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Could CGRP Antagonists Be Helpful in the Fight Against COVID-19?

Carrie E. Robertson, MD, FAHS

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When treating migraine patients in the current era of Coronavirus Disease 2019 (COVID-19), many institutions have moved away from face-to-face procedures like onabotulinumtoxinA injections,[1] sometimes transitioning to the newer CGRP antibodies for migraine prevention. However, despite our best efforts to mitigate viral transmission, many of our migraine patients may eventually be exposed to SARS-CoV2. While most patients will have mild to moderate symptoms, a subset will become severely ill, with possible complications including respiratory failure and acute respiratory distress syndrome (ARDS). Given the possibility of this level of severe respiratory illness, we should consider what effect blocking calcitonin gene-related peptide (CGRP) might have on these patients.

In addition to its location throughout the peripheral sensory and central nervous system, CGRP has been associated with perivascular neurons densely distributed in the myocardium and coronary vessels.[2,3] It is a potent vasoactive peptide and potential cardioprotective mediator in conditions such as heart failure and ischemia.[2-5] CGRP has also been found in pulmonary afferent nerve fibers and contributes to the vasodilation of pulmonary vasculature.[6] So what effect would exogenously blocking CGRP with our newer migraine therapies have on the outcome of acute respiratory failure?

Interestingly, some have hypothesized that excess release of neuropeptides such as CGRP might contribute to abnormal vascular reactivity observed in acute lung injury, raising the question of whether CGRP blockade might be beneficial in some cases.[6] In a study examining the effect of CGRP on acid-induced lung injury, CGRP gene-disrupted mice had significantly attenuated acid-induced injury, edema, and respiratory failure compared to controls.[7] Similarly, in an ovine model of the pulmonary response to noxious stimuli (smoke inhalation or burn), sheep who received pretreatment followed by continual infusion with a specific CGRP receptor antagonist, olcegepant (BIBN4096BS), had significantly attenuated airway hyperemia, pulmonary transvascular flux, and impaired pulmonary gas exchange compared to untreated controls.[6] While these animal models might suggest that CGRP blockade could benefit select patients with

From the Headache Division, Department of Neurology, Mayo Clinic, Rochester, MN, USA (C.E. Robertson).

Address all correspondence to C.E. Robertson, Department of Neurology, Mayo Clinic, College of Medicine, 200 First Street S.W., Rochester, MN 55905, USA, email: Roberston.Carrie@mayo.edu

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acute lung injury, they do not answer whether this type of blockade would benefit patients with deterioration from SARS-CoV2 pneumonia.

There is an evolving understanding of the clinical features and pathophysiology underlying the development of critical illness in patients with COVID-19. It is currently thought that SARS-CoV2 induces a type of cytokine storm, with fever, thrombocytopenia, lymphopenia, coagulopathy, hepatic damage, macrophage activation, and eventually ARDS and septic shock with multiple organ failure.[8-10] Early studies show that interleukin-6 (Il-6) elevation may correlate with increased severity of COVID-19, and some have suggested using it as a marker for severity assessment.[11,12] Blockade of Il-6 has shown promise as a treatment for the hyperinflammatory response of COVID-19 and additional trials are ongoing.[9,10] As CGRP is known to enhance cytokine-dependent Il-6 production,[13] one might hypothesize that our newer migraine treatments that block the CGRP pathway might also help mitigate the hyperinflammatory response in severe cases of COVID-19.

On April 9, 2020, Biohaven announced the plans to study vazegepant, a nasal spray high-affinity CGRP receptor antagonist, as a treatment for COVID-19 infection associated pulmonary complications.[14] It will be interesting to see if this medication, which is mechanistically similar to currently available gepants and is currently advancing to Phase 3 development for the acute treatment of migraine, is able to help patients with serious COVID-19 infections. Of course, given the ubiquitous distribution of CGRP, CGRP receptor antagonism during critical illness may also result in unintended consequences, both within and outside the cardiopulmonary system. It is not clear, for example, if temporary blockade of CGRP in these patients might predispose to worsening systemic hypertension, pulmonary hypertension,[5] or ischemic organ injury.[2,4,15]

If a CGRP receptor antagonist is ultimately found to be helpful in reducing the severe morbidity and mortality of these critically ill patients, this might inspire numerous additional investigative opportunities. For instance, would CGRP antagonists be more effective if given early and continuously, similar to the ovine model of acute lung injury, or is it more effective as a treatment after some level of respiratory compromise has occurred? Will it matter if the inhibition is of the CGRP receptor versus the ligand? Will CGRP inhibitors have a role in other hyperinflammatory states?

COVID-19 represents an unprecedented threat that has already led to widespread collaboration and innovation in academic medicine. This may also be an opportunity to rapidly advance our understanding of the systemic consequences of our newer migraine therapies.

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