Amiloride for SARS?

Possible disease modifying drug

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-1β [2] and TNF-α [3] induce the activation/expression of uPA.

In a literature search for readily available medications that inhibit uPA, the medication amiloride was found. [4] This is an anti-hypertensive drug, and this seems to be a unique feature of this medication. 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.

Thus, I suggest a clinical trial of using amiloride as an antihypertensive medication in hospitalized COVID-19 patients with severe/critical disease and hypertension or congestive heart failure. I have no information on the dose that would be required for the anti-uPA effect. Thus, I suggest that at least in initial patients, that the dose of mediation used be typical doses used to regulate blood pressure, and fibrin product levels or other labs be monitored to determine the uPA effect of the medication.

Amiloride should not be used in the treatment of COVID-19 or other forms of viral pneumonia unless the physician has first read at least the first of these references and clearly understands the disease mechanism they are trying to control.

Amiloride has side effects that need to me monitored, including possible hyperkalemia.

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[1] Mechanisms of severe acute respiratory syndrome coronavirus-induced acute lung injury. Gralinski LE, Bankhead A 3rd, Jeng S, Menachery VD, Proll S, Belisle SE, Matzke M, Webb-Robertson BJ, Luna ML, Shukla AK, Ferris MT, Bolles M, Chang J, Aicher L, Waters KM, Smith RD, Metz TO, Law GL, Katze MG, McWeeney S, Baric RS. mBio. 2013 Aug 6;4(4). pii: e00271-13. doi: 10.1128/mBio.00271-13. PMID:23919993

[2] IL-1 beta induces urokinase-plasminogen activator expression and cell migration through PKC alpha, JNK1/2, and NF-kappaB in A549 cells. Cheng CY, Hsieh HL, Sun CC, Lin CC, Luo SF, Yang CM. J Cell Physiol. 2009 Apr;219(1):183-93. doi: 10.1002/jcp.21669. PMID:19097143

[3] Tumor necrosis factor α stimulates expression and secretion of urokinase plasminogen activator in human dental pulp cells. Narita T, Muromachi K, Kamio N, Nakao S, Matsushima K, Hashizume H. J Oral Sci. 2012;54(4):329-36. PMID:23221158

[4] Bacterial endotoxin enhances colorectal cancer cell adhesion and invasion through TLR-4 and NF-kappaB-dependent activation of the urokinase plasminogen activator system. Killeen SD, Wang JH, Andrews EJ, Redmond HP. Br J Cancer. 2009 May 19;100(10):1589-602. doi: 10.1038/sj.bjc.6604942. PMID:19436306