Treatment of COVID-19 pneumonia and acute respiratory distress with ramatroban, a thromboxane A_2 and prostaglandin D_2 receptor antagonist: A 4-Patient Case Series Report

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Conflicts of Interest: Ajay Gupta and Kate Chander Chiang have filed a patent on the use of a dual receptor antagonist of the thromboxane A_2 and PGD_2 – DPr2 receptors for COVID-19. Martin Ogletree has filed a patent on use of thromboxane receptor antagonists for the treatment of COVID-19. Dr. Gupta is the son of the index case reported here. The other authors did not declare any conflict of interest.

ABSTRACT

COVID-19 associated pneumonia and acute respiratory distress syndrome are characterized by a lipid mediator storm with massive increases in lung and systemic thromboxane A_2 >> prostaglandin D_2. Thromboxane A_2 is a potent vasoconstrictor of pulmonary veins >> arteries, and thereby promotes an increase in pulmonary capillary pressures, transudation of fluid into the alveolar space, pulmonary edema and ARDS. Thromboxane A_2 also increases vascular permeability, contracts bronchial smooth muscle, triggers and amplifies platelet activation, and promotes a prothrombotic state. PGD_2 promotes a Th2 immune response that is atypical for viral infections and inhibits antiviral defense by suppressing interferon λ expression. D-dimers, urinary 11-dehydro-TxB_2, and IL-13, a Th2 cytokine, have emerged as key biomarkers of severity and organ failure in COVID-19. Ramatroban is an orally bioavailable, potent, dual antagonist of the thromboxane A_2 (TPr) and PGD_2 (DPr2) receptors. We report use of ramatroban in 4 COVID-19 outpatients, 22 to 87 years of age, with acute onset / worsening of respiratory distress and hypoxemia. All four patients experienced decrease in respiratory distress and increase in SpO_2, within hours of the first dose and thereby avoided hospitalization. By the 5^{th} day all 4 patients had complete resolution of respiratory distress and hypoxemia. Ramatroban (Baynas®, Bayer Yakuhin Ltd., Japan) has an established safety profile, having been indicated in Japan for the treatment of allergic rhinitis for over 20 years. As a broncho-relaxant, anti-vasospastic, anti-thrombotic and immunomodulator, ramatroban addresses the fundamental pathophysiologic mechanisms underlying respiratory and critical organ failure in COVID-19, and therefore merits urgent clinical trials that might impact the ongoing pandemic.

Abbreviations: Tx, thromboxane; 11dhTxB_2, 11-dehydro-thromboxane B_2; TPr, thromboxane prostanoid receptor; PG, prostaglandin; COX, cyclooxygenase; DPr2, D prostanoid receptor 2; URTI, upper respiratory tract infection; BALF, bronchoalveolar lavage fluid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; RSV, respiratory syncytial virus; IL, interleukin; MDSC, monocyte-macrophage derived suppressor cell; IFN, interferon; ARDS, acute respiratory distress syndrome; SpO_2, blood oxygen saturation by pulse oximetry**;** TGFβ, transforming growth factor beta; NK cells, natural killer cells; NETs, neutrophil extracellular traps

BACKGROUND

After symptomatic SARS-CoV-2 infection, 10-20% of patients require hospitalization for respiratory distress and hypoxemia.[1] Currently, only anti-SARS-CoV-2 monoclonal antibodies are approved for treatment of ambulatory patients with COVID-19.[2] Additional antiviral treatments are nearing approval, but they are expensive and not completely effective. There is an unmet medical need for an inexpensive, orally bioavailable drug with an excellent safety profile that can provide symptomatic relief, reduce hypoxemia and prevent hospitalization in outpatients with COVID-19. Identifying the correct therapeutic target is critical to discovering such a drug.

