

EDITORIAL



IL-6, IL-1 β and cytokine-targeted therapy for COVID-19 patients: two more reasons to take into account statins?



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Statins have recently been proposed as a potential adjunctive therapy for the Coronavirus disease 2019 (COVID-19) [1]. A number of retrospective studies support the potential protective role of statins against severe COVID-19 infection [2–5]. Increasing evidence shows that statins would be beneficial in patients who were on chronic statin treatment prior to getting COVID-19 infection [1,3–6]. On the contrary, only a few very small clinical studies have failed to show a link between statin use and better outcomes in patients with severe COVID-19 [5,7]. A retrospective single-center observational study has indicated that statin use during the 30 days prior to admission for COVID-19 is connected with a decreased risk of developing severe COVID-19, and a faster time to recovery among patients without severe condition [6]. Another retrospective analysis of 2,626 patients have also documented that antecedent statin administration in patients hospitalized with COVID-19 is linked to lower inpatient mortality [3]. Analysis of findings from the American heart association's COVID-19 cardiovascular disease Registry has confirmed that use of statins prior to hospitalization for COVID-19 relates to a significantly decreased risk for death and severe COVID-19, particularly among those with cardiovascular disease or hypertension when compared to patients without these underlying diseases, strongly supporting the continuation and aggressive initiation of statins and antihypertensive drugs among patients at risk for COVID-19 with these underlying medical conditions [4]. Concordantly, a large retrospective observational study recruiting patients from nineteen hospitals have found that statin use prior hospitalization is associated with lower SARS-CoV2 infection-related mortality in patients hospitalized for COVID-19 supporting the evidence that statin treatment should not be discontinued during the COVID-19 pandemic [5]. However, the authors conclude that potential beneficial effects of statins on mortality rates in COVID-19 patients need confirmation by a prospective randomized controlled trial [5]. On the same line, an observational cohort study using data from Danish nationwide registries conclude that recent statin exposure in patients with COVID-19 infection does not relate to an increased or decreased risk of all-cause mortality or severe infection [7]. COVID-19 represents the

infectious disease caused by the newly discovered coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) that developed in December 2019 in Wuhan, China, leading to a worldwide pandemic [1,3,6]. Statins represent the most commonly utilized drugs for hypercholesterolemia functioning as inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [3,8]. Statins have also emerged to have a strong anti-inflammatory effect [8–10]. The anti-inflammatory activity of statins has been associated with the ability of these drugs to reduce the level of inflammation biomarkers including Interleukin-6 (IL-6) [9]. However, the exact underlying mechanism behind the anti-inflammatory properties exhibited by statins still remain unclear [8]. Statins have been suggested to suppress the pro-inflammatory Interleukin-1 β (IL-1 β) [8]. IL-1 β represents a significant pro-inflammatory cytokine that is atypical in that is synthesized as an inactive precursor [8]. Caspase-1 (CASP1)-activating large protein complexes named inflammasomes represent key players in processing of pro-IL-1 β into its mature active form [8]. Statins have been detected to interfere with mature IL-1 β signaling [8]. It has been provided evidence that statins counteract inflammation associated with IL-1 β through induction of an anti-inflammatory 28-kDa form of the pro-inflammatory IL-1 β [8]. This statin-induced IL-1 β processing appears to be independent of CASP1-activating inflammasomes [8]. Interestingly, it has been demonstrated that the 28-kDa form of IL-1 β is not able to trigger IL-1-receptor-1 (IL-1R1) to signal inflammatory responses, therefore reducing inflammatory responses triggered by mature IL-1 β [8]. Remarkably, it has been highlighted that IL-6 expression may be triggered in response to IL-1 β implying that inhibition of IL-1 β by statins may also suppress IL-6 release [10]. COVID-19 is characterized by different clinical features ranging from asymptomatic to only mild symptoms in the majority of the patients [2,11,12]. However, some COVID-19 patients may present with systemic hyper-inflammation designated under the umbrella term of macrophage activation syndrome (MAS) or cytokine storm with significant mortality worldwide [2,11,12]. COVID-19 with MAS characteristically occur in subjects with adult respiratory distress syndrome (ARDS) and

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historically, non-survival in ARDS has been linked to unrestrained IL-6 and IL-1 β elevation [11,12]. Lung inflammation by SARS-CoV-2 infection has been linked to the expression of several pro-inflammatory cytokines including IL-1 β and IL-6 [2,12]. The binding of COVID-19 to the Toll Like Receptor (TLR) has been reported to elicit the release of pro-IL-1 β which is cleaved by CASP1, followed by inflammasome activation and production of active mature IL-1 β which is a mediator of lung inflammation, fever and fibrosis [12]. Increased IL-6 levels have been documented to predict respiratory failure in hospitalized symptomatic COVID-19 patients [2,11,12]. IL-6 has been recognized to cause pneumonia and MAS-Like Disease in COVID-19 [12]. Currently, COVID-19 has no approved proven effective treatment [1,13,14]. Many existing drugs have been suggested as possible repurposing candidates to cure or prevent COVID-19 counteracting one or more steps of SARS-CoV2 lifecycle or inhibiting the effects of SARS-CoV2 infection [13–15]. It has been underlined that management of patients with confirmed COVID-19 should be combined with appropriate anti-inflammatory strategies once immunologic complications take place [13–15]. Thus, numerous pharmaco-immunomodulatory therapeutic strategies have been

