Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CONFLICTS OF INTEREST

None declared.

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Potential of heparin and nafamostat combination therapy for COVID-19

Tang et al recently reported that, in COVID-19 infections caused by the novel coronavirus (SARS-CoV-2), heparin anticoagulant therapy lowers the mortality rate in patients who present with markedly elevated concentrations of D-dimer.[1] In other words, abnormal coagulation may influence the prognosis of COVID-19. This is extremely interesting. The article did not describe to what extent heparin improves the abnormal coagulation and further studies by this group are anticipated. The authors reported in that article[1] and a previous article[2] that the abnormal coagulation seen in non-survivors of COVID-19 clearly differs from the abnormal coagulation typically seen in other severe infectious diseases. Specifically, markedly decreased fibrinogen levels and markedly elevated fibrin degradation product (FDP) levels have been observed in COVID-19 non-survivors. These observations carry the characteristics of disseminated intravascular coagulation (DIC) with enhanced fibrinolysis rather than the DIC with suppressed fibrinolysis that is caused by infectious diseases (where FDP and D-dimer levels are mildly elevated and fibrinogen is not decreased).[3] Regarding this point, we state that a rapid and progressive decrease in fibrinogen levels should be noted with caution in COVID-19. Most reports concerning COVID-19 non-survivors have shown that D-dimer levels are significantly increased in these patients, and that prognosis can be predicted based on D-dimer elevations.[4-6] Tang et al analyzed abnormal coagulation using fibrinogen and FDP in addition to prothrombin time (PT), activated partial thromboplastin time (APTT), and D-dimer[2] and found that heparin treatment may be effective.[1] Their reports have been attracting attention to those perspectives. Because FDP increases more sensitively than D-dimer in DIC with enhanced fibrinolysis, evaluation of FDP rather than D-dimer may be an option to assess the prognosis of COVID-19.

Tang et al reported that heparin (particularly low molecular weight heparin) improves the prognosis of patients with high D-dimer level.[1] In Japan, anticoagulants used for DIC include heparin as well as antithrombin concentrates, recombinant human soluble thrombomodulin, and

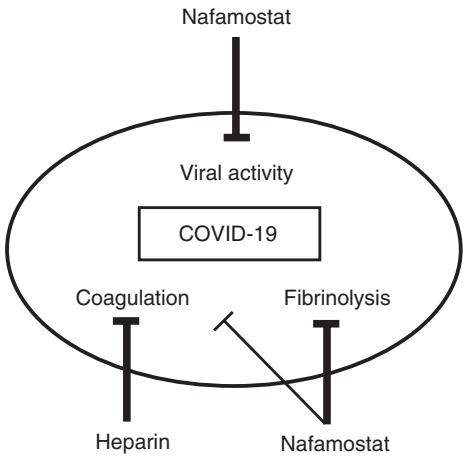

FIGURE 1 Anti-COVID-19 action by nafamostat (author's hypothesis). Nafamostat is anticipated to show anti-viral and anti-enhanced-fibrinolysis disseminated intravascular coagulation effects. Nafamostat has weak anticoagulant effects, and combination with heparin may therefore be effective

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nafamostat mesylate (NM). NM is a drug that has been used for more than 30 years in Japan for pancreatitis and DIC treatment, as well as dialysis (for preventing coagulation of perfused blood). NM is a serine protease inhibitor that potently inhibits proteolytic enzymes such as thrombin, plasmin, and trypsin.[7] The optimal amount differs depending on the purpose of use; for example, an approximately 10-fold higher dose is used for DIC than for pancreatitis. NM, unlike heparin, does not result in hemorrhagic side effects even at the doses used for DIC, representing a major advantage. NM is a drug used for the treatment of DIC, but possesses potent antifibrinolytic actions[7] and is therefore a compatible drug to treat DIC with enhanced fibrinolysis. An increasing amount of data in Japan shows that NM is extremely effective against DIC, even in patients with DIC and enhanced fibrinolysis associated with primary diseases such as aortic aneurysm or malignant tumor that do not improve. COVID-19, as described above, presents the characteristics of DIC with enhanced fibrinolysis, and NM is anticipated as a promising solution.

NM has been globally featured recently in the media for its suppressive actions against coronaviruses such as SARS-CoV-2.[8,9] Inoue et al noted that NM may effectively block the requisite viral entry process the new coronavirus uses to spread and cause disease.[8] In other words, NM may be effective against COVID-19 from both "anti-viral" and "anti-DIC with enhanced fibrinolysis" perspectives.

The disadvantage of NM is that it has weaker anticoagulation actions compared with its antifibrinolytic actions.[7] Combination with heparin may compensate for this weakness and further augment the positive effects (Figure 1). We look forward to future investigations.

CONFLICT OF INTEREST

The authors report no potential conflict of interest.

AUTHOR CONTRIBUTION

HO and HA wrote the manuscript.

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