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Letter to the Editor Response

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Response to Letter to the Editor From Abobaker and Darrat: "Circulating levels of Calcitonin Gene-Related Peptide Are Lower in COVID-19 Patients"

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Abbreviations: CGRP, calcitonin gene–related peptide; IL. Interleukin.

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We are very glad our manuscript showing lower levels of calcitonin gene–related peptide (CGRP) in COVID-19 patients [1] has elicited a fruitful scientific discussion about the potential risks of treating these patients with either peptide analogs or antagonists, particularly since the FDA has approved a clinical trial to test a CGRP antagonist as a treatment option against COVID-19 [2]. In the short time since the publication of the paper, several groups have shown their agreement with our proposal that restoring levels of CGRP could be beneficial for the patients, whereas CGRP antagonists may further harm pulmonary physiology [3, 4]. On the other hand, Abobaker and Darrat, in their Letter to the Editor [5], indicate that CGRP induces the release of interleukin (IL)-6 and could be involved in the cytokine storm which is so damaging for patients. We agree that CGRP, as all members of this peptide family, is multifunctional and influences numerous physiological pathways in a context-specific fashion, so it is very difficult to predict the whole picture by just studying a single parameter. This is why adequate animal models and, foremost, clinical studies are much more informative than in vitro experiments. Abobaker and Darrat bring to the discussion 2 animal models of lung injury caused by either smoke inhalation or acid exposure. In these models, CGRP inhibitors were applied, with positive outcomes. Unfortunately, these models are somewhat removed from the type of injuries suffered by COVID-19 patients. In our original manuscript, we referenced a much closer model: a viral infection with respiratory syncytial virus, which resulted in decreased CGRP expression in the lung, in a similar fashion as we found in humans. Furthermore, treatment with CGRP abolished airway hyperresponsiveness in these animals, fostering recovery [6]. From the clinical point of view, a very recent meta-analysis has found a strong correlation between headache symptoms and COVID-19 survival [4]. The authors point out that those patients that increase their CGRP expression to levels compatible with headache onset may compensate the loss of pulmonary CGRP and have a better chance at survival. Therefore, treating these patients with CGRP antagonists may reduce

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their headache symptoms but compromise their survival. In addition, IL-6 levels are more stable in COVID-19 patients suffering headaches than in those without them [7]. We also agree with Abobaker and Darrat that the results of the clinical trial with CGRP antagonists will shed information on whether this treatment is safe and efficacious on COVID-19 patients. We just want to warn the physicians following these patients to be especially vigilant in case unexpected complications arise. Unfortunately, CGRP agonists are not sufficiently developed to run a parallel clinical trial to demonstrate their potential to alleviate viral lung infections, including COVID-19.

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Additional Information

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