Review

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Covid-19 and liver cirrhosis: focus on the non-classical renin-angiotensin system and implications for therapy

Giovanni Sansoè[1], Manuela Aragno[2], Florence Wong[3]
Affiliations expand

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Abstract

Angiotensin-converting enzyme type 2 (ACE2) is the cell receptor of SARS-CoV-2, the viral agent of COVID-19. ACE2 and a network of further enzymes and receptors constitute the non-classical renin-angiotensin system. ACE2 cleaves angiotensin II, which promotes vasoconstriction, oxidative stress, liver and lung inflammation and fibrosis, into angiotensin 1-7 (Ang1-7), which binds to Mas receptors (MasR), resulting in arterial vasodilatation, natriuresis, anti-inflammatory and anti-fibrotic effects in tissues. Viral binding to ACE2 allows viral entry into human cells including hepatocytes, followed by viral replication and host cell depletion of ACE2. The coronavirus-dependent demise of ACE2 and its product (Ang1-7) leads to cytokine activation and cytokine-induced hepatocyte apoptosis and necrosis, which in turn decreases liver reserve and may induce hepatic injury. Approximately one third of patients with cirrhosis, especially those with decompensation, die after a median of 10 days from COVID-19 diagnosis, and nearly two-thirds of these deaths occur before intensive care unit admission for COVID-19-related pulmonary insufficiency. In these cases, liver function deteriorates rapidly after hospital admission, suggesting that cirrhotic patients frequently die from accelerated end-stage liver disease. Pharmaceutical interventions which may provide novel strategies to counter liver cirrhosis decompensation due to COVID-19 include non-peptidic MasR agonist AVE0991, which replaces the anti-inflammatory and anti-fibrotic effects of Ang1-7, and metallopeptidase neprilysin inhibitor candoxatrilat, which reduces Ang1-7 clearance and causes portal pressure reduction with increased natriuresis in experimental cirrhosis. Moreover, SF2809E,

an inhibitor of serine protease chymase (an enzyme generating most tissue angiotensin II) may also block TMPRRS2, a host serine protease that primes SARS-CoV-2 spike glycoprotein before adhesion to ACE2. These and further drugs deserve consideration in patients with COVID-19 and hepatic comorbidities.

Keywords: ACE2; Angiotensin 1-7; SARS-CoV-2; fibrosis; inflammation; neprilysin.