Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

Tocilizumab for severe COVID-19: A promising intervention affecting inflammation and coagulation

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The COVID-19 pandemic is causing significant morbidity and mortality worldwide. Although most patients experience predominantly a respiratory tract infection, a proportion of patients progresses to a more severe and systemic disease, characterised by treatment-resistant pyrexia, acute lung injury with adult respiratory distress syndrome (ARDS), shock, and multiple organ dysfunction, associated with substantial mortality [1,2].

Severe COVID-19 infection is associated with increased levels of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and several interleukins (IL), as well as other chemokines, inflammatory mediators, and damage-associated molecular patterns (DAMPs) [3]. In a subset of the most severely affected COVID-19 patients, a cytokine 'storm' profile can be found, characterized by high levels of proinflammatory cytokines and remarkably increased levels of TNF-α, IL-2, IL-6, granulocyte-colony stimulating factor, and several chemokines [4]. A cytokine storm is a hyper-immune phenomenon leading to an uncontrolled release of pro-inflammatory cytokines that will cause a systemic inflammatory state. It has been hypothesized that this pattern mimics secondary haemophagocytic lymphohistiocytosis (sHLH), an under-recognised, hyper-inflammatory syndrome characterized by fulminant hyper-cytokinaemia, excessive coagulation activation and multi-organ failure [5].

In the pathogenesis of severe COVID-19 the cytokine IL-6 seems to play a dominant role. Plasma levels of IL-6 are higher than usually seen in severe (bacterial) sepsis. In addition, increased IL-6 levels are a strong predictor of mortality and IL-6 levels were found to be related to more severe lung injury [6,7]. In a meta-analysis of 9 studies in patients with severe COVID-19 IL-6 levels closely correlated to the severity of the disease and –again- mortality [8]. This has also observed in other coronavirus infections, such as severe adult respiratory syndrome (SARS) or influenza A infection [9]. In view of this central role of IL-6 in the pathogenesis of severe COVID-9 infection, therapies specifically directed against this cytokine may be considered.

Tocilizumab is a monoclonal anti-soluble IL-6 receptor antibody an has been licensed for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and giant cell arteritis. It is also established treatment for Castleman's disease and the cytokine release syndrome that is seen as a complication of CAR-T cell therapy for lymphoproliferative malignancies and other cancer [10]. Interestingly, cytokine release syndrome is the consequence of an uncontrolled immune activation characterized by the occurrence of a 'cytokine storm' which is not very different from the one seen in the most severe COVID-19 patients [11]. Hence, tocilizumab has been proposed for patients with severe COVID-19 as well [12]. Initial clinical observations from China have shown an improvement in pneumonia and associated symptoms in patients with COVID-19 treated with tocilizumab [13]. Subsequently, several retrospective cohort studies have focused on the efficacy and safety of this treatment.

In this issue of the European Journal of Internal Medicine three groups of authors report on the use of tocilizumab in patients with severe COVID-19. Campochiaro et al. studied 65 patients with COVID-19 that were admitted to the hospital, of which 32 received tocilizumab [10]. It is not clear what determined the treatment with the antibody, as this was at the discretion of the attending physician. They observed a non-significant lower mortality in tocilizumab-treated patients (16% versus 33% in non-treated patients). In another study, Capra et al. included 85 patients with COVID-9 and respiratory failure and in this series 62 patients received tocilizumab, as soon as the antibody became available [14]. They observed a lower mortality (2 out of 62 patients (3.2%) in the tocilizumab group compared to 11 out of 23 patients (47.8%) in the untreated group. It should be mentioned, however, the untreated group should be considered as historic controls and it cannot be excluded that increasing insights in the optimal treatment of severe COVID-19 may have contributed to the result. Lastly, Morena et al. observed in 51 patients with severe COVID-19 that after initiation of tocilizumab there was a lowering of the body temperature, normalization of C-reactive protein (CRP) and a restoration of lymphopenia [15]. In this study side effects of tocilizumab were systematically assessed and the authors found hepatic enzyme elevation in 29%, thrombocytopenia in 14% and bacterial or fungal infections in 27% of patients.

These studies (and similar observations in the literature) suggest that tocilizumab may be a promising candidate to improve the outcome

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of patients with severe COVID-19 infections. However, these results need confirmation in a prospective and properly controlled randomized trial before this treatment can be advocated. Genentech has recently announced a phase III randomized controlled clinical trial with tocilizumab for severe COVID-19. In addition, side effects of tocilizumab seem significant and will not only need systematic evaluation but also proper offset against potential benefits of tocilizumab.

It is tempting to speculate why specific anti-IL-6 targeted treatment would be more effective than more general anti-inflammatory interventions, such as corticosteroids, intravenous immunoglobulin, or other cytokine blockers (such as anakinra). Apart from the prominent role of IL-6 in the host-defense response in COVID19 it may be that specific beneficial effects of tocilizumab on the coagulation abnormalities associated with COVID-19 are also relevant. Many patients with severe COVID-19 infections present with a coagulopathy that is reminiscent but also distinct of other systemic coagulopathies associated with severe infections, such as disseminated intravascular coagulation or thrombotic microangiopathy [16,17]. The occurrence of this coagulopathy in COVID-19 infected patients is associated with a higher risk of death. In addition, patients with this coagulopathy have a very high risk of thromboembolic complications [18]. In experimental and clinical studies in bacterial sepsis IL-6 was shown to be the pivotal cytokine in the upregulation and expression of tissue factor on mononuclear cells and possibly endothelial cells [19]. Infusion of a monoclonal anti-IL-6 antibody resulted in the complete abrogation of coagulation activation in experimental sepsis [20]. In addition, studies in cancer patients receiving recombinant IL-6 indicated that indeed thrombin is generated following the injection of this cytokine [21]. It might therefore be hypothesized that blockage of IL-6 activity in COVID-19 not only benefits the inflammatory response but also the activation of coagulation in these patients.

As there is at present not yet a specific and unequivocally effective treatment for COVID-19 it is important to develop and evaluate adjuvant treatment options. In view of its specific anti-inflammatory (and potentially coagulation-modulating) properties, tocilizumab is an interesting and potentially promising treatment modality that requires further evaluation regarding its efficacy and safety for severe COVID-19.

Declaration of Competing Interest

None.

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