6	1.6±0.6	1.3±0.8	7.3±2.8
Day 14 (mean±SD)	1.0±0.7	1.3±0.8	1.2±0.7	1.2±0.6	1.0±0.7	5.6±2.7
Mean Change from baseline (Day 0-14, 95% CI)	-0.3* (-0.4 to -0.2)	-0.3*(-0.4 to -0.1)	-0.4*(-0.5 to -0.2)	-0.4*(-0.5 to -0.2)	-0.3*(-0.4 to -0.2)	-1.7*(-2.2 to -1.2)
Day 28 (mean±SD)	0.9±0.7	1.1±0.7	0.8±0.5	1.0±0.6	0.9±0.7	4.6±2.6
Mean Change from baseline (Day 0-28, 95% CI)	-0.5*(-0.6 to -0.4)	-0.4*(-0.5 to -0.2)	-0.7*(-0.8 to -0.4)	-0.6*(-0.7 to -0.5)	-0.4*(-0.5 to -0.2)	-2.8*(-3.4 to -2.2)
Montelukast study group	**Wheezing**	**Shortness of breath**	**Expectoration**	**Cough**	**Chest tightness**	**Total asthma score**
Baseline (mean±SD)	1.4±0.7	1.5 ±0.8	1.5±0.6	1.6±0.6	1.4±0.7	7.5±2.5
Day 14 (mean±SD)	1.1±0.7	1.3±0.8	1.2±0.7	1.2±0.7	1.1 ±0.8	5.9±3.0
Mean Change from baseline (Day0-14, 95% CI)	-0.3*(-0.5 to -0.2)	-0.2*(-0.3 to -0.1)	-0.3*(-0.4 to -0.2)	-0.4*(-0.5 to -0.3)	-0.3*(-0.5 to -0.2)	-1.6*(-2.2 to -1.1)
Day 28 (mean±SD)	0.9±0.6	1.1±0.7	1.0±0.7	1.1±0.6	0.9±0.7	5.0±2.6
Mean Change from baseline (Day 0-28,95% CI)	-0.5*(-0.7 to -0.4)	-0.4*(-0.5 to -0.2)	-0.5*(-0.8 to -0.4)	-0.6*(-0.7 to -0.4)	-0.5*(-0.6 to -0.3)	-2.6*(-3.1 to -1.9)
Mean change diff in Monte vs Sera groups (Day 0-14, 95% CI)	0.0(-0.2 to 0.2)	0.0(-0.2 to 0.1)	-0.1(-0.3 to 0.1)	0.0(-0.1 to 0.2)	0.1(-0.1 to 0.3)	-0.1(-0.8 to 0.7)
Mean change diff in Monte vs Sera groups (Day 0-28, 95% CI)	0.0(-0.2 to 0.2)	0.0(-0.2 to 0.2)	-0.2 †(-0.3 to 0.1)	0.0(-0.2 to 0.2)	0.1(-0.1 to 0.3)	-0.3(-1.1 to 0.6)

**P <.001vs baseline (paired t test); † P =.01 between groups (unpaired t test)*

Table 4. Lung function tests after 28 days of montelukast and seratrodast treatment

Montelukast study group	**FVC (L)**	**FEV_1 (L)**	**PEF (L/s)**
Baseline (mean±SD)	2.615±0.5	1.994±0.3	4.188±1.2
Day 14 (mean±SD)	2.720±0.5	2.102±0.4	4.271±1.2
Mean Change (Day 0-14, 95% CI)	0.105 *(0.060 to 0.151)	0.108*(0.071 to 0.145)	0.083(-0.073 to0.239)
Day 28 (mean±SD)	2.792±0.5	2.232±0.4	4.387±1.2
Mean Change (Day 0-28, 95% CI)	0.177*(0.134 to 0.221)	0.217*(0.168 to 0.308)	0.199*(0.135 to 0.606)
Seratrodast study group	**FVC (L)**	**FEV_1 (L)**	**PEF (L/s)**
Baseline (mean ±SD)	2.463±0.6	1.984±0.4	4.135±1.3
Day 14 (mean±SD)	2.576 ±0.6	2.111±0.5	4.519±1.6
Mean Change (Day 0-14, 95% CI)	0.113*(0.065 to 0.161)	0.127(0.079 to 0.175)	0.384*(0.147 to 0.621)
Day 28 (mean±SD)	2.644 ±0.6	2.172±0.5	4.749±1.6
Mean Change (Day 0-28, 95% CI)	0.181*(0.128 to 0.235)	0.188*(0.138 to 0.239)	0.614*(0.397 to 0.832)
Mean change diff in Monte vs Sera groups (Day 0-14, 95% CI)	0.008(-0.058 to 0.074)	0.019(-0.041 to 0.079)	0.301(0.016 to 0.586)
Mean change diff in Monte vs Sera groups (0-28, 95% CI)	-0.004(-0.065 to 0.073)	0.029(-0.106 to 0.048)	0.416†(0. 15 to 0.682)

