The Association of Physicians of India
Indian College of Physicians


# Postgraduate Medicine

## Advances In Clinical Medicine Including Prevention

Volume XXVII
2013

*Editor*
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# Thromboxane A2 Receptor Blocker, Seratrodast: A Novel Controller Medication For The Management Of Asthma

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**Introduction:**

Asthma is a chronic inflammatory disease of the airways that is characterized by widespread obstruction of the airways, usually reversible, and bronchial hyper-responsiveness. As per GINA, Japanese and ICSI guidelines for management of asthma, medications to treat asthma can be classified as relievers or controllers. Relievers are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve its symptoms [1,2]. They include rapid-acting inhaled β2-agonists, inhaled anticholinergics, short-acting theophylline, and short-acting oral β2-agonists. Controllers are medications taken daily on a long-term basis to keep asthma under clinical control chiefly through their anti-inflammatory effects [1,2]. They include inhaled and systemic glucocorticosteroids, leukotriene modifiers, long-acting β2-agonists, sustained-release theophylline, cromones and anti-IgE.

"Inadequate control of asthma" was determined to be the common cause of the results obtained in the afore mentioned surveys, which was corroborated by other studies wherein patients had uncontrolled asthma despite guideline-based use of inhaled corticosteroids (ICS) and inhaled long-acting β2-agonists (LABAs) [3]. With respect to rise in uncontrolled asthma, the 2002 GINA guidelines stated: "it is reasonable to expect that in most patients with asthma, control of the disease can and should be achieved and maintained" [1]. To meet this challenge, the recent GINA guidelines of year 2011, not only incorporates updated scientific information but also describes a development of the aforementioned theme and a change in approach to asthma management, with asthma control, rather than asthma severity, being the focus of treatment decisions. The GINA guidelines define control of asthma as minimal chronic symptoms, minimal (infrequent) exacerbations, no emergency visits, minimal use of as-needed (rapid-acting) β2-agonists, no limitations on activities, daily peak expiratory flow (PEF) variation of less than 20%, near normal PEF and minimal adverse effects from medications [1,2]. In the stepwise approach to therapy recommended in the GINA guidelines, a reliever medication (rapid-onset bronchodilator, either short-acting or long-acting) should be provided for quick relief of symptoms. However, regular use of reliever medication is one of the elements defining uncontrolled asthma, and indicates controller treatment should be increased.[4].

Thus reducing or eliminating the need for reliever treatment is an important GINA goal and a measure of success of treatment, which is achieved by long-term management of asthma with controller agents[1,2]. Controllers alleviate and eliminate asthma symptoms, and normalize and maintain the conditions. As mentioned earlier they include inhaled and oral corticosteroids, long-acting β2 agonists (LABA), leukotriene receptor antagonists (LTRAs), theophylline, anti-IgE antibody, H1 receptor antagonists, Th2 cytokine inhibitor and last but not the least thromboxane A2 modulators.

**Thromboxane A2 & Thromboxane A2 Receptor in the Pathogenesis of Asthma**

Thromboxane A2 (TXA2), a cyclooxygenase product of arachidonic acid, has been implicated in the

pathogenesis of asthma. The recent demonstration that in man all the bronchoconstrictor prostanoids exert their effects by binding to the TXA2 receptor (TP receptor) has aroused a renewed interest in the role of TXA2 and TP receptor-related prostaglandins in asthma. In addition, the recent development of specific and potent TP receptor antagonists and inhibitors of thromboxane synthase (TX synthase) has provided tools to assess the role of these mediators in the pathophysiology of asthma [52]. Both GINA[10,11] and Japanese guidelines for management of asthma [95] have indicated the use of TXA2 modulators as controllers as step 1 for long-term management of asthma.

