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EDITORIAL COMMENT

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A CRITICAL Drug During a CRITICAL Time?*

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On March 11, 2020, the World Health Organization officially declared coronavirus disease-2019 (COVID-19) a pandemic. The disease is attributed to infection with severe acute respiratory syndrome coronavirus-2, a member of the family of zoonotic viruses Coronaviridae. More than a year later, although COVID-19 remains rampant, the global vaccination rollout has shown promising results in reducing cases and mortality week by week. Unfortunately, in patients with COVID-19, thrombotic complications remain prevalent, contributing to mortality and morbidity, particularly in the presence of cardiovascular comorbidities. A complex interplay between endothelial dysfunction, vascular inflammation, coagulopathy, and impairment of endogenous fibrinolysis plays key roles in the resulting high incidence of thrombotic complications (1). The search for a safe and effective thromboprophylaxis and treatment strategy therefore remains a top priority in the treatment of patients with COVID-19.

In this issue of *JACC: Basic to Translational Science*, Leucker et al (2) present the results of the CRITICAL (Crizanlizumab for Treating COVID-19 Vasculopathy) trial. The CRITICAL trial is a small, randomized, double-blind, placebo-controlled, single-center study whose aim was to assess the effects of crizanlizumab, a humanized monoclonal antibody to P-selectin, on the inflammatory and thrombotic markers in hospitalized patients with moderate COVID-19. The primary outcome of the trial was the difference in levels of P-selectin, with secondary outcomes assessing levels of D-dimer, von Willebrand factor, and C-reactive protein, as well as clinical parameters (World Health Organization ordinal scale for COVID-19 trials, time to discharge, and safety). Exploratory analyses investigating additional biomarkers of inflammation and thrombosis were also performed post hoc. A total of 54 patients were recruited in a 1:1 ratio, and with withdrawn consent and loss to follow-up, 22 patients in the active treatment group and 20 patients in the placebo group were included in the final analysis. The investigators observed a significant reduction in P-selectin (on days 3, 7, and 14) and increase in D-dimer levels (on day 3) compared with the placebo group, with no differences in clinical outcomes assessed, because of low event rates. On the basis of results from further analyses exploring markers of thrombosis (an increase in D-dimer and a decrease in prothrombin fragment 1.2), Leucker et al (2) concluded that crizanlizumab could possibly increase endogenous fibrinolysis, which could have an impact on outcomes in patients with COVID-19. Despite the role of P-selectin in inflammatory and thromboinflammatory responses, Leucker et al (2) report that treatment with crizanlizumab had no effect on levels of interleukin-6, tumor necrosis factor-alpha, and C-C motif chemokine ligand 2 and led to increases in interleukin-8 and interleukin-10, suggesting that crizanlizumab does not affect the inflammatory response associated with COVID-19. This supports further the investigators' conclusion that crizanlizumab is likely to modulate the equilibrium between coagulation and fibrinolysis in patients with

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COVID-19 by enhancing the latter. Some of the limitations of the study are the administration of only a single dose of crizanlizumab, the timing of administration with respect to the admission journey, and the relatively low-risk and small population with few clinical events, limiting the potential to correlate the biochemical findings to clinical outcomes.

We congratulate and applaud the investigators on carrying out this study investigating a novel pharmacologic target to potentially improve the outcomes of patients experiencing the devastating thrombotic complications of COVID-19. Although many pharmacologic agents targeting thromboinflammation in COVID-19 have been investigated, currently our therapeutic options remain limited (3). Antithrombotic drugs may represent a promising clinical strategy for patients with COVID-19, but their use must be weighed carefully, as it carries additional bleeding risks (3). Indeed, efforts to personalize antithrombotic treatment have been proposed (4).

The inhibition of P-selectin has previously been shown in animal models to promote thrombus resolution or, in other words, to improve endogenous fibrinolysis, and the changes in thrombotic profiles seen in this study support this observation (5). Crizanlizumab has also been trialed in phase 3 studies among patients with sickle-cell disease and has been shown to reduce the incidence of vaso-occlusive crises without increasing the risk for bleeding (6); hence it could potentially be a safer alternative to currently available antithrombotic drugs for patients with COVID-19. However, this high-risk group of patients will undoubtedly present specific clinical challenges. Further careful exploration is required to understand whether crizanlizumab reduces mortality among patients with COVID-19 and whether it remains efficacious and safe for more severe cases of this disease.

Although it is exciting that a new therapeutic agent could be available in the near future to manage the thrombotic complications of COVID-19 and potentially other thromboembolic diseases, some caution must be applied. The findings and conclusions from CRITICAL are highly limited by the small sample size, the moderate severity of the condition for the recruited patients, and low incidence of clinical adverse events encountered in this study. We look forward to further investigations of this therapeutic agent addressing its efficacy in patients with COVID-19 and other thromboembolic diseases.

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REFERENCES

1. Gencer S, Lacy M, Atzler D, van der Vorst EPC, Döring Y, Weber C. Immunoinflammatory, thrombohaemostatic, and cardiovascular mechanisms in COVID-19. *Thromb Haemost*. 2020;120:1629–1641.

2. Leucker TM, Osburn WO, Reventun P, et al. Effect of crizanlizumab, a P-selectin inhibitor, in COVID-19: a placebo-controlled, randomized trial. *J Am Coll Cardiol Basic Trans Science*. 2021;6:935–945.

3. Bikdeli B, Madhavan MV, Gupta A, et al. Pharmacological agents targeting thromboinflammation in COVID-19: review and implications for future research. *Thromb Haemost*. 2020;120:1004–1024.

4. Chaudhary R, Kreutz RP, Bliden KP, Tantry US, Gurbel PA. Personalizing antithrombotic therapy in COVID-19: role of thromboelastography and thromboelastometry. *Thromb Haemost*. 2020;120:1594–1596.

5. Diaz JA, Wrobleski SK, Alvarado CM, et al. P-selectin inhibition therapeutically promotes thrombus resolution and prevents vein wall fibrosis better than enoxaparin and an inhibitor to von Willebrand factor. *Arterioscler Thromb Vasc Biol*. 2015;35:829–837.

6. Abboud MR, Howard J, Cançado R, et al. Crizanlizumab versus placebo, with or without hydroxyurea/hydroxycarbamide, in adolescent and adult patients with sickle cell disease and vaso-occlusive crises: a randomized, double-blind, phase III study (STAND). *Blood*. 2019;134, 998-998.

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