considered to prevent COVID-19 hyper-inflammation and its potentially deadly complications [15]. These agents include specific immune modulators such as the humanized anti-IL-6 and anti-IL-1 receptor monoclonal antibody or, nonspecific immune-modulators such as corticosteroids or, inadvertent immune modulators such as statins [15,16]. The benefits of statins have been related to their immunomodulatory and anti-inflammatory effects since hyper-inflammation appears to play a critical role in possible life-threatening complications of COVID-19[1,2,4,5,12]. Even if statins are in general safe, it is essential to take into account drug-drug interactions when treating COVID-19 patients with antibiotics, antiviral drugs and protease inhibitors, since they might increase the risk of statin-related rhabdomyolyses [1,17]. Taken together, I hypothesize that the encouraging properties of statins, principally concerning their anti-inflammatory and immunomodulatory activity may represent the rationale for conducting prospective randomized controlled trials to verify whether statins may be advantageous in patients with COVID-19 and hyper-inflammation. I suppose that statins use might improve survival among patients suffering from COVID-19 by mitigating against the hyper-inflammation

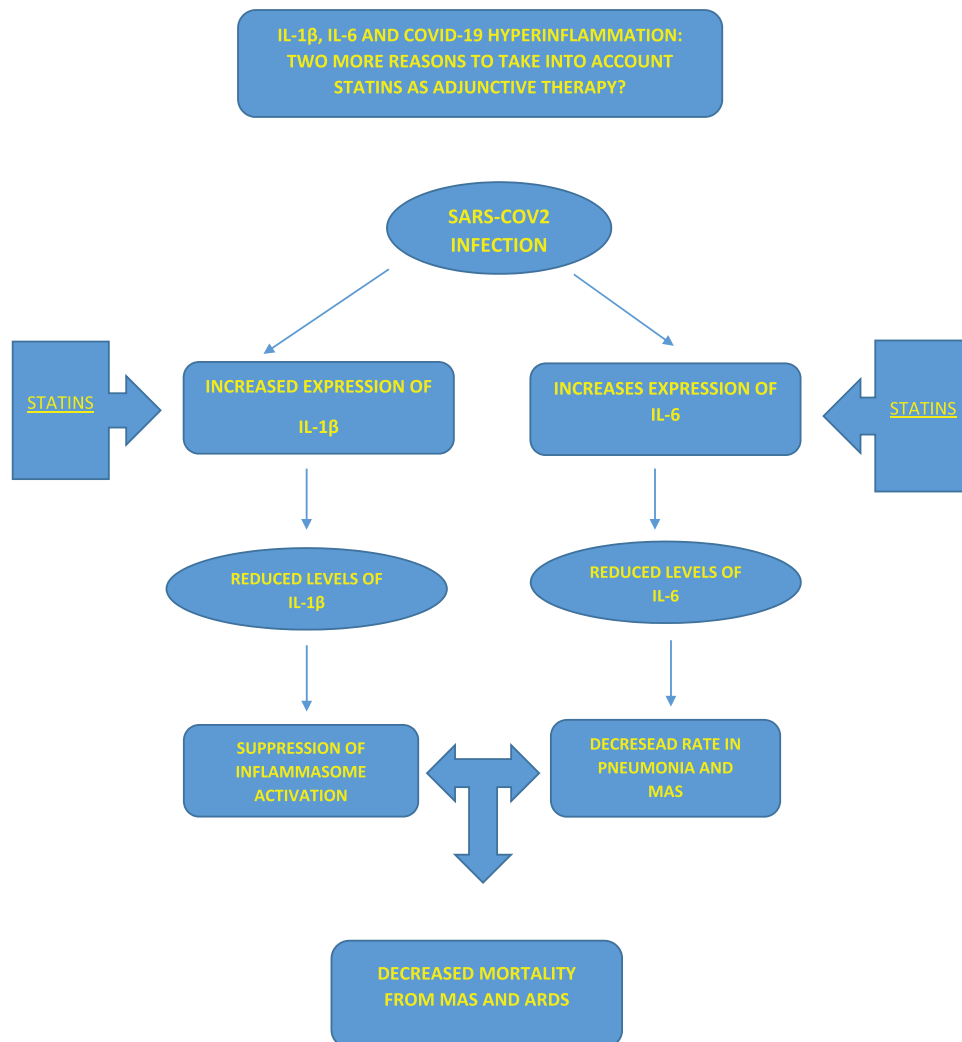


Figure 1. IL-1 β , IL-6 and COVID-19 hyperinflammation: two more reasons to take into account statins as adjunctive therapy?

through down-regulation of both IL-1 β and IL-6 (Figure 1). On this regard, I conjecture that statins may be more feasible in terms of estimating costs and benefits when compared with IL-6 and IL-1 receptor antagonist. I think that statins are low-cost drugs that might concomitantly control both IL-1 β and IL-6 overexpression, conversely IL-6 and IL-1 receptor antagonists are more expensive drugs that act on one or the other pro-inflammatory interleukin. Research studies are warranted to define whether statin use may be inserted among therapeutic options in the management of COVID-19 patients.

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Declaration of interest

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