A Review of the Possibility of Nafamostat Mesylate in COVID-19 Treatment

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Abstract
Nafamostat mesylate is a synthetic serine protease inhibitor, which inhibits various enzyme systems such as coagulation and fibrinolytic systems, the kallikrein–kinin system, the complement system, and the activation of protease-activated receptors. It also inhibits lipopolysaccharide-induced nitric oxide production, apoptosis, and interleukin (IL)-6 and IL-8 levels in cultured human trophoblasts. Moreover, it has been shown to act as an antioxidant in TNF-α-induced ROS production. It is sometimes used for the treatment of disseminated intravascular coagulation (DIC) and acute respiratory distress syndrome (ARDS), and it was usually used as an anticoagulant in extracorporeal circulation such as continuous renal replacement therapy (CRRT) of patients with chronic renal failure in Asian countries.

Recently, Nafamostat mesylate as a serine protease inhibitor prevents the fusion of the envelope of the SARS-CoV-2 with host cell surface membranes by inhibiting transmembrane serine protease 2 (TMPRSS2), a human cell surface serine protease. Nafamostat mesylate might have a potential antiviral activity.

Here we review recent studies that showed possible roles of Nafamostat mesylate in COVID-19. The therapeutic potential of Nafamostat mesylate in relation to the pathogenesis of COVID-19 are also discussed. It is thought that these findings could provide a basis for the use of Nafamostat mesylate as a potential therapeutic for COVID-19 in human in the situation with no definite treatment for COVID-19 established.

Keywords: Nafamostat mesylate, COVID-19, SARS-CoV-2, Anti-inflammation, Anticoagulation, Antiviral effect

Introduction
Coronavirus disease 2019 (COVID-19), which started in Wuhan in December 2019, is a pandemic caused by the newly emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (genus Betacoronavirus, family Coronaviridae). This virus has been reported in 227 countries with more than 21,866,088 confirmed cases and 773,726 deaths as of August 18, 2020 [1]. SARS-CoV-2 is transmitted primarily via the respiratory route in the form of droplets, and also by contact with fomites in the proximity of infected patients.

The clinical spectrum of COVID-19 encompasses asymptomatic infection, mild upper respiratory tract illness, pneumonia that may result in respiratory failure, multi-organ failure, and death.

Depending on the severity of the disease, WHO recommends the use of dexamethasone in severe cases in whom oxygen is needed and also specifies the use of anticoagulant, if necessary. Additionally, the CDC in the United States considers the use of remdesivir in the guideline. However, none of these drugs are definitive treatments so far.

Currently, there is no definite cure for COVID-19, a new infectious disease, and countries around the world are looking for drugs that may have a potential effect on COVID-19. Recently, there have been several papers on the life cycle for the SARS-CoV-2 and pathogenesis of COVID-19, alongside several studies on Nafamostat mesylate, which has potential therapeutic effects on the COVID-19 among existing drugs.
Therefore, it is interesting to explore its therapeutic effects on COVID-19. This review summarizes the recent data on Nafamostat mesylate research in treating COVID-19.

**Nafamostat Mesylate**

The compound Nafamostat mesylate belongs to the class of organic compounds known as guanidinobenzoic acids and derivatives [2]. Nafamostat, a synthetic serine protease inhibitor, is used as an anticoagulant in patients with disseminated intravascular coagulation (DIC) and prevents blood clot formation during extracorporeal circulation in patients undergoing continuous renal replacement therapy and extra corporeal membrane oxygenation in many Asian countries [2].

Nafamostat mesylate is the mesylate salt form of nafamostat, a broad-spectrum synthetic serine protease inhibitor, with anticoagulant, anti-inflammatory, mucus clearing, and potential antiviral activities [3]. Upon administration, nafamostat inhibits the activities of a variety of proteases, including thrombin, plasmin, kallikrein, trypsin, and Cl esterase in the complement system, and factors VIIa, Xa, and XIIa in the coagulation system [3]. Nafamostat mesylate inhibits various enzyme systems including the coagulation and fibrinolytic (thrombin, Xa, and XIIa), kallikrein–kinin system, and complement systems, pancreatic proteases and the activation of protease-activated receptors (PARs). Also, Nafamostat mesylate inhibits lipopolysaccharide-induced nitric oxide (NO) production, apoptosis, and interleukin (IL)-6 and IL-8 levels in cultured human trophoblasts [2]. It is shown to act as an antioxidant in TNF-α-induced ROS production [2].

One of the side effects of this drug is hyperkalemia, which results from that the drug and its metabolites may inhibit the amiloride-sensitive sodium conductance at the collecting ducts, resulting in an inhibition of potassium secretion [2]. In relation to these Na channels, Nafamostat mesylate may also decrease epithelial sodium channel activity and increase mucus clearance in the airways [3].