Lungs in COVID-19 patients with acute respiratory distress syndrome (ARDS) exhibit an abundance of proinflammatory lipid mediators with predominance of cyclooxygenase metabolites in bronchoalveolar lavage fluid (BALF), notably thromboxane B_2 (TxB_2) >> prostaglandin E_2 (PGE_2) > prostaglandin D_2 (PGD_2).[3] The massive increase in TxA_2 metabolites in BALF from COVID-19 associated ARDS,[3] and systemically in hospitalized COVID-19 patients,[4 5] led us to propose a critical role for TxA_2 - TxA_2 prostanoid receptors (TPr) signaling in COVID-19 associated respiratory distress. We hypothesized that TxA_2/TPr induced contraction of pulmonary veins elevates pulmonary capillary pressure and contributes to pulmonary edema and hypoxemia in COVID-19 pneumonia (Fig. 1). TPr signaling leads to constriction of intrapulmonary veins and small airways with 10-fold higher potency and greater reduction in luminal area than intrapulmonary arteries.[6] High local concentrations of TxA_2 can effectively shut down pulmonary venous blood flow, increase microvascular pressure and permeability, and force plasma into alveoli.[6] A selective TPr antagonist was previously reported to decrease pulmonary capillary pressure by selectively reducing post-capillary resistance in patients with acute lung injury.[7] Thromboxane A_2 and isoprostanes stimulate TPr-mediated activation of the TGFβ pathway,[8] and early, untimely TGFβ responses in SARS-CoV-2 infection limit antiviral function of natural killer (NK) cells and promote progression to severe COVID-19 disease.[9]

Theken and FitzGerald have proposed early administration of a TxA_2 antagonist as an antithrombotic agent to limit progression of disease in SARS-CoV-2 infection, and administration of an antagonist to block PGD_2 / D-prostanoid receptor 2 (DPr2, formerly referred to as CRTH2) in order to boost interferon lambda (IFN-λ) response in the upper respiratory tract, thereby limiting SARS-CoV-2 replication and transmission.[10 11] Ramatroban is the only dual TxA_2/TPr and PGD_2/DPr2 receptor antagonist available for clinical study and has been proposed as an antithrombotic and immunomodulator agent in COVID-19.[12 13] Archambault and colleagues also recently supported the use of ramatroban to block the deleterious effects of PGD_2 and TxA_2 in COVID-19.[3] Ramatroban has an established safety profile, having been used for over 20 years in Japan for the treatment of allergic rhinitis.[14 15] We report here a small case series of four consecutive COVID-19 patients with worsening respiratory distress and hypoxemia who were treated with ramatroban leading to rapid improvement in both respiratory distress and hypoxemia, thereby avoiding hospitalization and promoting recovery from acute disease.

The 1st case of severe COVID-19 pneumonia treated with ramatroban

S.D., an 87-year-old Indian lady, experienced sudden onset of fever, cough, diarrhea, anorexia, profound weakness, and slight shortness of breath, 10 days after a 2-hour flight from New Delhi to Indore, Madhya Pradesh, India. Patient had received the first dose of COVAXIN, a whole virion inactivated vaccine against SARS-CoV-2, 30 days prior to beginning of symptoms. On examination the patient was fully alert, oriented, and able to make intelligent conversation but lay listlessly in bed unable to ambulate. Patient weighed 42 kg and exhibited severe pre-existing muscle wasting and marked kyphosis. Vital signs revealed temperature, 102^{o} Fahrenheit; heart rate, 100 per minute; blood pressure, 90/60 mm of Hg; and respiratory rate, 22 per minute. Mucosa were moist, and mild pallor was present. There was no jugular venous distention or pedal edema. Chest examination revealed bilateral coarse rales especially prominent at both lung bases but no wheezes. Abdomen, cardiovascular, and neurological examinations were unremarkable. Patient was not taking any medications.

Past medical history included hypertension for over 40 years; thyrotoxicosis for over 30 years treated with radioiodine therapy in 1999; severe osteoporosis with kyphosis; bladder suspension surgery in 1999; coronary artery disease leading to acute myocardial infarction and cardiac arrest in 2015 which required coronary angioplasty and stent placement; chronic kidney disease with estimated glomerular filtration rate of about 20 mL/min (Table 2).

