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.

structure provides a hint of this possibility; the 2 high-mannose glycans are either on the uromodulin core backbone or located proximally on the arms, whereas the 6 complex-type N-glycans are primarily located distally on the arms. We suggest that any rotation or translation of the D8C or ZP domains toward each other could shield Asn^{275} and Asn^{513} from the Golgi mannosidases and enable those glycans to pass through to the cell membrane substantially unmodified (Figure 1c).

Having demonstrated the central importance of glycosylation to uromodulin function, the authors proceeded to analyze uromodulin binding to UPEC with cyro-ET both *in vitro* and in human clinical samples. They observed aggregation of hundreds of bacteria *in vitro* following the presentation of uromodulin. This aggregation could be prevented by molar excess of D-mannose that competed with the interaction of UPEC with uromodulin's N-glycosylated Asn^{275}, again emphasizing the importance of post-translational modification to uromodulin function. By plunge freezing bacterial aggregates from the urine of humans with UTI, the authors directly visualized UPEC enmeshed in uromodulin filaments. Bacterial aggregates from UTI in humans due to *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Streptococcus mitis* also demonstrated the presence of uromodulin in the aggregates.

Why is it important?

Together, these experiments demonstrate a clear role for uromodulin in immune defense through aggregating bacteria to prevent their adhesion to the urinary epithelia and enable their expulsion by micturition. This activity is dependent on the addition of sugar to uromodulin at specific sites such that it can bind UPEC. The work beautifully demonstrates a molecular mechanism and opens up exciting new avenues of investigation on the function of uromodulin.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Weiss GL, Stanisich JJ, Sauer MM, et al. Architecture and function of human uromodulin filaments in urinary tract infections. *Science*. 2020;369:1005–1010.
2. Pak J, Pu Y, Zhang ZT, et al. Tamm-Horsfall protein binds to type 1 fimbriated Escherichia coli and prevents E. coli from binding to uroplakin Ia and Ib receptors. *J Biol Chem*. 2001;276:9924–9930.
3. Garimella PS, Bartz TM, Ix JH, et al. Urinary uromodulin and risk of urinary tract infections: the Cardiovascular Health Study. *Am J Kidney Dis*. 2017;69:744–751.
4. Bates JM, Mohideen Raffi H, Prasadan K, et al. Tamm-Horsfall protein knockout mice are more prone to urinary tract infection. *Kidney Int*. 2004;65:791–797.
5. Stsiapanava A, Xu C, Brunati M, et al. Cryo-EM structure of native human uromodulin, a zona pellucida module polymer. *EMBO J*. 2020;39:e106807.
6. Stanisich JJ, Zyla DS, Afanasyev P, et al. The cryo-em structure of the human uromodulin filament core reveals a unique assembly mechanism. *Elife*. 2020;9:e60265.
7. Devuyst O, Olinger E, Rampoldi L. Uromodulin: from physiology to rare and complex kidney disorders. *Nat Rev Nephrol*. 2017;13:525–544.
8. Sarafini-Cessi F, Malagolini N, Hoops TC, Rindler MJ. Biosynthesis and oligosaccharide processing of human Tamm-Horsfall glycoprotein permanently expressed in Hela cells. *Biochem Biophys Res Commun*. 1993;194:784–790.
9. Schaeffer C, Santambrogio S, Perucca S, et al. Analysis of uromodulin polymerization provides new insights into the mechanisms regulating ZP domain-mediated protein assembly. *Mol Biol Cell*. 2009;20:589–599.

clinical nephrology

From confusion to clarity: RAS blockade in patients hospitalized with COVID-19

Raymond A. Geherty[1] and Matthew A. Sparks[1,2]

[1]*Division of Nephrology, Department of Medicine, Duke University School of Medicine, Durham, North Carolina, USA; and* [2]*Renal Section, Durham Veterans Affairs Health Care System, Durham, North Carolina, USA*

Correspondence: *Matthew A. Sparks, Division of Nephrology, Department of Medicine, Duke University School of Medicine, Room 1013 MSRB2, 2 Genome Court, Durham, North Carolina 27710, USA. E-mail: matthew.sparks@duke.edu*

Refers to: Cohen JB, Hanff TC, William P, et al. Continuation versus discontinuation of renin–angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. *Lancet Respir Med*. 2021;9:275–284; and
Lopes RD, Macedo AVS, de Barros E, et al. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: a randomized clinical trial. *JAMA*. 2021;325:254–264.

