Lack of Benefit of Renin-Angiotensin System Inhibitors in COVID-19

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There has been considerable interest in the potential role of renin-angiotensin system (RAS) inhibitors in patients with COVID-19 given that angiotensin-converting enzyme 2 (ACE2) is the functional receptor for SARS-CoV-2.[1] Because ACE inhibitors and angiotensin receptor blockers (ARBs) may upregulate ACE2, there is a theoretical concern that these agents might increase susceptibility to, or the severity of, SARS-CoV-2 infection. Conversely, ACE2 is the primary enzyme breaking down angiotensin II and, in the process, produces angiotensin 1-7, a physiological antagonist of angiotensin II. SARS-CoV-2 downregulates ACE2, potentially leading to an increase in angiotensin II and reduced levels of angiotensin 1-7. Excess and unopposed angiotensin II may be harmful, and in experimental models of lung injury, administration of RAS inhibitors, ACE2, and angiotensin 1-7 reduced pulmonary damage and mortality. Consequently, there has been uncertainty about the place of RAS inhibitors in patients with COVID-19.[1]

In this issue of *JAMA*, 3 randomized trials are reported[2,3] that extend the evidence base regarding the use of these agents in patients with COVID-19.[4] The Randomized, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial assessed the efficacy of initiating either an ACE inhibitor or ARB, compared with usual care, in 779 adult patients (721 critically ill and 58 non–critically ill) hospitalized for COVID-19 at 69 centers in 7 countries. Critical illness was defined as the need for at least 1 of the following organ supports in an intensive care unit: high-flow nasal cannula oxygenation, invasive or noninvasive mechanical ventilation, vasopressor, or inotropic infusion. Treatment was given for up to 10 days or until discharge, whichever came first. Neither ACE inhibitor nor ARB therapy were blinded, and doses were titrated according to the treating clinician's judgement. The primary outcome, evaluated over 21 days, was organ support–free days, a composite of hospital survival and duration of intensive care respiratory or cardiovascular support.

REMAP-CAP was terminated prematurely, on advice from the data and safety monitoring board, due to safety concerns. Among critically ill patients, median (IQR) organ support-free days was 10 (–1 to 16) in the ACE inhibitor group (n = 231), 8 (–1 to 17) in the ARB group (n = 217), and 12 (0 to 17) in the control group (n = 231), corresponding to median adjusted odds ratios of 0.77 (95% credible interval, 0.58-1.06) for the ACE inhibitor group and 0.76 (95% credible interval, 0.56-1.05) for the ARB group compared with usual care (with odds ratios <1 representing worse outcomes compared with control). Among critically ill patients, there was a 95% probability that the test treatments worsened this outcome. The posterior probabilities that ACE inhibitor and ARB initiation worsened hospital survival compared with control were 95.3% and 98.1%, respectively, with a similarly high probability that an ACE inhibitor and ARB reduced survival through 90 days. The findings in non–critically ill patients were inconclusive due to the small number of participants.

Although it is one of the largest trials of this type to date, REMAP-CAP was still relatively modest in size, with few "hard" events (eg, death). Outcome ascertainment was also

incomplete, because around 5% of patients withdrew consent and were excluded from analyses. Furthermore, 104 of 243 patients (42.8%) in the ACE inhibitor group and 132 of 236 (55.9%) in the ARB group did not complete the full treatment course, most commonly due to hypotension. By chance, baseline imbalances did not favor ACE inhibitors (more diabetes, kidney disease, severe cardiovascular disease, invasive and noninvasive ventilation, and vasopressor support). Although these aspects leave some uncertainty about the results of REMAP-CAP, it does seem reasonable to conclude that initiating RAS inhibitors in critically ill patients with COVID-19 leads to worse outcomes.

It is interesting to compare the results of REMAP-CAP with those of other randomized trials that investigated RAS inhibitors in patients with COVID-19. Previous trials had one of 2 distinct designs. Similar to REMAP-CAP, several trials randomized patients to initiation of RAS inhibitors,[5-10] while others randomized participants to discontinuation vs continuation of existing RAS inhibitor treatment.[11-15] Regarding the first approach, REMAP-CAP was the only trial to enroll mainly critically ill patients. This may explain why the earlier trials, including the Controlled Evaluation of Angiotensin Receptor Blockers for COVID-19 Respiratory Disease Trial (CLARITY), collectively did not suggest harm after the initiation of RAS inhibitors, although most other trials used an ARB rather than either an ACE inhibitor or ARB. It is unlikely that the probable harm in REMAP-CAP was specifically related to an interaction between RAS inhibition and SARS-CoV-2 infection, but rather the critical nature of the patients enrolled. RAS blockers are usually stopped in critically ill unstable patients at risk of hypotension and kidney dysfunction. In other trials, the continuation of RAS blockers in non–critically ill patients does not seem to lead to worse outcomes.

Self et al[3] report the results of 2 blinded, placebo-controlled, multicenter randomized trials with a shared placebo group as part of the fourth Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-4) program. These trials tested 2 investigational RAS agents: TXA-127, a synthetic angiotensin 1-7, and TRV-027, a β-arrestin biased ligand of the angiotensin II type 1 receptor. Each intervention was given via intravenous infusions for a maximum of 5 days. Both trials ran concurrently, recruiting adults hospitalized with severe COVID-19 and new-onset hypoxemia at 35 hospitals in the US. The TXA-127 trial included 343 patients and the TRV-027 trial included 290 patients. Exclusion criteria included hemodynamic instability in both trials and ARB use in the TRV-027 trial because TRV-027 acts as a functional antagonist of the angiotensin II type 1 receptor. The primary outcome was oxygen-free days, evaluated to day 28, with an adjusted odds ratio greater than 1.0 indicating benefit over placebo.

Compared with placebo, both TXA-127 (adjusted odds ratio [aOR], 0.88 [95% CI, 0.59-1.30]) and TRV-027 (aOR, 0.74 [95% CI, 0.48-1.13]) resulted in no difference in oxygen-free days. Mortality at 28 days was 22 of 163 (13.5%) in the TXA-127 group compared with 22 of 166 (13.3%) in the placebo group (aOR, 0.83 [95% CI, 0.41-1.66]) and 29 of 141 (20.6%) in the TRV-027 group compared with 18 of 140 (12.9%) in the placebo group (aOR, 1.52 [95% CI, 0.75-3.08]). Notably, both trials met the prespecified early stopping criteria because of a low probability (<5%) of efficacy and were thus halted at the first interim analysis. Indeed, in both trials there was a trend toward inferiority (ie, worse outcomes) compared with placebo. Once again, there is some residual uncertainty about these results because of modest sample sizes, low power, and baseline imbalances.

Neither the ACTIV-4 trials nor REMAP-CAP lend any support to the hypothesis that SARS-CoV-2 infection results in harmful unopposed angiotensin II activity that might be mitigated by RAS inhibition. The totality of evidence shows that ACE inhibitors and ARBs should not be initiated as a treatment for COVID-19, especially in patients who are critically ill. Conversely, the evidence from the randomized withdrawal trials suggests that existing treatment with an

RAS inhibitor does not need to be stopped in non–critically ill patients with COVID-19 if prescribed for an important indication (eg, heart failure).

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