Investigations: Nasopharyngeal and oropharyngeal swabs were positive for SARS-CoV-2 infection by RNA PCR with cycle threshold (Ct range < 20 cycles). Pulse oximetry revealed oxygen saturation of about 85-88%. Patient was admitted on April 9, 2021 to Medanta Hospital, Indore. CT scan revealed moderate multifocal, patchy ground glass opacities, and consolidation. There was septal thickening in the central and peripheral subpleural aspect of both lung parenchyma. Serial laboratory examinations during the course of the illness are listed in Table 1.

Hospital course: During the hospital stay, the patient was treated with high-flow nasal oxygen, prophylactic low-molecular weight heparin, intravenous remdesivir, antibiotics, and methylprednisolone. Patient continued to have fever, cough, shortness of breath, diarrhea, and profound weakness during the hospital stay. SpO2 on room air ranged between 82-86% (Table 2). After a hospital stay of 5 days, the patient was discharged upon her request on April 14, 2021. Discharge medications included oral oseltamivir, doxycycline, vitamin C, aspirin 75 mg once a day, 5 mg prednisolone, vitamin D_3, and nebulization with budesonide and salbutamol twice daily. Continued supportive management with betadine gargles, steam inhalation, and breathing exercises was advised.

Post-discharge course: On April 15, the day after discharge from the hospital, the patient had fever with a temperature of 101^{o} Fahrenheit. Pulse oximetry revealed an oxygen saturation (SpO2) of 82-84% on room air, and patient was continued on oxygen. Patient was profoundly

weak and unable to get out of bed without assistance. At this time all drugs including low-dose aspirin were discontinued, and the patient was started on ramatroban (Baynas®, 75 mg tablet) in a dose of one-half tablet (37.5 mg) orally twice daily. The patient was continued on oxygen using a nasal cannula and SpO2 was not checked on room air. After about 36 hours, having received three one-half doses of ramatroban, there was noticeable improvement in her general condition, and SpO2 increased to 90% on room air. The dose of ramatroban was increased to 37.5 mg in the morning and 75 mg at bedtime. Patient had complete resolution of cough and diarrhea over the next 3 days and started ambulating independently without assistance. Ramatroban was discontinued after 2 weeks due to non-availability, and the patient was switched to 75 mg aspirin daily. Patient had recovered almost completely by April 22, 2021, and gradually recovered fully over a period of next 3-4 weeks back to her baseline status. On October 10, 2021, 6 months after the acute COVID-19, a high-resolution, non-contrast CT scan demonstrated non-homogenous ground glass pattern with normal lung volumes and absence of lung fibrosis. Patient continues to be asymptomatic.

Table 1. Serial laboratory values

Analytes	**Before admission** **April 8, 2021**	**During hospital stay** **April 13, 2021**	**After discharge** **April 16, 2021**	**Reference Value**
Hemoglobin (g/dl)	11.7	12.1	12.0	13.0-17.0
Platelet count (per mm^3)	214,000	285,000	402,000	150,000-410,000
WBC count (per mm^3)	5040	12100	9010	4000-10000
Neutrophils (%)	77	80	86	38-70
Lymphocytes (%)	18	11	07	21-49
NLR (Neutrophil-Lymphocyte Ratio)	4.3	7.3	12.3	1.1-3.5
Serum CRP (mg/L)	7.86	35.9	15.3	0-5.0
D-dimer (ng FEU/mL)	600	650	659	<500

Case 2

A.K., a 33-year-old business manager in New Delhi developed sore throat, cough, loss of smell, altered taste, loss of appetite, high grade fever (104 -106^o Fahrenheit), profound weakness and severe body aches around April 17, 2021. A.K. had not received the COVID-19 vaccine. Patient has past medical history of mild hypertension, psoriasis and psoriatic arthropathy treated with homeopathy, nasal polyposis and recurrent upper respiratory infections every winter for past several years. Nasopharyngeal and oropharyngeal swabs taken the next day were positive for SARS-CoV-2 infection by RNA PCR with cycle threshold (Ct range) of 21 cycles.