Kidney International (2021) **99,** 1059–1061; https://doi.org/10.1016/j.kint.2021.02.034

KEYWORDS: ACE inhibitors; ARBs; hypertension; renin-angiotensin system; SARS-CoV-2

The public, scientific, and medical community continues to face unprecedented challenges in dealing with all aspects of the coronavirus disease 2019 (COVID-19) pandemic. Intense debate and research continue to focus on determining why some individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19, are asymptomatic or mildly symptomatic, whereas others manifest severe disease, which is often fatal. It was quickly recognized that SARS-CoV-2 uses the angiotensin-converting enzyme-2 (ACE2) protein, a key component of the renin-angiotensin system (RAS), to enter host cells.[1] This put inhibitors of the RAS, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), squarely in the crosshairs of confusion and speculation.[2] Several, but not all, preclinical animal studies and a few human cohort studies previously demonstrated that RAS blockade with ACE inhibitors or ARBs could increase ACE2 mRNA and activity in several organs and/or plasma and urine.[3] However, earlier in the pandemic, little was known about how RAS blockers modulate ACE2 expression in the lung.[3] Thus, concern existed about whether patients on RAS blockers were more susceptible to severe COVID-19. Alternatively, animal studies from the first SARS epidemic showed a possible beneficial effect of ARBs on lung parameters using a noninfectious mouse injury model (Spike protein and acid-induced lung injury),[4] suggesting the potential for RAS blockade to improve clinical outcomes. Observational studies have not demonstrated a clear association between the use of RAS blockers and susceptibility to SARS-CoV-2 infection or severe disease after using propensity scores and other statistical approaches to address the higher rates of comorbidity among users. Two recently published randomized clinical trials, REPLACE COVID[5] in *Lancet Respiratory Medicine* and BRACE CORONA[6] in the *Journal of the American Medical Association*, provide a more definitive answer to the most pressing clinical question: Does stopping or continuing RAS inhibitors in current users impact outcomes in patients hospitalized with COVID-19?

What did the studies show?

Both of these studies are randomized, open-label, controlled trials involving patients who were already on ACE inhibitors or ARBs and subsequently required hospitalization for COVID-19 (Table 1). Both trials randomized patients to continue or discontinue their ACE inhibitor or ARB. More important, both trials excluded individuals with an absolute contraindication to the continued use of RAS inhibitors, such as pregnancy or hypotension, or with strong indications, such as heart failure or nephrotic range proteinuria.

REPLACE COVID is a multicenter trial involving 20 sites in 7 countries with a total enrollment of 152 patients, the exact number that was needed for 80% power to detect a 25% difference in the primary composite end point, which was a global rank score based on (i) days to death during hospitalization, (ii) days on mechanical ventilation or ECMO, (iii) days requiring kidney replacement therapy, inotropes, or pressors; and for patients who did not fit into the previous 3 categories, and (iv) area under the curve (AUC) of a modified Sequential Organ Failure Assessment (SOFA) score. Similarly, there was no significant difference in any of the secondary end points examined, including all-cause death, length of hospitalization, ICU admission, or duration of mechanical ventilation.[5] Another potential concern with continuation of RAS inhibitors in patients with moderate to severe COVID-19 is the potential for adverse hemodynamic changes or renal hypoperfusion. There was no difference in systolic blood pressure, serum potassium concentration, or serum creatinine between the continuation and discontinuation arms in REPLACE COVID, although patients with hypotension (systolic blood pressure <100 mm Hg) or acute kidney injury at screening were excluded, as were patients with strong indications for RAS blockade, including nephrotic range proteinuria or heart failure. This finding diminishes the concern that continuing RAS inhibitors will lead to significant hemodynamic compromise or renal hypoperfusion in patients with COVID-19.