In addition, Nafamostat mesylate as a serine protease inhibitor prevents the fusion of the envelope of the SARS-CoV-2 with host cell surface membranes by inhibiting transmembrane serine protease 2 (TMPRSS2), a human cell surface serine protease that mediates the SARS-CoV-2 viral cell entry [3-7]. Thereby it can inhibit viral infection and replication. Nafamostat mesylate highly inhibits SARS-CoV-2 infection (Table 1) [4-8].

**Pathogenesis of COVID-19**

SARS-CoV-2 initially enters and replicates in epithelial cells of the upper respiratory tract [9]. This process explains the initial high viral load in the upper respiratory tract with increased levels of viral shedding and higher transmission [9]. Angiotensin converting enzyme 2 (ACE2) was identified as a cell entry receptor for SARS-CoV-2 [3]. ACE2 is a fundamental membrane protein that appears to be the host-cell receptor for SARS-CoV-2. In the early stage, SARS-CoV-2 utilizes its spike (S) protein to bind to the host cell membrane via the membrane-embedded glycoprotein ACE2 [10,11]. SARS-CoV-2 can enter all cells expressing ACE2 proteins and the virus utilizes ACE2 as its entry receptor [3,4,6,10]. SARS-CoV-2 infection activates the protease that cleaves the S protein, thus facilitating viral entry and activation [3-6,10,11]. The receptor-mediated virus entry is dependent on a serine protease, TMPRSS2 [3,4,6,7,9-11]. TMPRSS2 is an androgen-dependent enzyme overexpressed in prostate cancer tissues and involved in tempering organ inflammation as in pancreatitis [6]. This enzyme also exists in airway epithelial cells, cardiac endothelium, microvascular endothelial cells, kidney, and digestive tract, all possible

| Formulation | Nafamostat mesylate | Camostat |
|-------------|---------------------|----------|
| Administration [2,3] | intravenous | oral |
| Dose [2,3] | 50 mg i.v. drip per day | 200 mg three times a day |
| Safety [2,3] | Up to 0.8 mg/Kg/ Hour | Up to 900 mg daily |
| Molecular Weight [2,3] | 347 g/mol | 398 g/mol |
| Half life (T_{1/2}) [2,3] | 5-8 minutes | 100 minutes |
| Inhibition TMPRSS [2] | EC50 2nM [4,5]; 5nM [7] | EC50 10-100nM; 87nM [4,5] |

Table 1: Inhibitors of transmembrane serine protease 2(TMPRSS2), a human cell surface serine protease that mediates viral cell entry for SARS-CoV-2.
targets of SARS-CoV-2 infection [6]. Because alveola type 2 cells highly express both ACE2 and TMPRSS2 in the steady state, these cells might be the primary entry cells for SARS-CoV-2 in the lung [6]. This difference in tropism can be explained by an increased affinity for ACE2 receptors. Therefore, respiratory epithelial cells are susceptible to SARS-CoV-2 infection, and this virus causes pneumonia. This entry allows SARS-CoV-2 to readily replicate in the ACE2-bearing cells; consequently, inhibiting TMPRSS2 could potentially be an effective clinical therapy for COVID-19.

It is still not well understood why this viral infection leads to respiratory failure with a high mortality rate. However, several recent studies have presented the pathogenesis of COVID-19 leading to acute respiratory distress syndrome (ARDS) in later stage of pathogenesis in COVID-19.

COVID-19 pathogenesis and lethality could be due to an excessive immune response [6-8,11-14].