On April 18, 2021 the patient developed progressive shortness of breath and was started on oral favipiravir, hydroxychloroquine, doxycycline and multivitamins. SpO_2 checked in the morning was about 90%, declining to 82-85% by the evening. The shortness of breath worsened around midnight and during the early morning hours of April 19th, patient "could not catch his breath, was unable to speak, and was very anxious and restless." The SpO2 was 73% (Table 2). Patient could not be transferred to a COVID hospital because of nonavailability of hospital beds. Desperate attempts to secure an oxygen cylinder failed. Ramatroban was rushed to patient's home by Uber and first dose of 75mg was taken at 1:30 AM on the morning of April 19th. The "breathing improved in 25-30 minutes", the patient calmed down and fell asleep at 3 AM. Pulse oximetry remained disconnected while the patient was sleeping so as not to disturb him. Patient woke up at 11 AM at which time SpO2 on room air was 88-90%. On April 20th, oral temperature was 101° Fahrenheit, and SpO_2 was 90-92%. Ramatroban was administered in a dose of 75 mg twice daily for a total of 5 days. Patient continued to improve over the next 5 days (Table 2). On the 25th of April, patient noticed that the sputum was streaked with blood and oral acetylcysteine was started. A chest CT on April 27th revealed ground glass opacities involving bilateral lung fields with mild interstitial thickening giving the appearance of crazy-paving pattern. There were scattered areas of bronchopneumonic changes and consolidation involving both lungs. A few small fibrotic bands were noted in both lower lobes. The patient had made a near complete recovery by May 5th, and resumed work on May 10th. Patient continues to have altered taste and smell 7 months after the acute illness.

Case 3

S.B., a 22-year-old, healthy lady in New Delhi developed fever, cough, loss of smell and taste and body aches due to COVID-19. S.B. had not received COVID vaccination. S.B. was treated with favipiravir, steroids and multivitamins. Patient experienced progressively worsening shortness of breath and SpO_2 dropped to 85% on room air. Patient was prescribed Ramatroban 75 mg twice daily. Within about 6-8 hours after taking the first dose of ramatroban, respiratory distress improved and the SpO_2 increased to 89%. The next day SpO_2 increased to 90-91%. There was progressive improvement with complete resolution of respiratory symptoms over the next 5 days. On day 5, the SpO_2 was noted to be 94% on room air (Table 2). Patient has made a complete recovery from COVID-19.

Case 4

B.C., a 70-year-old man living in a rural area of Bihar, India developed high grade fever and cough presumably secondary to SARS-CoV-2 infection. Patient has a history of diabetes mellitus controlled with diet. B.C. was not taking any medications and had only received one dose of COVAXIN vaccine for COVID-19. Patient developed shortness of breath with SpO_2 measuring about 80% on room air. Two to three hours after taking 75 mg ramatroban, respiratory distress and cough improved, and the SpO_2 increased to 85%. After a total of 10 tablets taken over 5 days, dyspnea had resolved, and SpO_2 increased to 96% on room air (Table 2). Patient has made a complete recovery from COVID-19.

Table 2. Clinical course of COVID-19 patients with acute respiratory distress treated with Ramatroban

Patient Initials Gender Age (years) Comorbidity	Ramatroban (Baynas®) 75 mg tab	Clinical course; Blood oxygen saturation by pulse oximetry (SpO_2)		
		Time '0' Ramatroban started	Time to partial relief of dyspnea; and the first SpO_2 recorded on room air after initiating ramatroban treatment	Day '5' after taking 10 tablets of ramatroban^
S.D.; female, 87 yrs. Hypertension; Stage 4 CKD; CAD, MI and cardiac arrest 4 years ago	37.5 mg (½ tab) twice daily	Dyspnea ++ SpO_2 : 82%	24-36 hours; SpO_2 > 90%, 36 hours after 1st dose*	No dyspnea $SpO_2 \geq 95\%$
A.K., male, 30 yrs Hypertension, psoriasis, recurrent URTI	75 mg twice daily	Dyspnea +++ SpO_2 : 73%	1-2 hours; SpO_2 90%, 9 hours after 1st dose*	No dyspnea SpO_2 96%
S.B., female, 22 yrs	75 mg twice daily	Dyspnea ++ SpO_2 : 85%	4-6 hours; SpO_2 89%, 6-8 hours after 1st dose	No dyspnea SpO_2 94%
B.C., male, 70 yrs Diabetes mellitus	75 mg twice daily	Dyspnea ++ SpO_2 : 80%	2-3 hours; SpO_2 85%, 2-3 hours after 1st dose	No dyspnea SpO_2 96%

*SpO_2 on room air was not checked at earlier time points
^ For patients 2, 3, and 4, ramatroban could be administered only for a total of 5 days due to limited supplies.