**Cellular origin of TXA2**

TXA2 is synthesized by enzyme TX synthase, which has been found to be associated with alveolar macrophages [5, 6], bronchial epithelial cells and human lung fibroblasts. In addition to alveolar macrophages, TXA2 is the major product of the cyclooxygenase pathway in three types of human blood cells: platelets [7,8], eosinophils [9] and monocytes [10,11]. The eosinophils, which infiltrate the airway wall in asthma, are also an important source of TXA2 since human blood eosinophils obtained from asthmatics generate and release much more TXA2 than the other cyclooxygenase metabolites under resting conditions or after activation by PAF [12]. In addition, TXA2 originated from platelets may contribute to lung inflammation in asthma. Close association between platelets, eosinophils and monocytes or alveolar macrophages has been observed causing increase in TXA2 production [13].

**Heterogeneity of TP receptors**

Prostanoid TP receptors are distributed in both plasma membrane and cytosolic compartments. They are found in tissues rich in vasculature such as lung, heart, and kidney. Two G protein-coupled isoforms of this receptor have been subsequently described, TPα (placental/platelet) and TPβ (endothelial) that differ in length and sequence of the carboxyl-terminal tail distal to Arg328. Intra-receptor differences in C-terminal tail sequence allows for significant differences in their ability to internalize in response to agonist exposure [14]. For eg. TXA2 mimetic (analogue) was observed to bind to TPβ and not TPα.

**Biological activities of TXA2 and related PGs in airways**

1. **Bronchial Smooth muscle contraction**

Ligand binding studies on TP receptors have shown their existence on airway smooth muscle. Comparisons of the in vitro contractile potencies of TXA2 mimetic, PGF2α, PGD2 and 9α,11β-PGF2 on airway smooth muscle have shown that the TXA2 analogue is about two orders of magnitude more potent than the other PGs [15-17]. Experiments utilizing several TXA2 receptor antagonists have further supported the view that not only the TXA2 mimetic but also PGF2α, PGD2 and its metabolite 9α,11β-PGF2 contract bronchial smooth muscle by acting via direct stimulation of TP receptors. Thus, TXA2 and other prostanoids play an important role in airway smooth muscle contractions.

2. **Vascular smooth muscle contraction**

TXA2 is one of the most potent constrictors of human vascular smooth muscle as illustrated by its in vitro potency and efficacy on internal mammary arteries or saphenous veins [18,19]. The picture appears more complex than for the airway smooth muscle because different prostanoid receptors are involved in the control of the vascular tone and because the prostanoid effects vary with species, vascular sites and age. However, activation of vascular TP receptors invariably induces vasoconstriction.

3. **Plasma Extravasation**

TXA2 mimetic and with less potency, PGF2α, were found to potently induce plasma exudation in airways[20]. Plasma exudation induced by inhaled PAF or by leukotriene D4 (LTD4) instilled via the airway route was observed to be partly inhibited by TX synthase inhibitor and TP receptor antagonists, suggesting that TXA2 is endogenously released in response to inflammatory mediators other than prostanoids resulting in airway microvascular leakage.

### 4. Neuromodulatory effects

Prostanoids have potent neuromodulatory effects. Thromboxane receptor agonists were observed to elevate electrically induced norepinephrine release in an isolated arterial preparation, suggesting that TXA2 and related prostaglandins may have some vascular effects on adrenergic fibres that have been found to be in close association with bronchial vessels [21]. TXA2 has also been implicated in acting presynaptically to enhance the release or duration of release of acetylcholine, a potent bronchoconstrictor, from cholinergic nerves [21].

### 5. Mucous secretion

In human airway tissue implants, PGF2? and PGD2 significantly increased mucous glycoprotein release[22,23]. In addition, TXA2 was shown to increase tracheal mucous gel layer, which was inhibited by TP receptor antagonist. In the same study, the TP receptor antagonist was observed to attenuate mucous gel layer response caused by leukotrienes, indicating an indirect link between leukotrienes and TP receptors [24].