As with SARS-CoV-2 infection, the damage to the lung is due to an aggressive inflammatory reaction. This indicates that the disease severity also depends on a dysregulation of immune responses [6]. Excessive systemic immune activation and inflammation in patients suffering from COVID-19, with increased levels of TNF-alpha, IL-1 beta, IL-6, IL-10, monocyte chemoattractant protein-1 (MCP-1) and C-X-C motif chemokine 10 (CXCL10), is commonly reported in COVID-19 patients with severe symptoms and pneumonia [14-16]. The massive release of cytokines by the immune system can result in a cytokine storm. The cytokine storm is a result of an inefficient adaptive immune response [17,18]. Several research teams have reported the presence of a gross immune dysregulation in the lungs of COVID-19 patients with severe disease [9]. The presence of excessive levels of inflammation in COVID-19 patients with ARDS is further reinforced by the evidence of hypercytokinemia, the so-called cytokine storm [9]. Excessive infiltration of activated neutrophils into the alveoli and lung interstitial tissue is a common finding in severe COVID-19 [17]. Influx of IL-1 and tumor necrosis factor (TNF) secreting bone marrow-derived monocytes is also a finding in severe COVID-19 patients [9]. High levels of IL6 and IL8 also contribute to hypercoagulation by activating the complement and coagulation cascades, causing disseminated intravascular coagulation [19]. SARS-CoV-2 infection in the respiratory system can activate both NFkB and STAT3, which in turn can activate the IL-6 amplifier, leading to multiple inflammatory and autoimmune diseases [20]. Because IL-6 is a key functional marker of cellular senescence, the age-dependent enhancement of the IL-6 amplifier might correspond to the age-dependent increase of COVID-19 mortality [7]. Since IL6 may favor coagulation activation, it can explain thrombosis in the COVID-19 pathogenesis. The intensifying increases in levels of IL-6, TNF-alpha, NO and ROS secreted by macrophages substantially increases mortality by stimulating widespread cellular receptor-interacting serine/threonine-protein kinase mediated necroptosis [10]. This form of cell death is connected with massive increases in chemokines and ROS with ever amplifying levels of tissue damage, described as necroinflammation, leading to permanent lung failure [7]. Thus, suppression or control of cytokine release associated with excessive immune response can be the key target to treat COVID-19.

The complement system is well known for encouraging immune cell activation and proinflammatory states. Complement activation plays a critical role in the pathogenesis and disease severity of SARS-CoV-2 [21]. The deterioration of organ function following infection has largely been attributed to a maladaptive immune response [21], of which the complement system is a vital part [23]. The complement system is part of the innate immune response and made up of serine proteases that share the same ancestral genes as coagulation proteins [24]. This system functions in opsonization, generating pro-inflammatory mediators, and activating the membrane attack complex (MAC) [24]. This activation is generally triggered by different agents, which converge in the formation of C3 convertase [24]. Anaphylatoxins C3a and C5a, components of the complement cascade, are capable of activating neutrophils, mast cells, monocytes/macrophages, basophils, eosinophils, T cells, and B cells [21]. The secreted nucleoprotein dimers of MERS-CoV, SARS-CoV-1, or SARS-CoV-2 autoactivate mannose-binding lectin-associated serine protease 2 (MASP-2). MASP-2 activation leads to the generation of C3 convertase and the membrane attack complex (MAC) leading to lung injury [25]. Therefore, complement suppression may represent a therapeutic approach to treat COVID-19.

In patients with severe COVID-19, high rates of venous thromboembolism and disseminated intravascular coagulation due to dysregulation of the coagulation and fibrinolytic systems are reported [6,26]. The lungs of patients with COVID-19 have widespread vascular thromboses with microangiopathy and occlusion of alveolar capillaries [26,27]; significant new vessel growth through a mechanism of intussusceptive angiogenesis and also show the vessel with vascular endothelialitis and thrombosis [27]. COVID-19 results in both systemic arterial and venous thrombi even in mild infection, and a likely localized pulmonary microthrombosis resulting in severe and even atypical ARDS [26]. COVID-19 ARDS shows the evidence of hypercoagulation and an exhausted fibrinolytic system, which is the so-called DIC. The importance of hypercoagulation in the pathogenesis of severe COVID-19.

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is further emphasized by an analysis which revealed that 70% of fatal cases satisfied a diagnosis for DIC, while that was true in only 1% of survivors [28]. Thus, anticoagulants are needed to treat the severe COVID-19 patients.

**Suggested Roles of Nafamostat Mesylate in COVID-19 (Table 2)**

Nafamostat mesylate is a serine protease inhibitor that can exert a wide variety of actions.

It can prevent virus invasion by inhibiting TMPRSS2, thereby inhibiting virus fusion on the cell membrane. Therefore, its antiviral effects can be expected against COVID-19.

Nafamostat mesylate inhibits various enzyme systems involved in inflammation and can prevent COVID-19 progression by controlling proinflammatory states related with serine proteases including cytokine release, activation of the complement cascade, the kallikrein–kinin system, and ROS. It exerts anti-inflammatory activity in the airways by reducing inflammatory cytokine production as shown in the tracheal epithelial cells [29]. Therefore, Nafamostat mesylate has anti-inflammatory effects on excessive immune responses related to COVID-19.

In addition, Nafamostat mesylate has long been used as an anticoagulant, so it can possibly block COVID-19 ARDS progression to prevent thrombosis. It inhibits various enzyme systems such as the coagulation and fibrinolytic (thrombin, Xa, and XIIa), kallikrein–kinin, and complement systems associated with coagulation.

