COVID-19:

The role of IL-6 blockers in the treatment of patients who experience severe respiratory complications

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Introduction

The cytokine release syndrome (CRS), also called the cytokine storm, is one of the most serious syndromes associated with COVID-19. The CRS occurs when the immune system becomes over-stimulated, potentially resulting in increased alveolar-capillary blood-gas exchange dysfunction, leading to pulmonary fibrosis and, ultimately death[1]. In patients with COVID-19, high plasma levels of cytokines, including IL-2, IL-6, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A and TNF-α appear to be indicative of the CRS [2, 3]. For patients infected with COVID-19, the CRS is directly related to disease severity and prognosis. Furthermore, analysis of immune characteristics of patients with COVID-19 shows that IL-6 and GM-CSF are two key cytokines leading to the CRS [1].

Treatments that block key cytokines involved in the CRS associated with COVID-19 already exist. Therefore, repurposing existing drugs as potential treatments for COVID-19 is one of the main strategies being adopted in response to the global pandemic, alongside utilizing novel treatments and developing vaccines. Owing to their mode of action, several IL-6 blockers already licensed for other indications are being studied through clinical trials in patients hospitalized with confirmed COVID-19.

COVID-19: The Background

SARS-CoV-2 was discovered in Wuhan, China [4], in December 2019, and in February 2020 the disease was officially named Corona Virus Disease-19, abbreviated to COVID-19 [5]. Epidemiological data has since confirmed the route of transmission of COVID-19 to be from person to person [6]. Initially COVID-19 was likened to influenza, but evidence demonstrates it is markedly different both in its route of transmission, pathology and symptoms: many patients are initially asymptomatic, while others experience fever, persistent dry cough, myalgia and fatigue, however, a runny nose is a noticeably absent symptom in the case of COVID-19. Data gathered from patients with COVID-19 demonstrate that the virus impacts the respiratory system, with many patients developing pneumonia, which can potentially rapidly escalate into respiratory failure and even death [7].

Current evidence on the use of IL-6 treatments in patients with COVID-19

There is an ongoing study using EUSA's IL-6 antagonist siltuximab (SYLVANT). This is a single-center observational study in Bergamo, Italy, in patients diagnosed with COVID-19 and with serious respiratory complications. Patients received a single intravenous infusion of siltuximab at a dose of 11 mg/kg. Preliminary results from the first 21 patients treated with siltuximab and followed up for 7 days showed that 33% (n=7) experienced a clinical improvement as evidenced by a reduced need for oxygen support, and 43% (n=9) had a stabilized condition indicated by no clinically relevant changes. Three patients (14%) experienced worsening of their disease, 1 patient (5%) died and 1 patient (5%) experienced a cerebrovascular event. [8]. In addition, following administration of the IL-6 antagonist siltuximab, all patients with sufficient recorded values (16/21) experienced a decline in mean blood C-reactive protein (CRP) level through to Day 5, indicating a reduction in systemic inflammation. This CRP-lowering effect was maintained through to Day 7.

A second study, using Roche's IL-6 blocker tocilizumab, has also produced promising results among patients with COVID-19 [9]. Twenty patients across 2 hospitals in China, diagnosed as severe or critical COVID-19, were given tocilizumab in addition to standard care (including lopinavir, methylprednisolone, other symptom relievers and oxygen therapy). A single 400 mg intravenous dose of the IL-6 blocker tocilizumab was administered. Within a few days, the fever returned to normal and other COVID-19 related symptoms improved. In total, 15 patients (75%) had lowered their oxygen intake and one patient no longer needed oxygen therapy. CT scans showed that the lung lesion opacity absorbed in 19 patients (90.5%).

Impending studies involving IL-6 treatments in patients with COVID-19

Based on the promising results of other studies using IL-6 blockers, Regeneron is recruiting for a largescale interventional study using its drug sarilumab. The randomized phase 2/3 study aims to enroll 400 patients with COVID-19 who are hospitalized in the US. The study will be a randomized, double-blind, placebo-controlled study assessing efficacy and safety of sarilumab for hospitalized patients with COVID-19. The estimated study completion date is not until March 2021.

Tiziana Life Sciences is expediting development of TZLS-501, a novel, fully human anti-IL-6 receptor monoclonal antibody (mAb) for treatment of patients infected with COVID-19, using a proprietary formulation. The biotech company focuses on innovative therapeutics for inflammatory and autoimmune diseases. Details of the planned clinical studies are not yet available.

Discussion

Identifying appropriate strategies for the treatment and management of patients with COVID-19 is a continually evolving process. Current epidemiological and clinical data suggest that drugs that block or inhibit key cytokines involved in the CRS associated with COVID-19 may be a treatment option for infected patients. Two studies using IL-6 blockers for the treatment of COVID-19 have shown encouraging results, but further studies and larger patient numbers are required to confirm these findings.

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