

## Research Article

## Ticagrelor as a Unique Antiplatelet Drug for Management of Covid-19 Infected People with a Hyperviscosity Syndrome

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**Abstract:** The whole world agrees on the significance of finding a vaccine or a drug that will aid in the eradication of the novel SARS-COV-2 infection, this extremely contagious virus has gained the characteristic of being pandemic according to the world health organization, in addition to its reputation as a virulent and notorious virus that has succeeded to position the humanity in a critical situation in many settings as financial, political and health-wise. When taking the new theory of COVID-19 pathogenesis into consideration, which is "radical storm-hyperoxidative" in combination with "cytokine storm hyper-inflammatory status", we need to think of a drug that effects on both mechanisms of the pathogenesis. This dissertation investigates the potentiality of antiplatelet agents specifically Ticagrelor (due to its antiviral characteristics) rather than other agents in decreasing the hyper-viscosity syndrome complication of COVID-19, and reduce the patient's transformation to further late-stage issues such as disseminated intravascular coagulopathy (DIC) that is a direct way for death..

**Keywords:** Antiplatelet; Hyperviscosity syndrome; COVID-19; Radical storm; Ticagrelor; Oxidative stress.

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## INTRODUCTION

The novel COVID-19 has been categorized as pneumonia like respiratory illness with a distinctive feature of accompanied lymphocytopenia, although this isn't completely true, as this virus has multi-organ system involvement such as liver, gastrointestinal tract, circulatory system and neural system, all these organs have shown manifestations that confirm COVID-19 presence and its association in their abnormal functions. To understand the effects of COVID-19 on various systems, and how it leads to several abnormalities during early and late stages of the infection, it is important to briefly mention the two proposed theories about its pathogenesis.

At the beginning the primary theory was the cytokines storm hyper-inflammatory status, this theory focused mainly on the deterioration of the respiratory system with each stage during COVID-19 infection, it suggested the raise in pro-inflammatory mediators as IL-6, IL-8 and TNF-alpha, also the high secretion of Vascular endothelial growth factor, monocyte chemo-attractants protein-1, and the reduced E-cadherin on endothelial cells all of these factors increase the permeability of macrophages which in turn attacks the lung tissues due to the presence of the virus which

causes damage and pulmonary dysfunction with bilateral and peripheral ground-glass and consolidative pulmonary opacities on CT imaging specially in patients who have reached the late stage on this infection.(Moore & June, 2020),(Bernheim et al., 2020) Despite the proper management to maintain airways in critically ill patients as invasive and non-invasive mechanical ventilation, and the efforts made to maintain oxygen saturation above 95%, patients are still dying.(Aamendys-Silva, 2020) the failure of the previous theory to explain the reason of death or COVID-19 patients has led the world to think of the second theory which is the radical storm, in this theory it is proposed that SARS-COV-2 has succeeded to invade many cells other than the lung, such as RBCs these cells possess CD147 trans-membrane glycoprotein that contributes in the viral infusion via its structural proteins (E, M, N and S), this infusion leads to the replacement of Iron from the heme ring causing porphyria and hemochromatosis (iron overload). (Wang et al., n.d.),(Liu & Li, n.d.)

The second theory that is concerned with the RBCs rupture and the resulted increase in nonfunctional/functional Hemoglobin ratio is persuasive in explaining the hyper-viscosity syndrome in COVID-19 patients. Hyper-viscosity syndrome