### 6. Smooth muscle proliferation

TXA2 elicits the proliferation of human airway smooth muscle cells as well as vascular smooth muscle cells [25,26]. It may therefore participate in airway remodeling in asthma that includes airway smooth muscle hypertrophy and hyperplasia [27].

### 7. Airway hyperresponsiveness

The effects of TXA2 and related PGs on plasma exudation, acetylcholine release and smooth muscle proliferation support the potential role of TP receptor stimulation in the pathogenesis of airway hyperresponsiveness [28]. The airway mucosal edema due to plasma exudation and the smooth muscle proliferation contribute to thickening of the airway wall. In addition, plasma exudation may lead to liquid filling of the airway interstices formed between luminal epithelial projections. This liquid filling of airway interstices amplify the luminal narrowing due to airway smooth muscle contraction. The enhancing effect of TXA2 on cholinergic transmission is also a possible mechanism by which TXA2 may cause airway hyperresponsiveness [28].

Various thromboxane synthase inhibitors have been shown to prevent increased airway reactivity to allergens [29], PAF (30), LTC4, D4 [31,32] and B4 [33], bradykinin [34], endothelin [35], endotoxin [36] and ozone [37]. It has been suggested that these mediators induce airway hyperresponsiveness through the generation of TXA2, in parallel with other effects on the airway smooth muscle [38].

### 8. TXA2 in COPD

TXA2 is also involved in pathogenesis of COPD. It was demonstrated in patients with COPD that urinary excretion of 11-dehydro-TXB2, a TXA2 metabolite, was significantly higher than in healthy subjects, suggesting an enhancement of platelet TXA2 biosynthesis in such patients [39]. Thromboembolic events as pulmonary hypertension are complications of COPD and TXA2 may play an important role in these complications. It was shown that TXA2 level is significantly increased in patients suffering from COPD with pulmonary hypertension in comparison with that of normal subjects, suggesting TXA2 plays an important role in causing pulmonary hypertension [40].

The above biological activities of thromboxane A2 indicate that TXA2 is involved in various steps in progression of asthma. More importantly the direct action of prostanoids (TXA2, PGF2$\alpha$, PGD2 and its metabolite 9$\alpha$,11$\beta$-PGF2) via activation of TP receptors and the indirect action of leukotrienes and other agents on TP receptors through intricate pathways, give a new insight into the mechanisms underlying pathogenesis of asthma and suggest the importance of TP receptor modulation for management of asthma.

**Pharmacology Of Txa2 Modulators In Asthma**

Strategies for inhibition of TXA2 include inhibition of thromboxane synthase and antagonism of TP receptors.TX synthase inhibitors effectively suppress TXA2 synthesis; however, inhibition of TX synthase results in an increased availability of the precursor PGH2 with the possibility of prostanoid synthesis redirection from TXA2 to other prostaglandins according to the enzyme equipment of the cells [41].

Therefore, accumulated PGH2 or increased synthesis of prostaglandins, such as PGF2α and PGD2, may substitute for TXA2 in causing TP receptor stimulation or may increase the stimulation of other prostanoid receptors with a resulting reduction in the potential effects of TX synthase inhibition [41].

Bleeding tendency is one of the possible adverse effects of anti-TXA2 agents due to suppression of platelet aggregation. This is much more pronounced with TX synthase inhibitors because PGI2 production, which has anti-platelet aggregation activity, is enhanced by pathway blockade from PGH2 to TXA2 by TX synthase inhibitors [42].

**Thromboxane A2 receptor (TP receptor) antagonism**

As indicated earlier, the second way of modulation of TXA2 is by antagonizing TP receptors, which is better and safer than TX synthase inhibition. TP receptor antagonists not only inhibit the actions of TXA2, but also inhibit the activation of TP receptors by other prostanoids (PGF2α, PGD2 and its metabolite 9α,11β-PGF2). Additionally, TP receptors antagonists also act on the intricate pathways involved in activation of TP receptors by allergens, PAF, leukotrienes, bradykinin, endotoxin, endothelin and ozone.