Discussion

We present the first reported cases of COVID-19 treated with ramatroban (Baynas®), a dual antagonist of the TxA_2/TPr and PGD_2/DPr2 receptors. All four COVID-19 patients were characterized by respiratory distress that was new in onset or had worsened (Table 2). Despite severe hypoxemia, all patients were able to avoid hospitalization and recovered without any further need for steroids.

The rapidity of improvement following treatment with oral ramatroban is consistent with an acute hemodynamic effect. We hypothesize that this involves primarily blocking TxA_2 / TPr-mediated selective pulmonary venous constriction and pulmonary capillary hypertension. A consequent increased transcapillary pressure gradient across the pulmonary microvasculature leads to transudation of fluid from the vascular compartment into the alveoli and small airways[6] (Fig. 1).

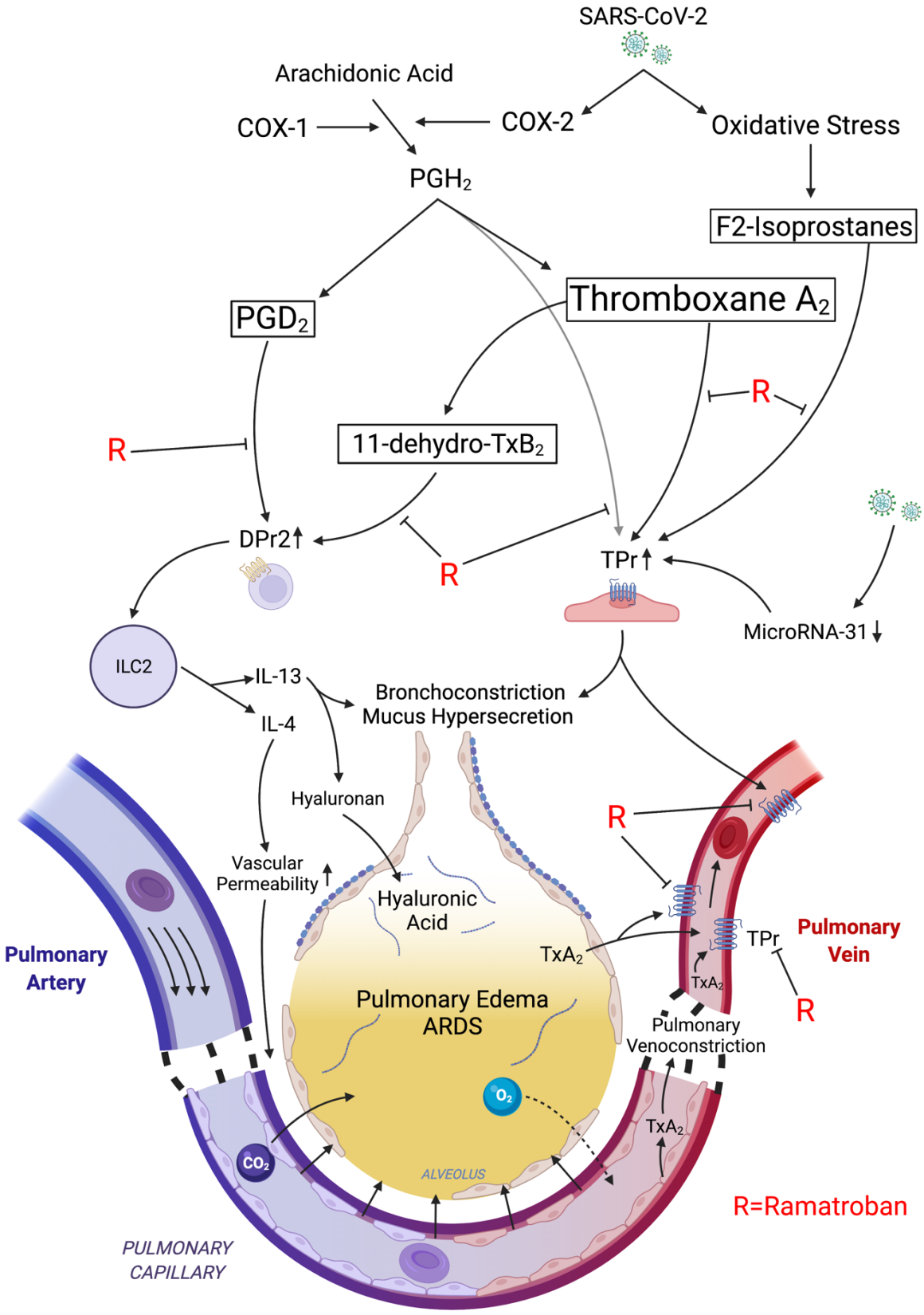
SARS-CoV-2
Arachidonic Acid
COX-1
COX-2
Oxidative Stress
PGH2
F2-Isoprostanes
PGD2
Thromboxane A2
R
R
11-dehydro-TxB2
DPr2↑
R
TPr↑
MicroRNA-31↓
ILC2
IL-13
IL-4
Bronchoconstriction
Mucus Hypersecretion
Hyaluronan
R
Vascular
Permeability↑
Hyaluronic
Acid
TxA2
TPr
Pulmonary
Vein
Pulmonary
Artery
TxA2
R
Pulmonary Edema
ARDS
Pulmonary
Venoconstriction
O2
TxA2
CO2
ALVEOLUS
R=Ramatroban
PULMONARY
CAPILLARY