which increasing the thickness and stickiness of the blood, defined as abnormal elevation in any of the blood components either cellular as erythrocytes, leukocytes, and platelets or acellular as proteins and cytokines (small proteins secreted by certain cells). The clinical manifestation of hyper-viscosity syndrome is presented as neurological, ocular (visual disturbances), various mucosal bleeding, gingival or nasal bleeding, cardiovascular disturbances, fatigue, malaise and shortness of breath.(Gertz & Kyle, 1995),(Mehta & Singhal, 2003). As seen in COVID-19 many factors contributes in increasing the thickness of the blood, first the high increase in macrophages number that are functioning in scavenging the free iron to decrease its overload in the body, second the loss of iron from the erythrocyte has left the hemoglobin nonfunctional and unable to bind oxygen, therefore led to hypoxia, and erythropoietin is responsible for the stimulation of erythropoiesis (production of new RBCs to maintain good delivery of O<sub>2</sub> to cells).("Erythropoiesis - an overview | ScienceDirect Topics," n.d.). However as COVID-19 resembles beta-thalassemia in its pathogenesis and iron overload, therefore there would be ineffective erythropoiesis which is known as death of developing immature erythroid, or the production of abnormal erythrocytes which lead to their lysis. It also important to mention that erythropoiesis is controlled by growth factors and microenvironment, in turn that explains the ineffective process in the presence of the virulent COVID-19.(Rivella, 2009)("Ineffective Erythropoiesis in  $\beta$ -Thalassemia," n.d.). This leads us to think about a blood thinning agent (anti-hyperviscosity) that aids in preventing this complication before its occurrence, and has a concomitant antiviral activity, which is Ticagrelor.

## DISCUSSION

Ticagrelor (cyclopentyl-triazolopyrimidine) is a reversible noncompetitive antagonist on ADP-P2Y<sub>12</sub> platelet receptor and inhibitor of equilibrative nucleoside transporter 1 (ENT1) so increasing intracellular adenosine amount, platelets have G-protein coupled receptor on its surface as ATP-PY<sub>2</sub> and ATP-PY<sub>12</sub> the mediate the influx of calcium therefore mediate the change in platelet shape and induce granules release to enhance fragile platelet aggregations, the activation of PY<sub>12</sub> receptor leads to inhibition of many components as cAMP that weakens the aggregate, so amplifying the aggregation and stabilization of the platelet, so its inhibition is a fundamental step in disrupting platelet aggregations and thrombus formation. Ticagrelor has been widely used in many conditions as acute coronary syndrome, ischemic heart disease, and previous myocardial infarction and as prophylaxis in PCI with stent.

The reason of selecting ticagrelor rather than other antiplatelet agents as clopidogrel and cangrelor is due to its pharmacokinetic and pharmacodynamics properties, first the half-life of Ticagrelor 7-12 hours,

while for Clopidogrel is 11 days, and for Cangrelor 3-5 minutes, so choosing ticagrelor is reasonable due to its unextreme half-life that allows for twice daily administration, second Ticagrelor has shorter onset of action of 2 hours compared to clopidogrel of 4-6 hours and its offset of action is also shorter 3-5 days for ticagrelor compared to 3-7 days of clopidogrel, third ticagrelor isn't metabolized by enzymes to be activated unlike clopidogrel, this characteristic contribute to have no serious drug-drug interaction and makes it readily active after oral administration unlike clopidogrel which is a prodrug. It is also noteworthy to mention that ticagrelor has predictable pharmacokinetic profile with rapid absorption after oral intake, and its plasma concentration is proportional to the administered dose unlike clopidogrel. This drug is metabolized to inactive metabolite that is easily excreted in the urine. A clinical trial to show the pharmacological properties of ticagrelor compared to another antiplatelet, it was shown that ticagrelor has higher affinity to P2Y<sub>12</sub> receptor and high selectivity to P2y<sub>12</sub> receptors. In addition, due to its noncompetitive reversible binding to the platelets compared to the irreversible manner of other antiplatelet as clopidogrel and prasugrel, this allows for better inhibition of platelets activation without an increased risk of bleeding (this is known as balanced separation between antithrombotic activity and increased bleeding risk.(Capodanno, Dharmashankar, & Angiolillo, 2010),(Ahmad & F. Storey, 2012). One of the important reasons behind the selection of ticagrelor is that, it has a unique inhibition of the reuptake of adenosine from the RBCs which results in detectable plasma concentrations of adenosine, the importance of adenosine as conducted in animal trial that it increases the release of antiplatelet factors such as nitric oxide and prostacyclin that in turn reduce the size of the infarct in the myocardium. Although this is not the only reason behind its selection, adenosine also exert an anti-inflammatory effect as it neutralize and reverse the effect of chemotaxis, neutrophil activation and platelet-leukocyte aggregates formation.(Gibson, 2016).

