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COVID-19 and Renin Angiotensin Blockers: Current Evidence and Recommendations

Running Title: *Messerli et al.; COVID-19 and Renin Angiotensin Blockers*

Franz H. Messerli, MD[1,2,3]; George C.M. Siontis, MD, PhD[1]; Emrush Rexhaj, MD[1]

[1]Department of Cardiology, Bern University Hospital, University of Bern, Bern, Switzerland; [2]Jagiellonian University, Krakow, Poland; [3]Division of Cardiology, Mount Sinai Health Medical Center, Icahn School of Medicine, New York, NY

Address for Correspondence:
Franz H. Messerli, MD
Swiss Cardiovascular Center
University Hospital Bern, Inselspital
Freiburgstr. 18, 3010 Bern, Switzerland
Tel: +41 77 468 13 63
Fax: +41 31 632 42 99
Email : messerli.f@gmail.com

UPDATE 4/17/20: The authors revised the first paragraph of the article with an update concerning the difference in the risk of pneumonia in patients who were taking ARBs versus those who were not. Also, the reference found in the second paragraph of page 4 has been revised.

RAS blockade and pneumonia

Both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) have repeatedly, but not consistently, been documented to slow progression of pulmonary complications in vulnerable patients. A previously published meta-analysis pointed towards a putative protective role of ACEIs and to lesser extent of ARBs in risk of community acquired pneumonia. ACEIs in 7 studies were associated with decreased pneumonia mortality compared with control treatment (OR 0.66, 95% CI 0.55–0.80). ARBs in one randomised controlled trial only, showed a reduction of borderline significance (OR 0.63, 95%CI 0.40–1.00).[1] These seemingly beneficial findings of renin angiotensin system (RAS) blockade on outcomes in pneumonia resurfaced in the recent literature in relation to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Several potential therapeutic/preventive approaches to address ACE2-mediated COVID-19 have been described, including the suggestion that ARBs could be administered in the form of a nasal spray to treat COVID-19. As pneumonia is a common potentially fatal complication in COVID-19 infection, we wondered whether RAS blockade could exert a favorable effect on pneumonia-related outcomes.

Evidence of ACEIs/ARBs therapy and viral infections of respiratory system

We systematically reviewed the literature for evidence from animal models and clinical data related to the role of ACEIs/ARBs and viral infections. We searched PubMed and EMBASE for original research on animals or humans investigating the impact of ACEIs/ARBs on viral infections. The following search terms were used: “viral”, “virus”, “infect”, “pneumonia”, “acute respiratory distress syndrome”, “acute lung injury” and “angiotensin”. Overall, we identified four studies[2-5] evaluating the role of ACEIs/ARBs in viral infections of respiratory system. In 3 studies of animal models[2-4], virus-induced lung injury and the role of losartan was tested; all

reported a key role of decreased renin-angiotensin system activation through losartan (Table 1). In one retrospective study[5], lower rates of death and intubation were noted among patients who continued to be on ACEIs during hospitalization (odds ratio 0.25; 95% confidence interval, 0.09–0.64). We did not find evidence supporting the continuation, withdrawal, or de novo initiation of ACEIs/ARBs in patients with SARS-CoV-2-infection.

COVID-19 and hypertension

Epidemiologic data suggest that patients with cardiovascular disease (CVD) and hypertension are more susceptible to SARS-CoV-2-infection and that the course of pneumonia is more severe in hypertensive relative to normotensive subjects. COVID-19-associated pneumonia death cases were marked by more comorbidities, such as CVD (22.7%) and hypertension (39.7%). Considerably higher is the prevalence of these co-morbidities in African American patients. However, susceptibility for infection and complications may be explained by advanced age and multiple comorbidities in many patients. Two large independent studies of influenza type A H1N1 have documented a higher prevalence of hypertension and diabetes. Thus, confounding is likely to be extensive.