Therefore, its anti-viral, anti-inflammatory, and anticoagulant properties might contribute to attenuate the symptoms, disease progression, and complications in COVID-19 patients.

Furthermore, Nafamostat mesylate may also decrease the epithelial sodium channel activity and increase mucus clearance in the airways related to the inhibition of the amiloride-sensitive sodium conductance [3].

**Conclusions**

After the COVID-19 outbreak, while checking on existing possible drugs, we discovered that Nafamostat mesylates had an inhibitory effect on TMPRSS2 which is involved in virus entry [4]. Accordingly, the division of nephrology shared information on the stability and experience of this drug mainly used in continuous renal replacement therapy (CRRT) or DIC, when the effective dose of in vitro research or actual patients have not been used. It has been used in patients with oxygen requirements since March 2020. The maximum safety capacity is known to be 0.8 mg/Kg/Hour, and 0.1 to 0.2 mg/Kg/Hour in the case of DIC; we used 0.14 to 0.18 mg/Kg/Hour in our hospital. The successful treatment of 3 high-risk elderly patients with underlying diseases was reported [30]. This drug has been used in 11 patients so far, and a marked improvement and no side effects such as anaphylaxis or bleeding relation to this drug were observed; however, hyperkalemia has been observed in two patients.

In the treatment of COVID-19 patients, the anti-inflammatory effect of Nafamostat mesylate and its role as a natural anticoagulant in relation to the pathogenesis of COVID-19 could play a role as a therapeutic agent for COVID-19. In the case of our patients, pneumonia progressed but not in the initial state of COVID-19 infection. It is estimated that the anti-inflammatory effect and anticoagulant action of this drug are the main effects rather than the antiviral effect of this drug.

The serine protease inhibitor Nafamostat mesylate has been in use for many years as an anticoagulant specifically in DIC and extracorporeal circulations such as CRRT or extracorporeal membrane oxygenation (ECMO), with very few side effects. It was identified as a potential target in the early stage of COVID-19 infection due to its inhibitory effect on SARS-CoV-2 membrane fusion. Its anti-inflammatory and anticoagulant effects can attenuate the progression of COVID-19. However, the human degradome consists of at least 1449 proteases and homologues, of which 399 are serine proteases [31]. The upregulation or downregulation of this class of molecules is deleterious and results in various diseased conditions like inflammation, cancer, skin diseases, atherosclerosis, immunological disorders, coagulation abnormalities, pulmonary and neuronal disorders, and other pathologies [31]. Therefore, long-term use of Camostat (an oral form of Nafamostat mesylate) for prophylactic purposes as an antiviral is not safe, particularly because of the uncertainty regarding when the COVID-19 pandemic will end. However, it may be considered that Nafamostat mesylate or Camostat can be used for a short-term in expecting anti-viral effects in COVID-19 patients diagnosed early or before symptom onset.

It is necessary to confirm its effectiveness through a large-scale clinical trial. Currently, clinical trials are being conducted in various countries worldwide, all of which are in progress (Table 3). The role of Nafamostat mesylate as an antiviral, anti-inflammatory, and anticoagulant has shown the potential to prevent disease progression at various stages of the pathogenesis of COVID-19.

In the absence of a definitive treatment, Nafamostat mesylate could be considered a treatment for COVID-19.
| Pathogenesis of COVID-19                                                                 | Nafamostat mesylate (a synthetic serine protease inhibitor)                                                                 |
|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| Early stage                                                                             | Interfere with SARS-CoV-2 entry: non-selective TM-PRSS2 inhibitor to hamper cell infection by SARS-CoV infection           |
| Virus entry                                                                             |                                                                                                                          |
| Excessive immune                                                                        | Inhibiting serine protease in the complement system                                                                      |
|                                                                                         | Inhibiting lipopolysaccharide-induced NO production, apoptosis, and IL-6 and IL-8 levels                                   |
|                                                                                         | Acting as an antioxidant in TNF-α-induced ROS production                                                                   |
|                                                                                         |                                                                                                                          |
| Later stage                                                                             |                                                                                                                          |
| Venous thromboembolism and disseminated intravascular coagulation                      |                                                                                                                          |
|                                                                                         | Inhibiting the coagulation and fibrinolytic systems                                                                      |
|                                                                                         | Inhibiting the complement system and the kallikrein–kinin system associated with coagulation                             |
|                                                                                         | Inhibiting IL-6 and IL-8 which contribute to hypercoagulation                                                             |

**Table 2:** Nafamostat mesylate, as a serine protease inhibitor, is a multi-action drug which inhibits multiple pathogenesis of COVID-19 [2-30].
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Conflict of Interest

Author has nothing to declare.

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