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Title
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Permalink
https://escholarship.org/uc/item/5ft476n6

Journal
Journal of Immunotherapy and Precision Oncology, 3(2)

ISSN
2666-2345

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Publication Date
2020-05-01

DOI
10.36401/jipo-20-11

Peer reviewed

Repurposing Interleukin-6 Inhibitors to Combat COVID-19

Abstract

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is a pandemic with major implications across the world. One of the most frequent causes of death from SARS-CoV-2 is fatal pneumonia from coronavirus disease 2019 (COVID-19), which is associated with the development of acute respiratory distress syndrome (ARDS). To date (as of April 2 2020), other than supportive measures, there are no efficient therapeutic options for COVID-19 related ARDS, though the Food and Drug Administration recently granted emergency authorization for the use hydroxychoroquine/chloroquine for this indication (which is usually given with azithromycin). Although the pathogenesis for ARDS is under investigation, one of the major culprits is considered to be cytokine storm, especially from interleukin 6 (IL-6) release. Herein, we review potential use of IL-6 inhibitors, several of which are approved for other disease conditions, as potential novel treatment for the management of COVID-19 related ARDS.

Introduction

As of April 2, 2020, the novel betacoronavirus--severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)--has led to 1,011,064 detected infected cases and has been found in about ~53,000 patients who have died throughout the worldwide [1]. Genome sequencing indicated that SARS-CoV2 has about 80% structural similarity to SARS-CoV (first reported in 2003) and is ~96% identical at the whole-genome level to a bat coronavirus [2]. Another betacoronavirus, Middle East Respiratory Syndrome virus, is reported to be more remotely associated with SARS-CoV-2 (~50% similarity), and is also a bat coronavirus [3]. Person-to-person spread of SARS-CoV-2 is considered to occur mainly by respiratory droplets (similar to influenza).

The range of symptoms due to SARS-CoV-2 varies from no or mild symptoms without respiratory complications (at least 80% of patients), to severe symptoms (with dyspnea and hypoxia, or greater than 50% of lung involvement) and critical cases (with respiratory failure, shock and multi-organ dysfunction). The overall case fatality rate (CFR) was ~2-3% according to the Chinese Center for Disease Control and Prevention [4]; overall case fatality may be lower in the USA and has been estimated to be ~0.1% by Fauci and colleagues in his recent New England Journal of Medicine editorial [5]. The difficulty in estimating CFR is mainly due to the fact that large numbers of people remain untested with either the polymerase chain reaction test that detects acute infection or, even more importantly, the antibody test that detects past infection and immunity; hence the denominator of cases is unknown.

Underlying disease conditions such as cardiovascular disease, diabetes, chronic respiratory disease and cancer as well as being elderly, especially among those over 80 years of age, has been linked to significantly higher fatality rates; however, again, the actual CFR is unclear because the denominator of infected cases with these comorbidities is unknown. Only about 1% of deaths occur in younger people and/or those of any age without comorbidities [6-8]. One of the major causes of death from SARS-CoV-2 is fatal pneumonia from coronavirus disease 2019 (COVID-19), which can lead to the development of acute respiratory distress syndrome (ARDS). The management of ARDS is mainly supportive, including hemodynamic monitoring, nutritional support, and oxygenation. In severe cases, management with mechanical ventilation or extracorporeal membrane oxygenation have been reported [9]. There have been recent studies, albeit poorly controlled, showing effectiveness for hydroxychloroquine combined with azithromycin [10], and the US Food and Drug Administration just gave emergency authorization to their use to combat COVID-19 [11].

The pathogenesis of SARS-CoV-2-related ARDS is still under active investigation. However, it has been implied that the viral infection can lead to an excessive immune reaction (cytokine storm), which is associated with extensive tissue and organ damage. One of the major culprits in cytokine storm is considered to be the burst of production of the cytokine interleukin 6 (IL-6) by activated leukocytes [12]. IL-6 promotes the differentiation of B lymphocytes and also stimulates the synthesis of acute phase proteins and is hence implicated in the pathogenesis of acute systemic inflammatory

syndrome with fever and multiple organ dysfunction (also known as cytokine release syndrome) [12, 13]. Indeed, preliminary reports suggest that high IL-6 levels were closely related with high serum SARS-CoV-2 nucleic acid level, and that IL-6 levels were significantly elevated among critically ill patients (10-fold higher than in those not in critical condition) [14]. Herein, we review IL-6 as a potential therapeutic target for the management of SARS-CoV2 infection.

IL-6 and its biologic role: IL-6 is a pleiotropic cytokine that contributes to the physiology of almost every organ system; it plays a vital role in the response to infection as well as injury, and participates in hematopoiesis, immunity, and inflammation [15]. In regard to immune effects, IL-6 is a potent and essential factor for the normal development and function of both B and T lymphocytes. IL-6 is also a central regulator of the acute-phase response in the liver and fever. IL-6 therefore appears to be a mediator of human conditions that involve prolonged inflammation.

Rapid synthesis of IL-6 contributes to host defense during infection and tissue injury, but excess IL-6 production and/or dysregulation of IL-6 receptor signaling mediates disease pathology. Indeed, aberrant expression of IL-6 is implicated in diverse human diseases, most notably infectious, inflammatory and autoimmune disorders, cancer, coronary artery and neurologic disease, and pregnancy problems [15].

IL-6 and its receptor system: IL-6 was cloned first by Hirano et al., in 1986 [16]. IL-6 gene transcription is induced in many different normal tissues

in response to stimuli, e.g., DNA and RNA virus infection, lipopolysaccharide, serum, bacterial endotoxin, inflammatory cytokines such as tumor necrosis factor (TNF), IL-1, and platelet-derived growth factor, and the interferons (IFNs) [15].