BRACE CORONA is a multicenter study involving 29 sites in Brazil with an enrollment of 659 patients, giving it 94.5% power to detect a difference of 2 days alive and out of the hospital at 30 days after randomization (the primary end point). Similarly, BRACE CORONA detected no difference in the primary end point, although there was a small but statistically significant difference in the secondary end point of mean length of hospitalization (7.8 days in the discontinue group vs. 6.7 days in the continue group). There was no statistically significant difference in the other secondary end points of death, invasive mechanical ventilation, and myocardial infarction, among others. With respect to potential concerns about hemodynamic compromise or

Table 1 | Comparison of REPLACE COVID and BRACE CORONA

	REPLACE COVID	BRACE CORONA
Trial design	Prospective, randomized, open label	Prospective, randomized, open label
Intervention being studied	Continuing vs. discontinuing ACEi/ARB	Continuing vs. discontinuing ACEi/ARB
Population included	Aged >18 yr Confirmed diagnosis with COVID-19 Taking ACEi or ARB before hospitalization No contraindication to start/stop RAS blockade	Aged >18 yr Confirmed diagnosis with COVID-19 Taking ACEi or ARB before hospitalization No contraindication to start/stop RAS blockade
Primary outcomes	Severity of illness (based on global rank score)	Days alive and out of hospital
Secondary outcomes (selected)	Length of hospitalization All-cause death Length of ICU stay AUC of SOFA score	Length of hospitalization Death at 30 d In-hospital death Cardiovascular death COVID-19 severity MI or new heart failure Mechanical ventilation
No. of patients	152	659
No. of centers	20 Hospitals 7 Countries	29 Hospitals in Brazil
Results	No difference in severity of illness No difference in length of hospitalization, ICU stay, mechanical ventilation, or all-cause death	No difference in days alive and out of the hospital Small difference in length of hospitalization (7.8 vs. 6.7 d) No difference in death at 30 d, progression of COVID-19, or need for mechanical ventilation or vasopressors

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AUC, area under the curve; COVID-19, coronavirus disease 2019; ICU, intensive care unit; MI, myocardial infarction; RAS, renin-angiotensin system; SOFA, Sequential Organ Failure Assessment.

renal hypoperfusion, there was no difference in requirement for pressors or in the rates of dialysis-dependent AKI between the study groups.[6]

Why are they important?

Overall, these 2 studies provide good news for clinicians and patients regarding the safety of RAS blockade in patients hospitalized with COVID-19. More granular differences may not have been detected by these studies given their relatively small sample sizes, and they do not address questions involving earlier modification of RAS blockade (both studies had 1.5–2 days of hospitalization before randomization) or patients who are not already taking ACE inhibitors or ARBs, but these answers will surely come with time as several randomized clinical trials are forthcoming.[7] Both trials excluded patients with contraindications to start or discontinue ACE inhibitors or ARBs (e.g., pregnancy, decompensated heart failure, or nephrotic range proteinuria) and cannot be generalized to these populations. The investigators of these clinical trials should be commended for their timely efforts to answer this pressing question with high-quality evidence. Both trials provide further evidence that it is safe to continue ACE inhibitors and/or ARBs in patients who are taking these medications before hospitalization for COVID-19, and who do not have other indications to start or stop them.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181:271–280.
2. Sparks MA, South A, Welling P, et al. Sound science before quick judgement regarding RAS blockade in COVID-19. *Clin J Am Soc Nephrol*. 2020;15:714–716.
3. Kreutz R, Algharably EAE, Azizi M, et al. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. *Cardiovasc Res*. 2020;116:1688–1699.
4. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. 2005;11:875–879.
5. Cohen JB, Hanff TC, William P, et al. Continuation versus discontinuation of renin–angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. *Lancet Respir Med*. 2021;9:275–284.
6. Lopes RD, Macedo AVS, de Barros E, et al. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: a randomized clinical trial. *JAMA*. 2021;325:254–264.
7. Edmonston DL, South AM, Sparks MA, Cohen JB. Coronavirus disease 2019 and hypertension: the role of angiotensin-converting enzyme 2 and the renin-angiotensin system. *Adv Chronic Kidney Dis*. 2021;27:404–411.