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Impact of Interleukin-6 Receptor Blockade With Tocilizumab on Cardiac Injury in Patients With COVID-19: A Retrospective Cohort Study

Dear Editor,

Myocardial injury is a common finding in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is associated with increased morbidity and mortality [1, 2]. Coronavirus disease 2019 (COVID-19) infection often has a maladaptive proinflammatory cytokine state, and interleukin-6 (IL-6) is believed to be a key mediator of respiratory failure, shock, and multi-organ dysfunction. Earlier in the COVID-19 pandemic, there was much anticipation and hope as to whether an IL-6 receptor inhibitor, tocilizumab, could improve outcomes in patients with COVID-19. Observational data have suggested a reduction in mortality [3]; however, in October 2020, there were multiple randomized controlled trials whose findings did not support the routine use of tocilizumab in COVID-19 [4–6]. These studies did not explore the relationship between tocilizumab and cardiac injury, nor did they address whether the timing of tocilizumab administration impacts this outcome. We examined the presence of cardiac injury and outcomes stratified by disease severity in patients with COVID-19 treated with tocilizumab at providers' discretion.

We studied a cohort of 489 consecutive adult patients with COVID-19 who were admitted to our center in Boston, Massachusetts, in March–April 2020. A total of 74 patients received off-label tocilizumab, 61 in the intensive care unit (ICU) and 13 in intermediate care. The 61 ICU patients were compared with 152 propensity-matched ICU patients who did not receive tocilizumab, and the 13 non-ICU patients were compared with 26 propensity-matched non-ICU patients. Baseline characteristics were matched for age, gender, body mass index, hypoxia, admission Glasgow Coma Scale, symptom duration before admission, and cardiovascular risk factors (hypertension, hyperlipidemia, CAD, diabetes). The time from symptom onset to treatment did not differ between ICU and intermediate care patients (ICU: median [IQR], 10 [9–11] days; vs intermediate care: median [IQR], 10 [7–16] days; $P = .88$), suggesting that intermediate care patients did not receive tocilizumab earlier in the disease course but rather had a lower severity of disease at administration.

Examining cardiac injury in both cohorts, tocilizumab treatment was not associated with a lower degree of cardiac injury, defined by the area under the curve (AUC) of high-sensitivity troponin (hs-cTnT; ICU: median [IQR], 482 [150–783]; vs control: median [IQR], 224 [112–697]; $P = .11$; intermediate care: median [IQR], 95 [25–208]; vs control: median [IQR], 41 [22–120]; $P = .4$). We next examined the change in hs-cTnT levels after tocilizumab in both cohorts. This did not show a greater reduction of hs-cTnT levels in the intermediate care– or ICU-treated patients. Instead, there was a signal toward higher values of hs-cTnT in tocilizumab-treated patients, determined by the slope change of hs-cTnT after tocilizumab using a mixed-effects linear model (Figure 1).

There were no differences in cardiac complications (defined as acute coronary syndrome, heart failure, or arrythmia) between tocilizumab-treated patients (ICU: 32 [52.5%]; vs control: 46 [37.7%]; $P = .08$; intermediate care: 2 [15.4%]; vs control: 3 [11.5%]; $P = 1.0$) and also no difference in all-cause mortality (ICU: 16 [26.2%]; vs control: 38 [31.1%]; $P = .6$; intermediate care: 4 [30.8%]; vs control: 2 [7.7%]; $P = .16$). Tocilizumab-treated ICU patients had an increased rate of infectious complications (defined as pneumonia, bloodstream or endovascular infections; ICU: 32 [52.5%]; vs control: 38 [31.1%]; $P = .009$), but there was no significant difference in intermediate care patients (intermediate care: 0; vs control: 2 [7.7%]; $P = .8$).