**Seratrodast**: It is an orally active quinone derivative and a potent TP receptor antagonist [43-47]. It was the first thromboxane receptor antagonist that was developed as an anti-asthmatic drug and received marketing approval in Japan in 1997, and has been in use from past 15 years as a controller therapy in the management of asthma.

Seratrodast has been shown to inhibit bronchoconstriction induced by TXA2, PGD2, 9α,11β-PGF2, PGF2α, leukotriene D4 (LTD4) and PAF [43, 44, 48], and has been observed to affect both immediate and late asthmatic responses [47, 49]. Seratrodast has been reported to reduce airway hyper-responsiveness to various stimuli [47, 49-51]. Seratrodast abolished the decrease in internal diameter of pulmonary arteries caused by vagal nerve stimulation or injection of acetylcholine [48]. Seratrodast administered orally at doses of 1-10 mg/kg 1 h before the challenge with antibody clearly inhibited the pulmonary pressure increase caused by Forssman anaphylaxis. At a dose of 10 mg/kg, seratrodast also inhibited the pulmonary pressure increase caused by LTD4 and TXA2 mimetic [52].

Pharmacokinetic profile of Seratrodast in plasma was determined in an open labeled, two treatment, two period, two sequence, single dose, comparative, randomized, two way crossover design under non fed condition with 14 days washout period in 26 healthy male subjects [53]. Seratrodast showed a long half of 22 hours with an approximate of 3.5 hours to attain maximal plasma concentration.Clinical studies of Seratrodast have been conducted on approximately 5000 patients (post-marketing surveillance study on 3000 patients and clinical studies in approximately 2000 patients) in various indications like asthma, chronic bronchitis, chronic pulmonary emphysema, perennial allergic rhinitis, and chronic cough (table-1).

**Table 1: Clinical studies on Seratrodast**

| SN | Test drug | Study Design | Duration of the study | Patients | Conclusion |
|---|---|---|---|---|---|
| 1 | Seratrodast 80 mg Vs Montelukast 10 mg | Double-blind, double dummy Randomized | 4 weeks | 205 Indian patients with Asthma on ICS therapy | 1. Significant improvement in FEV1, FVC and PEF; and in clinical symptoms of asthma such as Wheezing, shortness of breath, expectoration and chest tightness were observed 2. Greater reduction in sputum parameters such as levels fucose, ECP, albumin and expectoration as compared to Montelukast (54) |
| 2 | Seratrodast 80mg Montelukast 10mg | Double-blind, randomized | 8 weeks | 213 Asthma patients | Seratrodast is safe, and effective drug in treating patients with asthma and possesses reliable efficacy and safety similar to montelukast. (55) |
| 3 | Seratrodast 40 Zafirlukast 20 | Double-blind, randomized, Multi centric | 6 weeks | 220 Asthma patients | The control rate of seratrodast (71.68%) was significantly higher than that of zafirlukast (62.62%). (56) |
| 4 | Seratrodast 80mg od, Placebo, Pranlukast 112.5 mg t.i.d. | Randomized cross- over trial | 4 weeks | 16 Chronic Bronchitis patients | The cough threshold was significantly increased compared with placebo after four-week treatment with seratrodast, but not after treatment with pranlukast.<br>Thromboxane antagonism may be considered to be one of the therapeutic options for the treatment of chronic productive cough. (57) |
| 5 | Seratrodast 80mg OD | Open-label, crossover design study | 12 weeks | 10 Asthma patients | i. Seratrodast decreased the concentration of ECP in sputum significantly ($p < 0.05$).<br>ii. Seratrodast improves clinical symptoms and airway hyperresponsiveness by reducing airway inflammation. (58) |
| 6 | Seratrodast 80mg o.d. | Open label study | 8 weeks | 14 Chronic pulmonary Emphysema patients | i. The results revealed significant improvement of respiratory distress, evaluated on both the Hugh- Jones classification and the Borg scale, at week 8.<br>ii. Among the respiratory function parameters examined, only FVC was significantly improved. (59) |
| 7 | Seratrodast 80mg o.d. | | 24 months | 35 Asthma patients | The exacerbation rate in patients taking seratrodast after 12 months tended to be lower than in the other two patient groups ($P = 0.0743$).<br>In seratrodast group, the average dose of iBDP from 9 to 24 months after the initial step down was significantly lower than before the step down ($P < 0.0001$) and was not significantly different from the mean dose of iBDP in groups A or B. (60) |

