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LETTER TO THE EDITOR

Tocilizumab, Adipokines and Severe Complications of COVID-19

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To the Editor: A recent article published by Zhang et al. [1] discussed the possible mechanism of action of tocilizumab in the treatment of patients with severe COVID-19 and stimulated some considerations on the basis of our previous experience.

Obesity is considered as a major risk factor for serious COVID-19-related complications, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2].

The link between obesity and acute lung injury during infection can be partially explained by the activation of the renin-angiotensin system. It has been supposed that the virus uses an angiotensin-converting enzyme 2 (ACE2)-dependent mechanism of cellular entry; this receptor is also expressed in adipocytes, including ectopic adipocytes within the alveolar interstitial [3].

However, we can postulate that obesity may predispose to the development and progression of the COVID-19 disease through several mechanisms. Growing evidence demonstrated that adipose tissue is an active endocrine organ and secretes many substances known as "adipocytokines" such as adiponectin, leptin, resistin, visfatin, chemerin, tumor necrosis factor (TNF)-α, interleukin (IL)-6, factors of the complement system, growth factors, and adhesion molecules, involved in the regulation of several processes including inflammation and immunity. Then, an abnormal secretion of adipocytokines from fat tissue can contribute to development of the condition described as "cytokine storm" which characterized the severe form of SARS-CoV-2.

Tocilizumab, a humanized monoclonal antibody that acts as an IL-6 receptor antagonist, has shown remarkable efficacy and safety in the treatment of established rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis, giant cell arteritis, and cytokine release syndrome. Since March 3, 2020 the National Health Commission of China has formally included intravenous (IV) tocilizumab in the treatment program of COVID-19 for its capacity to reduce or reverse the cytokine storm [4]. Also, Italian guidelines support the use of IV tocilizumab in patients with severe or critical complication of COVID-19 [5]. Preliminary results showed clinical efficacy of the drug with reduction of temperature, improvement of respiratory function, decrease of C-reactive protein and mortality associated with a favorable safety profile [6, 7].

Among the possible mechanisms of action of tocilizumab in the COVID-19 infection, it seems of relevance to consider the effect on adipokines and on pro-thrombotic factors demonstrated in patients with RA [8, 9]. Indeed, this drug is able to increase serum levels of adiponectin and to reduce circulating leptin, chemerin, plasminogen activator inhibitor-1 (PAI-1), and fibrinogen [8–10].

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 [11, 12], also, low serum levels of adiponectin were reported as predictor of mortality in critically ill patients in intensive care units [13]. Leptin has pro-inflammatory properties stimulating the production of TNF-α, IL-6, and IL-12 and potential atherogenic effects [14].

Chemerin is a novel adipokine involved in inflammation (stimulates chemotaxis, macrophages, and dendritic cells, induces the release of IL-6), in coagulation and fibrinolysis; furthermore, elevated circulating chemerin levels correlate with endothelial dysfunction [14].

With these observations, we suggest that tocilizumab could be effective in the treatment of severe complications of patients with COVID-19, with a particular relevance in obesity, for its effect on adipocytokines and, in turn, in reducing

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the cytokine storm. Furthermore, the anti-thrombotic/fibrinolytic action of the drug appears relevant considering the high risk of hypercoagulability and venous or arterial thrombosis in critical phase of COVID-19 infection [15].

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Compliance with Ethical Standards

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