The complement system and COVID

Possible disease modifying drugs

In severe SARS-CoV infections there is diffuse alveolar damage, vascular leakage into the alveolar spaces, premature breakdown of fibrin clots and possible hemorrhage in the lungs. Similar pathology is seen with severe strains of influenza, including the 1918 and 2009 H1N1 influenza viruses. Urokinase plasminogen activator (uPA) has been found to play a central activating role in causing fibrosis and lung injury in SARS.¹

The inflammatory cytokines IL-1β² and TNF-α³ induce the activation/expression of uPA. uPA activates the conversion of plasminogen to plasmin which activates C3 via activation of thrombin by plasmin. uPA also activates uPAR (plasminogen activator urokinase receptor) which induces cell adhesion, migration, and proliferation.⁴

Activation of the complement cascade occurs as early as the first day following inoculation of animals with the SARS-CoV virus. Complement activation is known to increased vascular permeability, a feature of severe SARS-CoV infection that is associated with poor outcome. Baseline complement activity increases with age, and is consistent with the increase mortality with age in SARS. Furthermore, complement activation is predictive of the development of Acute respiratory distress syndrome (ARDS). Complement activation increases inflammation and promotes lysis of cells, causing the release of damage associated molecular patterns, (DAMPs) such as HMGB1. DAMPS can then further activate the inflammatory cascade and the complement system.⁵

In mice, SARS-CoV causes weight loss and lung injury, but does not usually cause death. When mice bred to be complement factor 3 deficient were infected with the SARS virus, they did not have any weight loss and had considerably milder disease. They had very similar viral titers, indicating the complement system was not required for clearance of the viral infection, but rather is responsible for increasing disease severity and pathology, apparently without providing significant protection from this disease.⁶

Thus, it is reasonable to explore mediations that might mitigate the activation of the complement cascade.

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\text{IL-1β and TNFα} \rightarrow \text{uPA} \rightarrow \text{Plasmin} \rightarrow \text{C3} \rightarrow \text{C3a, C3b and C5 activation}
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\text{DAMPs} \rightarrow \text{C1, C4} \rightarrow \text{C3} \rightarrow \text{C3a, C3b and C5 activation}
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Tissue plasminogen activator (tPA) (3.4.21.68) has a similar effect on plasminogen as does uPA. Later in the disease course of severe SARS, there is fibrin degradation and bleeding into the alveoli. This is followed by lung fibrosis.

In a literature search for readily available medications that inhibit uPA, the medication amiloride was found. This is an anti-hypertensive drug, and this seems to be a unique feature of this medication. This medicine may also inhibit tissue kallikrein, an enzyme that upregulates plasminogen. This is not the drug’s mechanism of action as a anti-hypertensive medication, but rather a side effect that may be useful in treating ARDS in SARS and severe influenza. It may reduce injury and help prevent late effects of the disease.

In COVID-19, the development of hypertension is part of the disease pathology in severe disease. Thus treatment is often needed for hypertension and congestive heart failure in severely and critically ill COVID patients.
Amiloride is a potassium-sparing diuretic. Hypokalemia has been found in 93 percent of patients with severe or critical COVID-19, as a result of urinary loss of potassium resulting from degradation of ACE2. Amiloride may decrease potassium loss; however, potassium levels will still need to be monitored.

While perhaps not as potent in accelerating SARS pathology, tPA also converts plasminogen to plasmin. tPA is released from endothelial under beta-adrenergic stimulus. Propanolol, another antihypertensive medication, inhibits tPA activity. This mechanism involves the NO pathway. Since the TLR – NF-κB pathway also promotes NO, propanolol may or may not impact the tPA in this disease, depending where it intercedes in the release of tPA. Propanolol or other beta-adrenergic blocking antihypertensive might have a beneficial role in treating hypertension during severe or critical COVID-19 and reducing risk of arrhythmias.

The beta blocker labetalol has been identified as potentially having SARS-CoV viral papain-like protease (PLPro) enzyme inhibitory effects. PLPro is a viral enzyme helps evade immunity. Thus theoretically, labetalol might: 1) lower blood pressure, 2) protect the heart from arrhythmias caused by long QTc, 3) inhibit tPA, and 4) inhibit viral PLPro. Nevertheless, labetalol is a weak beta-adrenergic blocker than is propanolol and may not inhibit tPA as affectivity. More study of this agent is needed, but it is a reasonable candidate drug for COVID patients requiring treatment for hypertension.

Statins also impact the PAI-1 and tPA. Statins induce tPA and inhibits plasminogen activator inhibitor-1. Thus, statins have an anti-fibrosis effect on wound healing by promoting the degradation of fibrin products. With SARS, severe influenza, and COVID-19, this effect may increase lung damage. Additionally atorvastatin has been found to increase the expression of ACE2 in the heart of animals. This may or may not be a class effect. Satins also downregulate ICAM-1, a protein whose expression is required for Killer T-cells to adhere and eliminate viral-infected cells. I suggest avoiding statin drugs during COVID-19 infection and recovery.

COVID-19 patients with elevated D-dimer, a fibrin degradation product levels have a higher mortality rate. Heparin and warfarin inhibit coagulation factor Xa which promotes cleavage of prothrombin to thrombin, which activates C3. Ticlopidine is another medication that may decrease hypercoagulability in COVID-19 but is of special interest as molecular modeling suggests it may also inhibit SAS-CoV-2 PLPro activity.

Thus, I suggest a clinical trials using amiloride as an antihypertensive medication in hospitalized COVID-19 patients with severe/critical disease and hypertension or congestive heart failure. Propanolol and labetalol are additional medications that have potential to modify this diseases pathogenicity. Heparin may also be helpful in severe and critical cases.

I have no information on the dose of amiloride that would be required for the anti-uPA effect or dose of a betablocker would be required for anti-tPA effects. Thus, I suggest that at least in initial patients, that the dose of mediations used be typical doses used to regulate blood pressure, and fibrin product and complement factor levels be monitored to determine the effects of the medications on uPA, tPA and C3 activity.
Warning: I advise against the use of these medications in the treatment of COVID-19 or other forms of viral pneumonia unless the physician has first read the source material cited herein and clearly understands the disease mechanism they are trying to control.


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