| SN | Test drug | Study Design | Duration of the study | Patients | Conclusion |
|---|---|---|---|---|---|
| 8 | Seratrodast 40mg o.d., Placebo | Double blind, randomized | 6 weeks | 45 Asthma patients | i. Seratrodast treatment decreased the amount of sputum (p = 0.005), dynamic viscosity (p = 0. 007), and albumin concentration (p = 0.028).<br>ii. Nasal clearance time of a saccharin particle was shortened in the seratrodast group at week 4 (p = 0.031) and week 6 (p = 0.025), compared with the placebo group. (61) |
| 9 | Seratrodast 80mg/d Terfenadine 120 mg/d | Double-blind Multi-center | - | 234 Allergic Rhinitis patients. | The improvement rate of nasal obstruction nasal discharge and sneezing at the final evaluation in the seratrodast group was significantly superior to Terfenadine group, 51.4% vs. 34.7% (p=0.016). (62) |
| 10 | Seratrodast 40mg o.d. | Open label study | 4 weeks | 45 Asthma patients | The ratio of urinary eicosanoids might be a possible predictor of the effects of TXA2 receptor antagonist. (63) |
| 11 | Seratrodast 80mg o.d., Placebo | Double blind, randomized, | 4 months | 31 Asthma patients | Seratrodast in asthma may inhibit activated eosinophil infiltration in part by modulating the expression of chemokines in bronchial tissues. (64) |
| 12 | Seratrodast 80mg/d or 120mg/day | Double blind, randomized | 8 weeks | 183 asthma patients | i. Seratrodast at a dose of 120 mg daily produced an increase in forced expiratory volume in 1 second (FEV1) from baseline that was linearly correlated with its plasma concentrations<br>ii. A lower percentage of predicted FEV1 (i.e., more severe obstruction) was associated with higher slopes, and greater increases in FEV1. (65) |
| 13 | Seratrodast 20/40/80mg/d | Randomized, | 4 weeks | 155 allergic rhinitis patients | Improvement rates for nasal obstruction, nasal discharge and sneezing showing "marked improvement" or better in the 20mg, 40mg, and 80mg daily doses. (66) |
| 14 | Seratrodast 4mg/day, 40mg/day or 80mg/day | Multi-center, Double-blind Comparative Study | 4 weeks | 224 Allergic Rhinitis | Improvement rate evaluation of nasal symptoms, was dose-dependently.In the subject group whose main complaint was nasal obstruction & duration of disease was 1 year or longer, improvement rate in nasal symptoms (final evaluation) was similarly dose-proportional. (67) |
| 15 | Seratrodast 80mg/day | Open label study | 12-24 weeks | 19 Allergic Rhinitis | Seratrodast appears to be highly effective in treating perennial allergic rhinitis and safe in a long-term period. (68) |

| SN | Test drug | Study Design | Duration of the study | Patients | Conclusion |
|---|---|---|---|---|---|
| 16 | Seratrodast 20 or 80mg/day | | 4 weeks | 38 Allergic Rhinitis | 1) In the 80mg/day group, changing rates of nasal volume and minimum cross section showed significant improvement after 4 weeks.<br>2) Improvement rate in nasal obstruction in the 80mg/day group was higher than that in the 20mg/day group. 69 |

