Involvement of interleukin 6 in SARS-CoV-2 infection: siltuximab as a therapeutic option against COVID-19

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ABSTRACT

The aim of the study was to explore the involvement of interleukin 6 in SARS-CoV-2 infection, and to position the drug siltuximab in the management of severe forms of COVID-19. A bibliographic search was performed in Pubmed on the immune response to the disease, and in ClinicalTrials.gov on clinical trials with interleukin 6 blockers. Interleukin 6 is involved in the cytokine cascade, which originates as a consequence of an excessive immune response secondary to viral infection, aggravating lung affectation. Blockers of this cytokine (tocilizumab, sarilumab and siltuximab) are being studied as a strategy for treating the disease. Siltuximab is a monoclonal antibody indicated in Castleman's disease that could be administered in a single dose of 11 mg/kg in severe forms of COVID-19 that have increased interleukin 6.

INTRODUCTION

In December 2019, a cluster of patients with pneumonia of unknown cause was reported in Wuhan (China). After analysis of respiratory samples, scientists isolated a new virus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the outbreak of coronavirus disease 2019 (COVID-19). The virus spread rapidly with an increasing number of infected patients in multiple countries, and the World Health Organization (WHO) declared the disease pandemic. Since the start of the pandemic to the date of this report, more than 2 285 000 cases have been detected in 213 territories around the world and more than 155 000 people have died.[1]

COVID-19 is a zoonotic disease and person-to-person transmission occurs primarily via direct contact or through droplets spread by coughing or sneezing from an infected individual. The main signs and symptoms include fever (87.9%), dry cough (67.7%), fatigue (38.1%), sputum production (33.4%) and shortness of breath (18.6%). Approximately 13.8% of patients have severe disease (dyspnoea, respiratory frequency ≥30/min, blood oxygen saturation ≤93% and PaO_2/FiO_2 ratio 50% of the lung field within 24–48 hours) and 6.1% are critical (respiratory failure, septic shock and multiple organ dysfunction).[2]

Our hypothesis is the possibility of using the drug siltuximab in the management of patients with severe COVID-19 infection. Hence the main objective of our study was to explore the involvement of interleukin (IL) 6, the target of action of siltuximab, in SARS-CoV-2 infection.

METHODS

A bibliographic analysis was performed using the terms 'cytokine' and 'COVID-19 or SARS-CoV-2' in Pubmed. Articles were filtered by study type (article, review or clinical trial) and date of publication (last 5 years), without restriction by language. In addition, clinical trials of SARS-CoV-2 infection with drugs that block IL-6 were examined at ClinicalTrials.gov using the search criteria 'COVID-19' as disease and 'IL-6 blocker' as other terms. References of the retrieved articles and trials were followed-up.

RESULTS

SARS-CoV-2 induces excessive and aberrant non-effective host immune responses that are related to severe lung pathology. The lung injury is more pronounced in critically ill patients, associated with a cytokine storm, which is characterised by increased plasma concentrations of the proinflammatory cytokines IL-1β, IL-6, IL-12, tumour necrosis factor and interferon γ.[3] It produces a cytokine release syndrome, with a pattern similar to that of secondary haemophagocytic lymphohistiocytosis, that correlates with the severity of the disease and adverse outcomes, due to the important role cytokines play in the immunity and immunopathology of the viral infection.[4]

The greatest risk factors for cytokine release syndrome are the presence of a large area of lung injury (≥50%) with decreased levels of CD4 and CD8 T lymphocytes (<50% of the minimum normal range), and increased levels of IL-6 in peripheral blood. Secondary haemophagocytic lymphohistiocytosis is an under-recognised, hyperinflammatory syndrome characterised by a fulminant and fatal hypercytokinaemia with multiorgan failure whose cardinal features include unremitting fever, cytopenias and hyperferritinaemia.[4]

IL-6 is one of the key mediators of autoimmunity, inflammation, viral cytokine storms and cytokine release syndrome induced damage. Moreover, IL-6 can suppress normal T cell activation, which may explain the presence of lymphopenia, compromising an effective adaptive immune response.[5] In a study on cytokine status in peripheral blood of 123 patients with SARS-Cov-2, above normal IL-6 levels were found in only 30% of patients with mild COVID-19 compared with 76% in those with severe disease.[6] IL-6 levels could be used as one of the bases for predicting the outcome and prognosis of COVID-2019.

