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colleagues<sup>2</sup> would have made it possible to classify subjects by severity more finely, thus identifying subgroups more likely to benefit from treatment. Indeed, the presence of other organ failure in patients was not detailed except for mechanical ventilation, suggesting low-grade CRS.

Second, two findings highlighted by the authors are the decrease in C-reactive protein (CRP) and the disappearance of fever, features also reported in another study of tocilizumab in COVID-19 by Hermine and colleagues.<sup>3</sup> Tocilizumab use is associated with an expected decrease in CRP because of its pharmacological effect. Hence the biological results suggest only tocilizumab usage, and considering the decrease of CRP as efficiency in COVID-19 treatment could be an overstatement.

Third, supplementary material shows that the standard-of-care consisted of atazanavir and hydroxychloroquine, two off-label treatments for COVID-19, further reducing the external validity of the study. In addition, up to 38% of patients in the severe group received corticosteroids, a treatment now recommended by the World Health Organization for severe COVID-19.<sup>4</sup> Overall, isolating the individual effect of tocilizumab among these therapies is difficult, particularly in an observational study, because we do not have the results of the control group.

These limitations call into question the authors' conclusion that tocilizumab may reduce mortality in COVID-19, especially since the publication of randomized clinical trials with negative results on mortality (Hermine and colleagues<sup>3</sup> and Stone and colleagues<sup>5</sup>). Further prospective studies are mandatory to define tocilizumab's place in the therapeutic arsenal for COVID-19.

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## Response



### To the Editor:

We reported our real-world experience with the coronavirus disease 2019 (COVID-19) during the beginning of the global pandemic as it affected the Northeastern part of the United States when there were no Food and Drug Administration-approved medications to treat COVID-19.<sup>1</sup> Our study reflected clinical practice based on available data during that time period. In the absence of proven therapies, tocilizumab was considered a good candidate for immunomodulatory therapy, based on experience with treatment of the cytokine-release syndrome in other disease conditions. To deploy the medication to those who would likely derive the greatest benefit, we selected patients with an oxygenation requirement and an elevated C reactive protein level. Though using a standard definition of cytokine-release syndrome may have been useful, our study definitions reflected real-world clinical decision-making rather than a preplanned intervention.

As the letter writers point out, our findings of decreased C reactive protein and disappearance of fever in those treated with tocilizumab suggest a biologic impact from tocilizumab use. In addition, we suggest that tocilizumab may impact survival and mechanical ventilation rates, as reported in our results. Regarding the external validity of the study, protease inhibitors and hydroxychloroquine have now been demonstrated to not be effective in randomized controlled trials for COVID-19 treatment. Therefore, we believe it is unlikely for these agents to have impacted study outcomes significantly, particularly that of mechanical ventilation. Furthermore, though it is certainly a limitation, treatment with additional agents has been a common occurrence with COVID-19 treatment-related trials and is by no means unique to our study.

Acknowledging the limitations of a retrospective design, our study did suggest clinical benefit with tocilizumab use, particularly in reducing the proportion of patients whose condition requires mechanical ventilation. Several observational and randomized controlled trials have since replicated these findings. The recently published global phase 3 EMPACTA clinical trial has shown that tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, although it did not improve survival.<sup>2</sup> Moreover, a large retrospective evaluation by Narain et al<sup>3</sup> of >5,000 hospitalized patients with COVID-19 on combination therapy reported superior survival outcome for corticosteroids with tocilizumab use when compared with standard of care treatment and treatment with corticosteroids alone or in combination with anakinra.

We thank Mombrun and Valette for their letter and their thoughtful assessment of the evidence. We agree that further prospective studies are mandatory to define tocilizumab's place in the therapeutic arsenal for COVID-19.

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## Could Atomoxetine-Oxybutynin, a Combination of Medications Being Explored for OSA Management, Have Any Effect on Sleep Bruxism or Jaw Muscle Tone?



### To the Editor:

We read with great interest the paper in *CHEST* (June 2020) from Taranto-Montemurro et al<sup>1</sup> assessing the effects of a medication combination, atomoxetine-oxybutynin (ato-oxy), on different endotypic traits of OSA. The ato-oxy combination is a mixture of noradrenergic and antimuscarinic agents, and it was reported to increase genioglossus muscle responsiveness to negative esophageal pressure swings of approximately threefold in a previous study.<sup>2</sup> The use of medications for individuals with specific clinical manifestations of OSA is an important avenue to personalized medicine or an adjunct therapy to CPAP or oral appliance use. Because our group has an interest in sleep bruxism (SB), a sleep motor manifestation associated with repetitive jaw muscle activity with occasional tooth grinding,<sup>3</sup> a clinical question emerged: Could the ato-oxy combination also induce a rise in SB frequency or in jaw muscle tone?

Such a question is supported by the fact that genioglossus muscle responsiveness is under the control of the hypoglossal XII motoneurons and the masseter, temporalis, and digastric jaw muscles at the level of the trigeminal network. The brainstem trigeminal and the facial motor nuclei are also modulated by noradrenergic and muscarinic substances.

Although the association of OSA and SB is still debated, evidence supports a concomitance with breathing events