**Discussion**

TXA2 is an important mediator in the regulation of eosinophil degranulation [70]. TXA2 increases eosinophil degranulation resulting in greater ECP release. Seratrodast decreased (ECP) concentrations in sputum of asthma patients [54]. The decrease in ECP levels with Seratrodast was significantly greater than that observed with Montelukast (-27.20 vs. -23.55 ng/ml, $p<0.05$) indicating dominance of TXA2 over leukotrienes in modulating eosinophil degranulation (54). This implies that TP receptor antagonism may have a better impact than cyteinyl leukotriene receptor antagonism over severity of asthma.

**Effect on airway microvascular leakage**

In patients with asthma, plasma-protein leakage in the airway appears to correlate with indirect indexes of airway inflammation [71]. Being a major plasma protein, albumin level in sputum has been suggested to be a biochemical marker for microvascular leakage [72]. In a 4-week comparative clinical trial conducted in 205 Indian patients [54], significantly greater reduction in sputum albumin levels were observed with Seratrodast compared to Montelukast (-37.51 vs. -32.82 mg/dl, $p<0.05$).

**Effect on dynamic viscosity and elasticity of sputum**

In various studies, sputum fucose levels have been used as biochemical marker for viscosity and elasticity of respiratory mucus [73]. Fucose, a respiratory mucus glycoprotein, is produced by goblet cells and submucosal gland cells in the respiratory mucosa [74], and largely contributes to viscoelasticity of nasal mucus. The relative levels of fucose in respiratory mucus depend on degree of hypertrophy and hyperplasia of airway smooth muscle, which is increased by TXA2. Seratrodast, by TP receptor antagonism, inhibits the influence of TXA2 on airway smooth muscle which in turn affects the level of fucose in respiratory mucus. Seratrodast has been observed to decrease the levels of sputum fucose [54, 61] resulting decrease in dynamic viscosity and elasticity of sputum.

**Effect on peak expiratory flow (PEF) and other lung function parameters**

Prostanoids are the major inflammatory mediators involved in airway smooth muscle contraction/bronchoconstriction. Various pre-clinical studies have indicated predominant role of prostanoids in airway smooth muscle contraction compared to that of leukotrienes [75]. Seratrodast was observed to have a radical impact on PEF in clinical trial conducted on Indian patients [54]. A mean change of 0.614 L/sec from baseline was observed with Seratrodast in comparison to 0.199 L/sec with Montelukast, equivalent to 24.9L/min higher PEF with seratrodast ($P<0.05$).

In addition to PEF, significant improvements in other lung function parameters (FVC and FEV1) from baseline have been observed with Seratrodast in various clinical studies [54, 59, 62, 66, 69, 76], indicating the efficacy of TP blockers in alleviating bronchoconstriction.

**Effect on amount of mucous secretion**

TXA2, and other prostanoids PGF2? & PGD2, significantly increases mucous glycoprotein release and

tracheal mucus gel layer [24] that indicates increase in sputum secretion. In various clinical studies, Seratrodast has been observed to limit the sputum secretion action of prostanoids [61, 62, 66, 76]. In a clinical trial comparing the efficacy of Seratrodast with Montelukast, significantly greater reduction in expectoration was observed with Seratrodast than with Montelukast [54].

**Effect on airway hyper-responsiveness**

In a 12-week study in 10 asthma patients [57], Seratrodast improved airway hyper-responsiveness by reducing airway inflammation indicating close association of TP receptor antagonism with improvement in airway hyper-responsiveness. TP receptor antagonism results in direct inhibition of actions of prostanoids on TP receptors and indirect inhibition of effect of allergens, leukotrienes, bradykinin, PAF, endothelin, endotoxin and ozone on TP receptors [47; 49-51]. The decrease in airway hyper-responsiveness by Seratrodast can also be correlated with reduction in ECP that contributes to airway hyper-reactivity[77].