The use of IL-6 blockers seems to be promising for the management of the massive cytokine storm associated with the development of the typical lung damage and consequent acute respiratory distress syndrome occurring in the most aggressive patterns of SARS-CoV-2 infection.[7] The drugs that block IL-6 are tocilizumab, sarilumab and siltuximab.

Tocilizumab was studied in the treatment of 21 patients with severe and critical COVID-19. Clinical data showed that the symptoms, hypoxaemia and computerized tomography opacity changes were improved immediately after treatment with tocilizumab in most patients, suggesting that this drug could be an efficient therapeutic option for the treatment of COVID-19.[8]

Sarilumab is currently being used in hospitals as an alternative to tocilizumab due to its shared mechanism of action, specifically binding to both soluble and membrane bound IL-6 receptors. This drug is cheaper and helps meet the growing demand for IL-6 blockers in the COVID-19 crisis; however, sarilumab takes 2–4 days to reach its maximum concentration as it is administered subcutaneously. Its ability to reduce the morbidity and mortality of SARS-CoV-2 pneumonia is being explored in various clinical studies: "Cohort multiple randomised controlled trials open-label of immune modulatory drugs and other treatments in COVID-19 patients—sarilumab trial", "Evaluation of the efficacy and safety of sarilumab in hospitalised patients with COVID-19", "Treatment of moderate to severe coronavirus disease in hospitalised patients" and "Sarilumab COVID-19".[9] Preliminary studies of the hospitals that have used the drug indicate a similar efficacy to tocilizumab although with delayed normalisation of IL-6 levels.

DISCUSSION

Siltuximab could be considered as a therapeutic strategy to treat severe cases of SARS-CoV-2 infection with increased IL-6 levels. Siltuximab is a human–murine chimeric monoclonal antibody that forms high affinity, stable complexes with soluble bioactive forms of human IL-6. The drug prevents the binding of human IL-6 to both soluble and membrane bound IL-6 receptors, thus inhibiting the formation of the hexameric signalling complex with gp130 on the cell surface and avoiding activation of the Janus kinase/signal transducer and activator of transcription signalling pathway.[10] Siltuximab is indicated for the treatment of adult patients with multicentric Castleman's disease, a rare lymphoproliferative disorder driven by dysregulated production of IL-6.[11]

According to the technical sheet, the recommended dose is 11 mg/kg given over 1 hour as an intravenous infusion administered every 3 weeks. Because the half-life of siltuximab is 16.3±4.2 days[10] and the SARS-CoV-2 infection is an acute process, we think that a single dose would be sufficient for IL-6 downregulation.

Before drug administration, it is necessary to confirm that absolute neutrophil count is $\geq 1.0\times10^9$/L, platelet count is $\geq 75\times10^9$/L and haemoglobin is <170 g/L, due to the analytical alterations that the treatment can cause.[10] Siltuximab was well tolerated; the most common adverse events were hypertension (13%), fatigue (8%), nausea (7%), neutropenia (7%) and vomiting (5%).[12] Several studies have shown that IL-6 decreases the activity of cytochrome P450, so siltuximab may result in increased metabolism of substrates because enzyme activity will normalise.[13]

The efficacy of siltuximab can be measured indirectly by suppression of C reactive protein. Determination of IL-6 concentrations in serum or plasma during treatment should not be used as a pharmacodynamic marker, as siltuximab–neutralised antibody–IL-6 complexes interfere with immunologically based IL-6 quantification methods.[14]

Other drugs with anti-inflammatory and immunomodulator properties are being studied to be used together with antiviral treatment, such as the IL-1 blocker anakinra and the Janus kinase inhibitor baricitinib.[15]

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