Figure 1. **Proposed mechanisms of rapid relief in respiratory distress following ramatroban administration during acute SARS-CoV-2 infection.** SARS-CoV-2 induced expression of COX-2 generates PGH_2 which is converted into thromboxane A_2 >> PGD_2. Oxidative stress associated free radicals initiate non-enzymatic peroxidation of arachidonic acid leading to F2-isoprostane generation. PGH_2, TxA_2 and F2-isoprostanes stimulate thromboxane prostanoid receptors (TPr) which are overexpressed in COVID-19 due to decrease in microRNA-31. TPr stimulation induces pulmonary venoconstriction leading to an increase in transcapillary pressure in pulmonary microvasculature, and transudation of fluid into the alveoli, thereby causing impaired gas exchange and ARDS. TxA_2/TPr axis also induces bronchoconstriction and mucus secretion. TxA_2 is rapidly converted to 11-dehydro-TxB_2 in the lungs. PGD_2 and 11-dehydro-TxB_2 stimulate the DPr2 receptor on Th2 and ILC2 cells leading to release of type 2 cytokines, IL-4 and IL-13. IL-4 promotes vascular permeability thereby exacerbating fluid transudation while IL-13 induces hyaluronic acid accumulation and mucus hypersecretion. Ramatroban inhibits the DPr2 and TPr receptors thereby promoting pulmonary vasorelaxation, bronchorelaxation and improving capillary barrier function, while attenuating the maladaptive type 2 immune response and mucus secretion, thereby alleviating pulmonary edema and ARDS. Tx, thromboxane; PG, prostaglandin; TPr, thromboxane prostanoid receptor; DPr2; D-prostanoid receptor 2; Th2; T helper 2; ILC2; innate lymphoid class 2

Notably, U-46619, a TxA_2 mimetic in a concentration of 1 nM is sufficient to reduce guinea-pig pulmonary venous luminal area by 50%.[6] A 50% reduction in luminal area increases vascular resistance by 4-fold, indicating that sub-nanomolar concentrations of thromboxane A_2 could produce meaningful increases in pulmonary venous resistance.[6] This is consistent with the measured effect of ifetroban, a selective TPr antagonist which reduced pulmonary venous resistance and capillary pressure in patients with acute lung injury.[16] Moreover, TPr antagonism has been shown to attenuate airway mucus hyperproduction induced by cigarette smoke[17] and reduce tissue edema in mouse models of acute lung injury.[18] In the cases presented here, we hypothesize that TPr blockade with ramatroban rapidly reduced pulmonary capillary pressures, improved ventilation-perfusion matching, promoted resolution of edema, reduced bronchoconstriction and airway mucus hyperproduction, improved lung compliance and gas exchange, and thereby mitigated respiratory distress and hypoxemia (Fig. 1 and Table 3).