Possible mechanisms

SARS-CoV-2, the recently identified strain responsible for the current COVID-19 epidemic, relies on ACE2 protein as a cellular entry receptor by binding with its spike (S) protein, similar to SARS-CoV. ACE2 participates in a pathway that is counter-regulatory to the effects of angiotensin II, and the cardio-renal protective effect of ARBs may be due in part to increased metabolism of angiotensin II by ACE2. Importantly, ACE2 expression protects from lung injury, an action which is downregulated by binding of SARS-CoV via its spike protein.

Experimentally and in humans, RAS blockade has been shown to upregulate ACE2 activity, thereby potentially antagonizing some effects of COVID-19. Injection of SARS-CoV spike protein into mice worsens acute lung failure in vivo that can be attenuated by inhibiting the RAS pathway.[2] Conversely, speculation has been put forward that the enhanced ACE2 expression with RAS antagonists might increase the number of binding sites thereby increasing the odds of infection with SARS-CoV-2.

Clinical implications

Given that ACE2 is a cellular entry receptor for SARS-CoV-2, careful evaluation of efficacy and safety of antihypertensive therapy with RAS blockade is needed. There is experimental and clinical evidence that RAS blockade can mitigate pulmonary outcome in some forms of viral pneumonia. Presently, there are no data regarding a favorable effect of RAS blockade on pulmonary outcome in SARS-CoV-2-infected patients. Whether or not infectivity to viral infection is increased in patients treated with RAS blockers remains unknown. However, recent news media coverage of this issue have provoked concern and unfortunately even motivated some patients to discontinue RAS blockers all together. Of note, the RAS effects among available blockers is markedly different. Direct renin inhibitors (DRIs) has been shown to diminish activity of the RAS and also downregulate ACE2 in animal models. Thus with DRIs, RAS blockade and cardio-pulmonary protection is maintained, but ACE2 seems to be downregulated

In general, RAS blockers are efficacious and well-tolerated drugs with few adverse side effects. However, once fever and dehydration set in, the RAS will become up-regulated to the extent that its blockade can result in profound hypotension, syncope, cardiovascular collapse,

renal failure and shock. More often than not, this sequence of events occurs unexpectedly and is abrupt.

Recommendations

Presently, all guidelines recommend continuing ACEI/ARBs in patients diagnosed with COVID-19 infection. Until the evidence in aggregate becomes firmer (and it will), we recommend the following with regard to COVID-19 and RAS blockade:

1. In noninfected patients and patients at risk, there is currently no valid reason to discontinue RAS blockade;
2. In healthy subjects at risk, evidence is not (yet?) sufficient to prophylactically recommend RAS blockade;
3. If apprehension about increased infectivity persists, patients on ACEIs or ARBs could temporarily be switched to a direct renin inhibitor;
4. In COVID-19-positive patients on RAS blockers, the drugs should be continued;
5. In febrile patients with pulmonary symptoms on RAS blockers, close monitoring of blood pressure and renal function is advisable; RAS blockers should be discontinued only as clinically indicated.

Conclusions

CVD in general, and hypertension and diabetes specifically, are prevalent in SARS-CoV-2-infected patients. RAS blockers are extensively used for CVD and hypertension therapy. There is inconsistent evidence to suggest that RAS blockers exert a favourable effect on pulmonary outcome in viral pneumonia, but no data are available specifically for SARS-CoV-2-infected patients. Conversely, patients with CVD and hypertension seem to be prone to SARS-CoV-2-

infection, although this most likely is due to confounding. RAS blockade should be continued in infected patients as clinically indicated. Present evidence is insufficient to recommend use of RAS blockade prophylactically in subjects at risk or therapeutically in those infected with SARS-CoV-2.

