Title
Repurposing Interleukin-6 Inhibitors to Combat COVID-19

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

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

ISSN
2666-2345

Authors
Kato, Shumei
Kurzrock, Razelle

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 hydroxychloroquine/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 | Drug Trade Name | Company | Mechanism                  | Indication                                                                                     |
|-------------------|-----------------|---------|----------------------------|------------------------------------------------------------------------------------------------|
| Siltuximab        | Sylvant         | Janssen | Anti-IL6                    | Castleman Disease                                                                           |
| Tocilizumab       | Actemra         | EUSA    | Anti-IL6 receptor           | Rheumatoid arthritis                                                                         |
| Sarilumab         | Kevzara         | Genentech/ Roche | Anti-IL6 receptor         | Giant cell arteritis                                                                          |
|                   |                 | Sanofi-Regeneron | Anti-IL6 receptor         | Polyarticular juvenile idiopathic arthritis                                                   |
|                   |                 |          |                             | Systemic juvenile idiopathic arthritis                                                        |
|                   |                 |          |                             | Chimeric antigen receptor T cell-induced cytokine release syndrome                           |

**Comment re trials launched for Covid-19**

| Drug Generic Name | Drug Trade Name | Company | Mechanism                  | Indication                                                                                     |
|-------------------|-----------------|---------|----------------------------|------------------------------------------------------------------------------------------------|
| Siltuximab        | Sylvant         | Janssen | Anti-IL6                    | Castleman Disease                                                                           |
| Tocilizumab       | Actemra         | EUSA    | Anti-IL6 receptor           | Rheumatoid arthritis                                                                         |
| Sarilumab         | Kevzara         | Genentech/ Roche | Anti-IL6 receptor         | Giant cell arteritis                                                                          |
|                   |                 | Sanofi-Regeneron | Anti-IL6 receptor         | Polyarticular juvenile idiopathic arthritis                                                   |
|                   |                 |          |                             | Systemic juvenile idiopathic arthritis                                                        |
|                   |                 |          |                             | Chimeric antigen receptor T cell-induced cytokine release syndrome                           |

**References**

- Clinicaltrials.gov (NCT04322188) [22, 24]
- Clinicaltrials.gov NCT04317092
- Clinicaltrials.gov NCT04306705
- Clinicaltrials.gov NCT04315298
References:

1. Coronavirus disease (covid-19) situation reports. World Health Organization 2020: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
2. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-273.
3. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet 2020;395:565-574.
4. Wu Z and McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (covid-19) outbreak in china: Summary of a report of 72314 cases from the chinese center for disease control and prevention. JAMA 2020
5. Fauci AS, Lane HC, Redfield RR. Covid-19 - navigating the uncharted. N Engl J Med 2020;382:1268-1269.
6. Report of the who-china joint mission on coronavirus disease 2019 (covid-19). https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
7. Adashek JJ, Hajjar J, Chemaly RF, et al. Are cancer patients at higher risk of death with covid-19? 2020
8. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with covid-19 in wuhan, china: A retrospective cohort study. Lancet 2020;395:1054-1062.
9. Ramanathan K, Antognini D, Combes A, et al. Planning and provision of ecmo services for severe ards during the covid-19 pandemic and other outbreaks of emerging infectious diseases. Lancet Respir Med 2020
10. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of covid-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020:105949.
11. Fact sheet for patients and parent/caregivers emergency use authorization (eua) of hydroxychloroquine sulfate for treatment of covid-19 in certain hospitalized patients. https://www.fda.gov/media/136538/download
12. Cascella M, Rajnik M, Cuomo A, et al.: Features, evaluation and treatment coronavirus (covid-19). Statpearls, Treasure Island (FL), 2020
13. Baas T, Taubenberger JK, Chong PY, et al. Sars-cov virus-host interactions and comparative etiologies of acute respiratory distress syndrome as determined by transcriptional and cytokine profiling of formalin-fixed paraffin-embedded tissues. J Interferon Cytokine Res 2006;26:309-317.
14. Chen X, Zhao B, Qu Y, et al. Detectable serum sars-cov-2 viral load (rnaemia) is closely associated with drastically elevated interleukin 6 (il-6) level in critically ill covid-19 patients. medRxiv 2020
15. Hong DS, Angelo LS, Kurzrock R. Interleukin-6 and its receptor in cancer: Implications for translational therapeutics. Cancer 2007;110:1911-1928.
16. Hirano T, Yasukawa K, Harada H, et al. Complementary DNA for a novel human interleukin (bsf-2) that induces b lymphocytes to produce immunoglobulin. Nature 1986;324:73-76.
17 Rose-John S. IL-6 trans-signaling via the soluble IL-6 receptor: Importance for the pro-inflammatory activities of IL-6. Int J Biol Sci 2012;8:1237-1247.

18 Kurzrock R, Redman J, Cabanillas F, et al. Serum interleukin 6 levels are elevated in lymphoma patients and correlate with survival in advanced hodgkin's disease and with b symptoms. Cancer Res 1993;53:2118-2122.

19 Seymour JF, Talpaz M, Hagemeister FB, et al. Clinical correlates of elevated serum levels of interleukin 6 in patients with untreated hodgkin's disease. Am J Med 1997;102:21-28.

20 Ebrahimi B, Tucker SL, Li D, et al. Cytokines in pancreatic carcinoma: Correlation with phenotypic characteristics and prognosis. Cancer 2004;101:2727-2736.

21 Srirangan S and Choy EH. The role of interleukin 6 in the pathophysiology of rheumatoid arthritis. Ther Adv Musculoskelet Dis 2010;2:247-256.

22 van Rhee F, Casper C, Voorhees PM, et al. Long-term safety of siltuximab in patients with idiopathic multicentric castleman disease: A prespecified, open-label, extension analysis of two trials. The Lancet Haematology 2020;7:e209-e217.

23 El-Osta HE and Kurzrock R. Castleman's disease: From basic mechanisms to molecular therapeutics. Oncologist 2011;16:497-511.

24 van Rhee F, Fayad L, Voorhees P, et al. Siltuximab, a novel anti-interleukin-6 monoclonal antibody, for castleman's disease. J Clin Oncol 2010;28:3701-3708.

25 Ascierto PA, Fox BA, Urba WJ et al. SITC statement on anti-IL-6/IL-6R for COVID-19. Society For Immunotherapy of Cancer, 2020; https://www.sitcancer.org/research/covid-19-resources/il-6-editorial

26 https://www.gene.com/media/press-releases/14843/2020-03-23/genentech-announces-fda-approval-of-clin

27 Xu X, Han M, Li T, et al. Effective treatment of severe covid-19 patients with tocilizumab. ChinaXiv preprint 2020

28 https://www.clinicaltrialsarena.com/news/eusa-pharma-siltuximab-study-covid-19/

29 https://www.genengnews.com/news/regeneron-sanofi-launch-clinical-trial-of-kevzara-as-coronavirus-treatment/

30 Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with covid-19 with convalescent plasma. JAMA 2020