The etiology of cardiac injury in COVID-19 is likely multifactorial and, in part, a consequence of a hyperinflammatory response syndrome. This study, which examined whether blockade of IL-6 could reduce cardiac injury in COVID-19 when given to either patients who were critically ill or those with less severe illness, did not demonstrate a benefit and, in fact, suggested a signal toward harm. It is worth emphasizing that disease duration in severe and intermediate subgroups in this study was similar: 10 days between symptom onset and tocilizumab administration. Whether cardiac injury and cardiac complications could be reduced if tocilizumab were administered earlier, before the hyperinflammatory syndrome, remains unknown. The limitations of this study include small numbers, absence of information on steroid use, and the lack of standardized criteria for tocilizumab treatment. Future analyses of the randomized controlled trials of tocilizumab use in COVID-19 are needed to assess possible secondary benefits, particularly to determine whether earlier initiation of tocilizumab could impact cardiac injury and other outcomes.

Acknowledgments

Financial support. This work was supported by NHLBI T32 HL094301 (B.W.).

Potential conflicts of interest. Dr. Stone reports research grants and consulting fees from Genentech and Roche, outside the submitted work. Dr. Di Carli reports grants from Gilead Sciences and Spectrum Dynamics and personal consulting fees from Janssen and Bayer, outside the submitted work. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

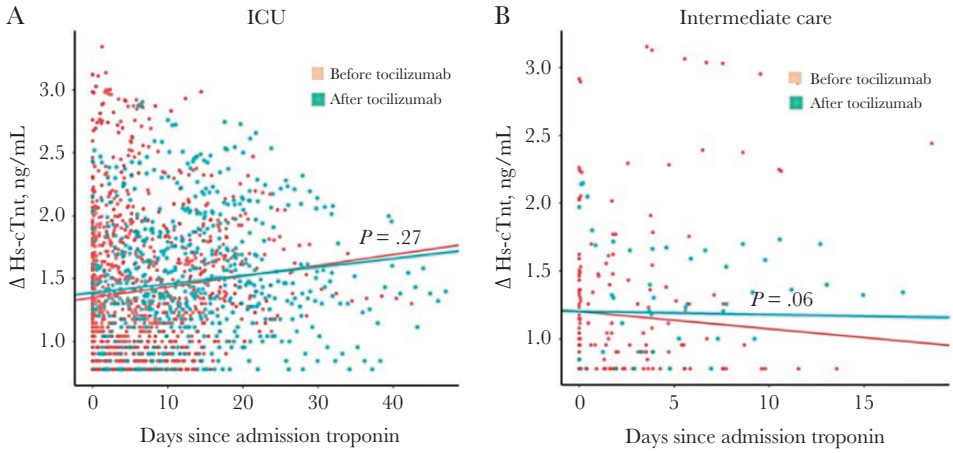

Figure 1. hs-cTnT after treatment with tocilizumab in ICU and intermediate care patients. Shown is the slope of the rate of change in hs-cTnT before and after tocilizumab treatment in ICU (A) and intermediate care (B) patients. ICU: slope = 0.009 before vs 0.007 after tocilizumab; $P = .27$; intermediate care: slope = –0.01 before vs –0.002 after tocilizumab; $P = .06$. Abbreviations: hs-cTnT, high-sensitivity troponin; ICU, intensive care unit.

Author contributions. B.W. and A.W. designed the study. B.W., G.Z., A.K., J.P., J.S., M.D.C., S.N., and A.W. collected the data or provided scientific interpretation of the data. G.Z., B.W., and A.W. performed the statistical analysis. B.W. and A.W. analyzed the data. B.W. and A.W. drafted the manuscript. All authors revised the manuscript critically for important intellectual content and approved the final version of the manuscript.

Patient consent. The authors attest that they are in compliance with the ethical standards of the Helsinki Declaration, human studies committees of the authors' institutions, and Food and Drug Administration guidelines, including patient consent where appropriate.

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Received 15 November 2020; editorial decision 7 January 2021; accepted 12 January 2021.

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DOI: 10.1093/ofid/ofab012