**Effect on cough threshold**

Seratrodast was observed to increase cough threshold in patients with chronic bronchitis, indicating involvement of prostanoids in chronic cough. Previous in vitro studies have shown the involvement of cyclooxygenase products of arachidonic acid metabolism, especially TXA2, to be involved in increased mucus secretion in respiratory tract [41], which in turn stimulates mechanoceptors causing cough. In clinical study conducted by Ishiura et al [56] in patients with chronic bronchitis, Seratrodast, after 4 weeks of treatment, was observed to increase cough threshold indicating that inflammatory mediators such as prostanoids can adjust the sensitivity of cough reflex despite the direct stimulation of mechanoreceptors by excessive mucus in chronic bronchitis. Pranlukast, on the other hand, did not increase cough threshold, implying that cysteinyl leukotriene is probably not involved in modulation of airway cough sensitivity.

**TP receptor antagonists and Cysteinyl leukotriene receptor antagonists**

There are various inflammatory pathways involved in the pathogenesis of asthma that involve secondary TXA2 synthesis by multiple agonists including leukotrienes [78]. This is corroborated by various studies wherein inhibiting TXA2 prevented increased airway reactivity to allergens [29], PAF [30], LTC4, D4 [31,32] and B4 [33], bradykinin [34], endothelin [35], endotoxin [36] and ozone [37].

Both GINA [1,2] and Japanese asthma guidelines [79] recommend the use of cysteinyl leukotriene receptor antagonists and TP receptor antagonists for managing uncontrolled asthma. Considering the role of TXA2 in pathogenesis of asthma and the efficacy of TP receptor antagonists over cysteinyl leukotriene receptor antagonists, TP receptor antagonism could soon become a new paradigm in management of uncontrolled asthma.

**Conclusion**

Since the identification and isolation of the first prostaglandins in the 1960s, the cyclooxygenase product (prostanoids) of arachidonic acid have been implicated in asthma [41]. TXA2 has been implicated in airway smooth muscle contraction, vascular smooth muscle contraction, airway microvascular leakage, bronchoconstriction through neuromodulatory effects, increased nasal mucous secretion, airway remodeling and airway hyper-responsiveness [41]. All bronchoconstrictor prostanoids i.e. PGD2, PGF2? and TXA2, act via thromboxane A2 receptors (TP receptors), that are distributed in both plasma membrane and cytosolic compartments found in tissues rich in vasculature such as lung, heart, and kidney [80]. Seratrodast effectively improves nasal obstruction, lung function parameters, cough threshold [56], airway hyper-responsiveness [57] and mucociliary clearance [54], and helps in reduction of average dose of inhaled corticosteroids [61]. Mucous secretion and sputum viscosity are significantly decreased by Seratrodast [54,61]. Clinical symptoms of asthma, like wheezing, breathlessness, expectoration, cough and chest tightness are significantly improved [54]. A better control over exacerbation rate was observed with

Seratrodast in comparison to cysteinyl leukotriene receptor antagonists like Pranlukast, Zafirlukast and Montelukast [56]. Both GINA guidelines and Japanese guidelines for management of asthma recommend the use of Seratrodast in uncontrolled asthma. With the implication of involvement of TXA2 in pulmonary hypertension in COPD patients and increase in levels of TXA2 during COPD [40], respiratory distress syndrome [14] and chronic pulmonary emphysema [59], Seratrodast could be effective in these respiratory disorders other than asthma. The first Indian study conducted by Zuventus Healthcare Ltd., on Seratrodast in patients with mild to moderate asthma indicated better reduction of sputum ECP, sputum albumin and expectoration with Seratrodast in comparison to that of Montelukast [54]. Seratrodast showed significantly greater improvement in PEF compared to Montelukast [54], indicating better control over asthma than Montelukast. Further evidence from clinical studies and clinical usage in Indian patients is suggested to firm up the role of seratrodast in patients with asthma, allergic rhinitis and COPD.

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