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Disclosures

None

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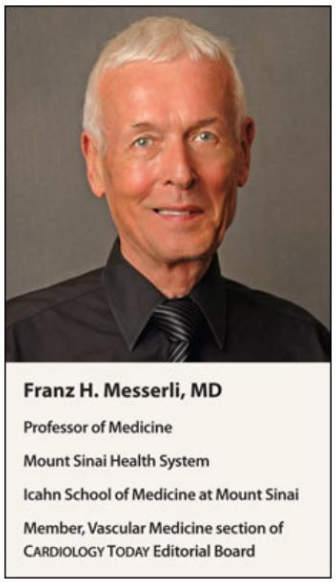
Table 1. Studies on animal models and humans evaluating the role of ACEIs/ARBs in viral infections of respiratory system.

First author	Year	Setting	Subjects	ACEIs/ARBs	Virus	Summary of findings
Kuba K., et al.[2]	2005	Animal model for acute lung injury	ACE2 knockout and control wild-type mice	Losartan	SARS-CoV	In mice with SARS-CoV Spike-Fc–mediated acute lung injury, administration of losartan resulted in lower changes in lung elastase and wet to dry weight ratios of lungs.
Yang P., et al.[3]	2014	Animal model of acute lung injury	4-week-old wild-type C57BL/6 mice & 4-week-old ACE2 knockout mice	Losartan	Influenza A H7N9 virus	In an experimental mouse model of severe ALI undiced by influenza H7N9 virus, losartan administration resulted in a decrease of the nucleoprotein copy and viral titers in the lungs of infected ACE2 knockout mice
Yan Y., et al.[4]	2015	Animal model of acute lung injury	mice (not further specified)	Losartan	Influenza A H5N1 virus	In mice with ALI induced by avian influenza A H5N1 viral infection, losartan resulted in less lung edema (wet/dry lung weight ratio), lowered lung injury scores and reduced number of infiltrating leukocytes. However, the viral load in the lung tissue was not affected.
Henry C., et al.[5]	2018	Retrospective cohort study	Adult patients with a positive respiratory viral PCR test	ACEIs/ARBs (not further specified)	Rhinovirus; Influenza A; Metapneumovirus; RSV; Influenza B; Parainfluenza 1-3; Adenovirus	In a cohort of 1055 patients hospitalized with acute respiratory illness that tested positive for respiratory virus by PCR, half (539 patients) developed pneumonia. Among those with pneumonia, continued use of ACE inhibitors but not ARBs during hospitalization correlated with decreased odds of mortality or intubation.

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; ACE, angiotensin-converting enzyme; SARS-CoV: severe acute respiratory syndrome-coronavirus; AT1, angiotensin 1; RAS, renin–angiotensin system; ALI, acute-lung injury; RSV, respiratory syncytial virus; PCR, polymerase chain reaction.

Corresponding author:



Franz H. Messerli MD
Professor of Medicine, Division of Cardiology, Mount Sinai Health Medical Center, Icahn School of Medicine, New York, New York

Franz H. Messerli, MD, is an expert in hypertensive cardio-vascular disease and preventive cardiology. He presently is Professor of Medicine at Mount Sinai Health Medical Center, Icahn School of Medicine in the Division of Cardiology. After earning his medical degree from the University of Bern Medical School in Switzerland, Dr. Messerli completed his post-graduate training in internal medicine and cardiology at the University of Bern. This was followed by a research fellowship at the Clinical Research Institute and the Hotel Dieu Hospital in Montreal, Canada.

Before coming to New York, Dr. Messerli was for many years director of clinical research at the Ochsner Clinical Foundation and Clinical Professor of Medicine at Tulane University School of Medicine in New Orleans. He served on the Cardiorenal Advisory Committee of the Food and Drug Administration (FDA) and is or has been a member of the editorial board of Circulation, Journal of the American College of Cardiology, European Heart Journal, American Journal of Cardiology, Journal of Hypertension, etc. On his CV there are more than 800 publications and he has been first author on several papers in the New England Journal of Medicine, Lancet, Jama, Annals of Internal Medicine etc. As principal investigator he participated in numerous clinical trials. For his scientific achievements Dr. Messerli has received several awards among them recently a honoris causa doctorate from the Jagiellonian University in Krakow, Poland.