IL-6 signals through a cell-surface type I cytokine receptor consisting of the ligand-binding IL-6 receptor alpha (IL-6Rα) chain (CD126) and the signal-transducing component gp130 (also known as IL-6 signal transducer or CD130); the latter is the common signal transducer for several cytokines including, but not limited to, leukemia inhibitory factor, oncostatin and IL-11, and is expressed in protean tissues. In contrast, the expression of CD126 is limited to specific tissues. As IL-6 interacts with its receptor, it prompts the gp130 and IL-6R proteins to form a complex, thus activating the receptor. These complexes bring together the intracellular regions of gp130 to trigger a signal transduction cascade through certain transcription factors such as JAKs and STATs. In addition to the membrane-bound receptor, a soluble form of IL-6R (sIL-6R) exists; sIL-6R has agonist activity. The complex of IL-6 and sIL-6R can bind to gp130 on cells that do not express the IL-6R and, therefore, these cells may respond to IL-6 even in the absence of IL-6R [17].

Therapeutic implications of IL-6: Suppressing IL-6 is an innovative therapeutic strategy in several diseases and has salutary effects. In cancer, high levels of circulating IL-6 are observed in almost every type of tumor studied and predict a poor outcome [18-20]. Furthermore, elevated IL-6 levels are strongly associated with several of the striking phenotypic features of cancer.

Inflammatory diseases may also be triggered by IL-6.   Therapeutic agents targeting the IL-6 axis are effective in rheumatoid arthritis and Castleman disease (a rare disorder that involves an overgrowth of lymph nodes) and specific IL-6 inhibitory agents are approved for these conditions (**Table 1**) [21-24]. Applications are being extended to other settings of acute and chronic inflammation. Most recently, anti-IL-6 agents are being explored for activity in patients afflicted with corona virus (SARS-CoV-2) [25].

Repurposing IL-6 inhibitors for corona virus (SARS-CoV-2; COVID-19) infection

Considering that IL-6 that may play a critical role in driving the hyperactive inflammatory response in the lungs amongst critically ill patients with coronavirus disease 2019 (COVID-19), the respiratory illness that is produced by SARS-CoV-2 infection, multiple Food and Drug Administration (FDA) approved IL-6 inhibitors are now being repurposed to be used for the management of SARS-CoV-2 infection.

As an example, tocilizumab (FDA-approved anti-IL-6 monoclonal antibody), which is used for conditions including rheumatoid arthritis, giant cell arteritis and cytokine release syndrome from chimeric antigen receptor T-cell therapy, is produced by Genentech/Roche and is being tested among patients with severe COVID-19 pneumonia [26]. This study will be an important follow up on the anecdotal report from the Chinese group wherein they successfully used tocilizumab for patients with severe-critical COVID-19 infection [27]. They showed improvement in the majority of patients in terms of oxygen intake (75% [15/20]) and CT of chest findings (95% [19/20]) as well

as a decrease in serum C-reactive protein (84% [16/19]). Most patients (95% [19/20]) were discharged within an average of 13.5 days after the tocilizumab was started [27].

EUSA Pharma also announced a study of siltuximab (IL-6 targeted monoclonal antibody approved by the Food and Drug Administration [FDA] for Castleman disease) [22-24] for patients with COVID-19 with serious respiratory complications ("Siltuximab In Serious COVID -19; SISCO Study, clinicaltrials.gov [NCT04322188]") [28]. Finally, Regeneron Pharmaceuticals and Sanofi launched a trial with sarilumab (IL-6 receptor antagonist approved by the FDA for rheumatoid arthritis) for treatment of severe COVID-19 (clinicaltrials.gov, NCT04315298) [29].

The studies using IL-6 inhibitors, along with other clinical trials examining hydroxychloroquine and azithromycin (clinicaltrial.gov: NCT04321278, NCT04322396 and NCT04322123), antivirals such as remdesivir (NCT04292899 , NCT04292730), and recovered patient plasma [30], have been activated in record speed, along with intense efforts to examine other drugs and develop a vaccine, in order to combat COVID-19. Indeed, the model of rapid clinical trial activation and clinical development of treatments spurred by the SARS-CoV-2 and assisted by the FDA, may be a long-lasting positive legacy of this pandemic and, if successful, may be exploited to overcome other diseases such as cancer as well.

Table 1: Examples of IL-6 inhibitory molecules, their FDA-approved indications, and plans for testing against COVID-19.

Drug Generic Name	Siltuximab	Tocilizumab	Sarilumab
Drug Trade name	Sylvant	Actemra	Kevzara
Company	Janssen EUSA	Genentech/ Roche	Sanofi-Regeneron
Mechanism	Anti-IL6	Anti-IL6 receptor	Anti-IL6 receptor
Indication	Castleman Disease	Rheumatoid arthritis Giant cell arteritis Polyarticular juvenile idiopathic arthritis Systemic juvenile idiopathic arthritis Chimeric antigen receptor T cell-induced cytokine release syndrome	Rheumatoid arthritis
Comment re trials launched for Covid-19	One study recruiting as of 3/30/2020: Observational case-control study (NCT04322188).	Three studies recruiting as of 3/30/2020: Phase II study for COVID-19 pneumonia (NCT04317092) Tocilizumab vs. Continuous Renal Replacement Therapy among COVID-19 cytokine release syndrome (NCT04306705). Patients randomized to combination with favipiravir and tocilizumab or either of the drug (NCT04310228).	One study recruiting as of 3/30/2020: Evaluation of efficacy and safety of sarilumab in hospitalized patients with COVID-19.3 (NCT04315298).
References	Clinicaltrials.gov (NCT04322188) [22, 24]	Clinicaltrials.gov NCT04317092 NCT04306705	Clinicaltrials.gov NCT04315298

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