Adenosine is a purine nucleoside that is formed locally at sites of hypoxia and tissue damage, through degradation of released adenosine triphosphate (ATP)/adenosine diphosphate (ADP)(Bertil B. Fredholm, 2011). By interacting with four types of cellular receptors (A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub>), it exerts its biological effects, which include cardioprotection, vasodilatation, inflammatory regulation, and platelet function inhibition (B. B. Fredholm, 2007). Adenosine is a neuromodulator and has multiple physiologic actions, including effects on the cardiac, vascular, renal, and central nervous systems. Adenosine reduces heart rate, slows atrioventricular nodal conduction, decreases the glomerular filtration rate, and causes vasodilation of peripheral, cerebral, and coronary vessels. Adenosine is believed to have a direct effect on the sinoatrial and atrial-ventricular nodes, resulting in bradycardia

(RONGEN et al., 1999). Adenosine is considered a broad spectrum anti-viral agent, it greatly affects negative RNA viruses as para-influenza, measles, respiratory syncytial virus and rabies, whereas its effect is weaker on positive RNA viruses as polio and herpes simplex, as Corona virus is a positive RNA virus, adenosine will have a minimal effect on hence the use of ticagrelor will be as adjuvant therapy rather than monotherapy.(De Clercq, Bergstrom, John, & Montgomery, 1984) Also, It directly stimulates pulmonary vagal C fibers through activation of A1 receptors (Hong et al., 1998), and it is possible that the dyspnea in humans is a direct consequence of pulmonary C-fiber activation. Because if that Ticagrelor also augmented other adenosine-induced physiological responses (including the sensation of dyspnea and coronary blood flow velocity) in healthy subjects (Wittfeldt et al., 2013) so that the administration of ticagrelor will cause dyspnea in 14% of the patients, nausea 4%, dizziness 5% and loss of consciousness in less than 2% of the patients. ("ticagrelor - UpToDate," n.d.), it is important to reverse dyspnea because it is a critical issue in COVID-19 patients, and to do so administering theophylline (adenosine receptor antagonist) to reverse dyspnea without interfering with adenosine anti-viral activity. Theophylline, also known as 1,3-dimethylxanthine, is a methylxanthine drug. The fact that theophylline and adenosine compete for the adenosine receptor and have contrasting pharmacologic activities has led to speculation that pharmaceutical adenosine,(Ujhelyi et al., 1994). The stimulation of the release of endogenous epinephrine and norepinephrine, inhibition of phosphodiesterase (thus increasing cyclic adenosine monophosphate [cAMP] concentrations), and, most notably, behaving as a competitive antagonist of the adenosine receptor (Rall, 1990)

To be more specific about its anti-inflammatory effects, in asthma and COPD (inflammatory diseases) adenosine exert and agonist effect via A2A receptor this prevent the inflammatory cells as macrophage to infiltrate in the lung as seen in COVID-19 patients, also it has an antagonist effect on A2B receptor, therefore prevent mast cell degradation and further activation of pro-inflammatory mediators. Another example, in ischemia adenosine show agonist activity on A2A receptor that will down regulate the production of free radicals and pro-inflammatory cytokines, also will reduce the transformation of inflammatory cells to tissues and prevent further necrosis. Thus, due to the presence of previously mentioned features in COVID-19, it is rational to use a drug that increase the presence of adenosine in the plasma as Ticagrelor.(Haskó, Linden, Cronstein, & Pacher, 2008).

We conclude that Ticagrelor has Broad spectrum indirect antiviral effect against Flaviviruses, Exerts beneficial effects on systemic nitric oxide bioavailability, Diminishes biomarkers of oxidant stress

and inflammation in patients, and Prevent lung tissue damage. So we recommend to investigate the effect of Ticagrelor as adjunctive therapy for patient with COVID-19.

## CONCLUSION

In summary, COVID-19 with its worldwide spreading and impact attract the research area toward the development of successful management protocol. it is pivotal to give a prophylactic agent in COVID-19 patients against the hyper-viscosity issue that will lead to further complications, therefore giving a prophylactic dose of Ticagrelor has dual benefits in fighting the virus and preventing CV complications . Preventing the progression of COVID-19 to its late stage would risk many lives, and reduce the financial burden in managing late stage COVID-19 cases. Indeed large randomized clinical trials are needed to assert the advantages of using Ticagrelor in COVID-19.

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