Lung TxA_2 generation is sufficiently elevated in symptomatic COVID-19 that TPr activation may affect other critical organ functions. For example, coronary vascular effects might include vasospasm and thrombosis resulting in angina, arrhythmias and/or myocardial infarction.[19] In the cerebral circulation, TPr activation can increase blood-brain barrier permeability,[20] which may contribute to brain fog in COVID-19. The potential of TPr blockade to affect function of these and other critical organs merits focused COVID-19 research.

In COVID-19, TPr activation by massively elevated levels of TxA_2 and isoprostanes may be further compounded by increased expression of TPr resulting from suppressed expression of microRNA-31.[21] MicroRNA-31 suppression in endothelial progenitor cells, as found in coronary

artery disease patients, leads to higher TPr expression,[22] suggesting potential for exacerbation of TxA_2 mediated effects in COVID-19 patients with underlying cardiovascular disease.

Table 3. Proposed effect of antagonizing Thromboxane A_2/TPr and Prostaglandin D_2/DPr2 signaling by ramatroban in patients with COVID-19

COVID-19	Thromboxane A_2/TPr	Prostaglandin D_2/DPr2
Endogenous agonists for the receptors	Thromboxane A_2 F2-Isoprostanes Prostaglandin H_2	Prostaglandin D_2 11-dehydro-thomboxane B_2
Acute effects of antagonism (minutes-hours)	Hypoxemia ↓ , V/Q mismatch ↓ Bronchoconstriction ↓ Pulmonary edema ↓ ⇑ Pulmonary microvascular permeability ↓ Pulmonary capillary pressure ↓ Pulmonary venous constriction ↓ NK cell SARS-CoV-2 killing ↑ ⇑ TGFβ ↓	Hyaluronan accumulation ↓ ⇑ IL-13 ↓ Antiviral ⇑ IFN-λ ↑
Subacute short-term effect of antagonism (days-weeks)	Microvascular thrombosis ↓ Anti-inflammatory (thromboinflammation ↓)	Antiviral activity ⇑ Th1 Response ↑ Th2 Response ↓
Long-term effect of antagonism (weeks-months)	Brain fog ↓, Brain edema ↓ ⇑ Blood-brain barrier ↑ Lung fibrosis ↓ ⇑ TGFβ ↓	Depression ↓ Activity ↑

PGD_2 / DPr2 signaling also promotes allergic inflammation by stimulating Th2 and innate lymphocyte class 2 (ILC2) cells as in asthma (Fig. 1).[23 24] The maladaptive immune response in COVID-19 is characterized by a shift from Th1 to Th2 with basophilia, eosinophilia, lymphopenia and an increase in plasma levels of type 2 cytokines produced by Th2 cells, including IL-4 and IL-13.[25-27] IL-4 is known to impair the barrier function of endothelial cells, leading to microvascular leakage and edema formation (Fig. 1).[28] IL-13 increases hyaluronan accumulation in mouse lungs,[29] and mucus overproduction in cultured human bronchial epithelial cells,[30] and is correlated with ARDS, need for mechanical ventilation, acute kidney injury (AKI), and mortality in COVID-19.[31] The IC_{50} of ramatroban for inhibiting IL-4 and IL-13

production induced by 100 nM PGD_2 is 103 and 118 nM, respectively.[23] Whether ramatroban inhibits hyaluronan accumulation in ARDS remains to be investigated.

