Coronary microvascular dysfunction in the context of long COVID-19: What is the effect of anti-inflammatory treatment? Author's reply

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We have read with great interest the "Letter to the Editor" by Patoulias et al. [1] with comments on our study [2].

The anticipated more severe course of COVID-19 is partially mediated by endothelial damage. Cytokines, including IL-1, IL-2, IL-6, IL-7, and TNF alpha, which regulate the immune response, are among the causes of the deterioration of the condition of patients who suffer from proinflammatory cytokine storm that occurs during SARS-CoV-2 infection [3]. IL-6 promotes vascular remodeling via increased transforming growth factor-β1(TGF-β1)-mediated matrix metalloproteinases (MMPs)2 and 3 signaling. During COVID-19, a wide spectrum of complications affecting organs appears to be caused by a "cytokine storm", with an increased inflammatory and immune response [4]. Subsequent activation of matrix MMPs leads to endothelial vasodilatory dysfunction resulting in increased coronary resistance, impaired flow-mediated dilation (FMD), and finally impaired coronary flow reserve. Under physiological conditions, the endothelial glycocalyx promotes flow-mediated dilation by transducing the shear stress [5]. Pathophysiological conditions, such as inflammation and oxidative stress, are associated with glycocalyx structural alterations, and its damage by pro-inflammatory cytokines such as IL-1 and IL-6 leads to alterations in vascular permeability with associated interstitial fluid shift and generalized edema [6]. Currently, there is no specific treatment: anti-inflammatory, antioxidant, or limiting the viral replication and aiming at the sequels of thrombo-inflammation, which results in acute oxidative stress in the course of infection. Nevertheless, some drugs aiming precisely at inhibiting the inflammatory cascade could become a promising therapeutic strategy for limiting the burden of coronary endothelial damage. Since IL-6 is a drug target for several diseases of inflammatory origin, pharmacological blockers of the IL-6 signaling pathway, including tocilizumab, were postulated to blunt the abnormal SARS-CoV-2-induced cytokine release and could thus limit endothelial damage. It has already been demonstrated that treatment with tocilizumab limits endothelial inflammatory dysfunction and improves endothelial glycocalyx thickness with subsequent significant improvement in vasodilatory function, as assessed by FMD [7].

The subjects enrolled in our pilot study included both those previously hospitalized in the COVID-19 center and COVID-19 convalescents treated without hospitalization, who received specialistic post-COVID outpatient care. The "ambulatory COVID-19" subpopulation had 17 subjects, whereas the remaining 7 had been previously hospitalized. As result, the number of subjects where specific treatment (including tocilizumab, remdesivir, or convalescent plasma) had been applied was too low to provide statistically relevant data. Therefore those subjects could be described only as a very small case series without any

analyses. Furthermore, numerous comorbidities affecting endothelial function make this group relatively heterogenous, which could blur the clarity of "tocilizumab-effect" assessment. Hence, we have decided to present only the raw data on the whole population without subsequent sub-analyses. Nevertheless, we believe that the authors of the letter have a great idea for performing such analyses, which should be conducted on a greater number of cases preferably from numerous centers and we are ready to provide our data for such analysis.

Article information

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