**P <.001vs baseline (paired t test); † P =.01 between groups (unpaired t test); L=Liters; L/sec=Liters per second*

Table 5. Summary of sputum analysis

Montelukast study group	Fucose (mg/ml)	ECP (ng/ml)	Albumin (mg/dl)
Baseline (mean±SD)	0.246±0.02	35.40±3.76	86.34±4.99
Day 14 (mean±SD)	0.235±0.01	21.68±4.60	71.70±4.44
Mean Change (Day 0-14, 95% CI)	- 0.011*(-0.017 to - 0.005)	-13.71*(-14.63 to -12.79)	-14.63*(-15.67 to -13.60)
Day 28 (mean±SD)	0.221±0.01	11.84±4.37	53.52±4.86
Mean Change (Day 0-28, 95% CI)	-0.025*(-0.03 to -0.01)	-23.55*(-24.64 to -22.47)	-32.82*(-34.09 to -31.55)
Seratrodast study group	**Fucose (mg/ml)**	**ECP (ng/ml)**	**Albumin (mg/dl)**
Baseline (mean ±SD)	0.245±0.01	36.18±3.37	89.35±4.96
Day 14 (mean±SD)	0.235±0.01	17.83±3.98	73.92±3.29
Mean Change (Day 0-14, 95% CI)	-0.010*(-0.013 to -0.006)	-18.35*(-19.36 to -17.35)	-15.42*(-16.44 to -14.41)
Day 28 (mean±SD)	0.223±0.01	8.989±4.41	51.84±6.19
Mean Change (Day 0-28, 95% CI)	-0.022*(-0.026 to -0.019)	-27.20*(-28.38 to -26.01)	-37.51*(-39.20 to -35.81)
Mean change diff in Monte vs Sera groups (Day 0-14, 95% CI)	-0.001(-0.0056 to -0.0077)	-4.641†(-5.996 to -3.285)	-0.79(-2.232 to - 0.6952)
Mean change diff in Monte vs Sera groups (Day 0-28, 95% CI)	0.0023(-0.0046 to -0.0091)	-3.642 †(-5.242 to -2.043)	-4.685 †(-6.792 to -2.579)

**P <.001vs baseline (paired t test); † P <.001 between groups (unpaired t test)*

Table 6. Adverse events reported during the study period

Adverse event	Montelukast adverse event n=60 (patients n= 39)	Seratrodast adverse event n=63 (patients n= 44)
Alanine aminotransferase (ALT) increased	18	26
Aspartate aminotransferase (AST) increased	13	11
Eosinophil count increased	7	4
Leukocyte count increased	13	14
Lymphocyte count increased	1	-
Platelet count decreased	2	1
Serum creatinine increased	5	-
Abdominal distention	1	-
Acne	-	1
Dizziness	-	1
Headache	-	1
Dyspnea	-	1
Nausea	-	1
Vomiting	-	1
Diarrhoea	-	1

Seratrodast not only inhibits bronchoconstriction induced by TXA2, prostaglandin D2 (PGD2) and prostaglandin F2α (PGF2α), which is mediated through a TXA2 receptor, (prostanoid pathway) but also that induced by leukotriene C4 (LTC4), leukotriene D4 (LTD4) and antigen, which is mediated in part through TXA2 synthesis (leukotriene pathway) [33,34]. In contrast, montelukast selectively binds the Cysteinyl leukotriene receptor$_1$ (CysLT$_1$) and inhibits actions of only LTD$_4$ [35]. This multi-receptor blockade by seratrodast might be the reason for higher PEF improvement seen in seratrodast group as compared to montelukast. Therefore, blockade of TXA$_2$ receptors could be considered as an alternate to the leukotriene antagonism in the management of asthma.

It has been shown that mucociliary transport function is generally disturbed in asthmatic patient which increases accumulation of bronchial secretions and forms mucus plugs leading to airway obstruction and exacerbation of asthma. Fucose is a marker of glycoproteins in the mucus [36]. It determines the viscosity of the sputum. More fucose means more viscous sputum and lesser mucociliary clearance [37]. In the current study fucose levels in sputum were reduced after the seratrodast and montelukast treatment (P <0.001) (Table 5).

Albumin is regarded as a marker of sputum viscosity which agglutinates individual cilia and destroys coordinated ciliary motion leading to impairment of mucociliary clearance [33]. Plasma protein leakage (sputum albumin) in the airways is correlated with airway inflammation, severity of asthma and PEF values [24,27]. In the current study sputum albumin concentration measured in patients treated with seratrodast was significantly lower than that of montelukast, indicating pronounced attenuation of microvascular permeability and reduction of albumin leakage into the mucosa associated with airway inflammation. These results are in accordance with the earlier clinical trials [38], confirming the role of seratrodast in improving mucociliary clearance and reducing bronchial inflammation.

Patient compliance and drug safety was similar in both treatment groups. The common adverse events reported were increase in the hepatic enzymes, in patients treated with montelukast and seratrodast (Table 6). The number of cases reported to have elevated liver enzymes did not differ between the two groups (P=.29).

This study has elucidated the potential of seratrodast in the improvement of eosinophilic chemokines mediated airway inflammation, lung function parameters, clinical symptoms, airway hyperresponsiveness, plasma protein leakage (sputum albumin) and mucociliary clearance. Given the treatment benefits achieved with seratrodast, this controller medication can potentially help in better management of asthmatics.

5. CONCLUSION

Seratrodast, a TXA$_2$ receptor antagonist, was found to be better in the improvement of PEF, Reduction in expectoration, ECP and albumin levels as compared to montelukast. Seratrodast can be recommended as a controller medication in mild to moderate asthma.

DISCLAIMER

The abstract of this manuscript was presented in the conference.

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“http://onlinelibrary.wiley.com/store/10.1111/resp.12416_6/asset/resp12416_6.pdf?v=1&t=igt56pv1&s=21d4df912a835f0f85d548fc65bd161760874fbd”

ETHICAL APPROVAL

The study was approved by institutional ethics committee of Chatrapati Shahuji Maharaj Medical University, Lucknow and Central Ethics Forum, an Independent Ethics Committee located in Sion, Mumbai.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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