



Authors' Reply to: Tocilizumab, Adipokines and Severe Complications of COVID-19

Bin Liu¹ · Zhigang Qi²

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We thank Fioravanti et al. [1] for their comments regarding our article on the use of tocilizumab in the treatment of novel coronavirus pneumonia (COVID-19) [2]. The article highlighted the possibility that tocilizumab may inhibit the occurrence and development of a cytokine storm by regulating adipokines, such as adiponectin, and inducing antithrombotic/fibrinolytic effects by regulating chemerin in patients with obesity with COVID-19 [1]. The ideas are relatively novel, and we are interested in discussing the viewpoint of this article on the basis of the existing evidence.

Studies from several countries have found that a higher body mass index is related to an increased hospitalization rate and a greater need for mechanical ventilation, independent of hypertension and diabetes mellitus [3–5]. Similarly, obesity is a critical risk factor for being hospitalized with COVID-19 as has been highlighted by many studies [6–8]. It is known that receptor-mediated endocytosis is the most common pathway for a virus to enter cells, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a beta coronavirus that gains cellular entry via angiotensin converting enzyme 2 (ACE2), a cell surface receptor. It is expressed predominantly in the kidneys, blood vessels, heart, and most importantly in lung AT2 alveolar epithelial cells, and is the receptor used by SARS-CoV-2 to mediate clathrin-dependent endocytosis and infect lung cells [9].

On the one hand, several recent surveys have shown that *ACE2* gene expression or ACE2 levels are upregulated in the bronchial biopsy, bronchoalveolar lavage, or blood in patients with obesity [10, 11]. Altered serum levels of ACE2

related to obesity might contribute to a greater virus uptake and a higher risk of developing severe COVID-19 [10]. On the other hand, SARS-CoV-2 infection triggers a cytokine storm, an excessive immune response, which causes a devastating systemic injury, particularly in patients with obesity, which in itself is a chronic multi-organ inflammatory disease. Immune cells accumulated in visceral adipose tissue, together with paracrine adipocytes, release a variety of cytokines (such as interleukin [IL]-1 β , IL-5, IL-6, and IL-8) that can lead to pulmonary and systemic inflammation [12–14]. In this manner, a more intense cytokine storm is produced, which may account for a greater risk of intensive care unit admission and higher mortality rates in patients with obesity with severe COVID-19.

Adipokines are cytokines secreted mainly by white adipose tissue, involved in inflammation, endothelial dysfunction, and atherosclerosis, and may be a molecular link between rheumatoid arthritis, metabolic syndrome, and the risk of cardiovascular disease [15, 16]. As described in Fioravanti et al.'s article [1], adiponectin is an adipokine with insulin-sensitizing and anti-atherogenic properties. Hypoadiponectinemia has been shown to be associated with obesity, diabetes, metabolic inflammatory syndrome, and inflammation [17, 18]. Furthermore, low serum levels of adiponectin were reported as predictor of mortality in critically ill patients in intensive care units [1]. Leptin has pro-inflammatory properties stimulating the production of tumor necrosis factor- α , IL-6, and IL-12. Chemerin is a novel adipokine involved in inflammation (stimulates chemotaxis, macrophages, and dendritic cells, and induces the release of IL-6), coagulation, and fibrinolysis. Furthermore, elevated circulating chemerin levels correlate with endothelial dysfunction [18]. It appears that if tocilizumab can increase adiponectin levels and reduce circulating leptin and chemerin, we can think of this as a mechanism to treat cytokine storms and reduce the risk of thrombosis in patients with obesity with COVID-19. However, the effects of tocilizumab on adipokines are still controversial. Schultz et al. and Fioravanti

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✉ Zhigang Qi
qizhigang058518@163.com

¹ Nephrology Department, Wuxi People's Hospital Attached to Nanjing Medical University, Wuxi 214023, Jiangsu, China

² Department of Pharmacy, Wuxi People's Hospital Attached to Nanjing Medical University, Wuxi 214023, Jiangsu, China

et al. showed that after several months of tocilizumab treatment, the adiponectin level was increased, but resistin and leptin serum levels were not significantly changed [19, 20]. Inconsistently, Tournadre et al. showed no change in resistin and adiponectin levels, but a reduction in leptin serum levels after tocilizumab treatment [21]. In contrast, Hoffman et al. showed adiponectin levels were decreased, and leptin levels remained unchanged after 4 months of tocilizumab treatment [22]. More importantly, studies on the effects of tocilizumab on the regulation of adipokine levels in patients with obesity with COVID-19 have not yet been conducted.

There are several ways in which COVID-19 may affect the management of thrombotic disease. First, the direct or indirect effects of SARS-CoV-2 infection, such as through severe illness and hypoxia, may predispose patients to thrombotic events. Preliminary reports suggest that disseminated intravascular coagulation can easily occur in patients affected by COVID-19 [23, 24]. Additionally, the severe inflammatory response, critical illness, and underlying traditional risk factors may all predispose to thrombotic events, similar to prior virulent zoonotic coronavirus outbreaks [25, 26]. A recent study from China, using the Padua model, reported that 40% of hospitalized patients with COVID-19 were at a high risk of venous thrombus embolism [27]. Thus, venous thrombus embolism risk stratification for hospitalized patients with COVID-19 should be undertaken. Hospitalized patients with COVID-19 who have respiratory failure or co-morbidities (e.g., active cancer or heart failure) [28], patients who are bedridden, and those requiring intensive care should receive pharmacological venous thrombus embolism prophylaxis, unless there are contraindications. The choice of drug should be based on recommendations in existing guidelines [29, 30].

Although limited evidence suggests that tocilizumab can significantly reduce serum chemerin levels in patients with rheumatoid arthritis, and is not related to the disease treatment response [20], it appears a potential mechanism to reduce the risk of thrombosis in patients with obesity with COVID-19. However, tocilizumab is not available for the prevention and treatment of thrombotic disease in hospitalized patients with COVID-19 until its efficacy is fully confirmed.

In conclusion, we can speculate that in patients with obesity with severe COVID-19, cytokines secreted by immune cells after SARS-CoV-2 infection together with those produced by adipocytes contribute to a more intense cytokine storm. Tocilizumab has been used in such patients, showing preliminarily good efficacy and safety. Whether tocilizumab is responsible for these effects by regulating adipokines is still controversial and needs to be further confirmed. On the present evidence, hospitalized patients with COVID-19 are at a high risk of thrombotic disease owing to inflammation, hypoxia, immobilization, endothelial damage, and diffuse

intravascular coagulation. Although limited evidence suggests that tocilizumab can reduce serum chemerin levels, a novel adipokine involved in inflammation, coagulation, and fibrinolysis, it appears a potential mechanism to reduce the risk of thrombosis. However, tocilizumab is not available for the prevention and treatment of thrombotic disease in hospitalized patients with COVID-19 until its efficacy is fully confirmed.

Compliance with Ethical Standards

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Conflict of interest Bin Liu and Zhigang Qi have no conflicts of interest that are directly relevant to the content of this letter.

Author contributions ZQ designed the article. BL and ZQ co-wrote the first draft of the manuscript, which was critically revised by ZQ.

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