The early beneficial effects of ramatroban may be additionally attributed to an enhanced antiviral activity due to TxA_2 / TPr and PGD_2 / DPr2 antagonism. First, TxA_2 / TPr activation stimulates activation of the TGFβ pathway,[8] and early, untimely TGFβ responses in SARS-CoV-2 infection limit antiviral function of natural killer (NK) cells.[9] Second, PGD_2/DPr2 signaling suppresses innate mucosal antiviral responses by inhibiting expression of IFN-λ, the first line of defense against viruses at mucosal surfaces. Notably IFN-λ is markedly suppressed in the upper respiratory tract in COVID-19.[32] An increased expression of phospholipase A_2 group IID and PGD_2 in the elderly may further suppress IFN-λ expression,[33] thereby impairing their antiviral responses and contributing to the increased morbidity and mortality observed consistently in the elderly with COVID-19.[11] Surprisingly, expression of nasal and pharyngeal PGD_2 and DPr2 in SARS-COV-2 infection remain to be investigated even though there is significant elevation of PGD_2 levels in alveolar lavage fluid,[3 34] and expression of PGD_2 synthase and DPr2 in COVID-19 kidneys.[35] Interestingly, 11-dehydro-TxB_2 (11dhTxB_2), a major stable metabolite of thromboxane A_2, serves as a full agonist of DPr2 receptors, and urinary 11dhTxB_2 levels are markedly increased in COVID-19 and correlate with length of hospitalization, mechanical ventilation and mortality.[36] In rabbits infused with TxB_2, 11dhTxB_2 was the first major metabolite to appear and remained a prominent product in blood for the remainder of the infusion. Enzymatic conversion of TxB_2 to 11dhTxB_2 was not detected in blood cells or plasma.[37] The dehydrogenase catalyzing formation of 11dhTxB_2 was tissue bound and widespread with the highest activity in lung, kidney, stomach and liver.[37] The above suggests that elevated lung TxA_2 is rapidly converted to 11dhTxB_2 which may exert effects in the lungs via DPr2. In a neonatal mouse model of severe respiratory syncytial virus-induced bronchiolitis, treatment with a DPr2 antagonist decreased viral load and improved morbidity associated with upregulating interferon (IFN)-λ expression.[10 33] Whether ramatroban enhances innate NK cell responses and IFN-λ responses by TPr and DPr2 antagonism, respectively, and reduces SARS-CoV-2 viral load remains to be investigated.

Currently, there is no treatment for the persisting symptoms following recovery from acute illness, referred to as long-haul COVID. Long-haul COVID is often characterized by neuropsychiatric manifestations including “brain fog,” anxiety or depression, fatigue and problems with mobility, dyspnea due to lung fibrosis and lung diffusion impairment, and microvascular thrombosis persisting for > 4 months in about 25% of patients.[38 39] Despite persistence of ground glass opacities 6 months later in patient 1, lung fibrosis was not detected. This is consistent with inhibition of the process triggering lung fibrosis by ramatroban in an animal model of silicosis that is associated with markedly increased pulmonary thromboxane A_2 and PGD_2.[40] Moreover, in well-established animal models of depression, elevation in PGD_2 mediates depression-like behavior, while ramatroban restores object exploration and social interaction.[41] The above suggests that ramatroban may help prevent and/or treat certain long-haul COVID symptoms (Table 3).

This report has several limitations. Only 4 patients could be treated with ramatroban, and the duration of treatment was brief due to very limited availability of the drug in India. Only the first patient had laboratory studies performed. Patients 2, 3 and 4 were not examined by a physician and the clinical course was reported by patients or their relatives.

During the ongoing pandemic, there is an unmet need for a drug that can provide rapid relief of respiratory symptoms, respiratory distress and hypoxemia; halt progression of disease and avoid hospitalization, since the latter is associated with poor outcomes for the patient and added burden on the healthcare system. Ramatroban (Baynas®, Bayer Yakuhin, Ltd., Japan) has been safely used for the treatment of allergic rhinitis in Japan since 2000.[15] The usual adult oral dose of 75 mg twice daily achieves an average plasma concentration of about 0.1 mg/L or 240 nM which is sufficient to inhibit pulmonary venous constriction, platelet activation, and release of type 2 cytokines (Table 3).

The rapid and salutary responses to ramatroban reported here, its diverse actions targeting the major pathobiologic mechanisms underlying COVID-19 (Table 1 and Fig. 1), coupled with its oral bioavailability and an excellent safety profile make ramatroban an attractive therapeutic agent to test in randomized controlled clinical trials.

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