Editorial: Tocilizumab, a Humanized Therapeutic IL-6 Receptor (IL-6R) Monoclonal Antibody, and Future Combination Therapies for Severe COVID-19

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Abstract
Vaccinated, non-vaccinated, and immunosuppressed individuals will continue to be infected with SARS-CoV-2. Therefore, there is a priority to develop treatments that reduce the severity of COVID-19 in patients who require hospital admission. Interleukin-6 (IL-6) is a proinflammatory cytokine. In 2011, a humanized monoclonal antibody to the IL-6 receptor (IL-6R), tocilizumab, was approved by the US Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, and Castleman’s disease. In 2017, tocilizumab was approved to treat chimeric antigen receptor (CAR) T-cell therapy–induced cytokine release syndrome (CRS). In 2021, the results of the REMAP-CAP clinical trial (NCT02735707) and the COVID-19 Therapy (RECOVERY) clinical trial (NCT04381936) supported FDA Emergency Use Authorization (EUA) for tocilizumab to treat hospitalized patients with moderate and severe COVID-19. Monoclonal antibodies are currently in clinical development or undergoing clinical trials to treat COVID-19. Further clinical trials will provide safety and efficacy data on targeting IL-6 and IL-6R and provide rationales for more personalized combination treatments to control the systemic effects of SARS-CoV-2 infection in hospitalized patients with moderate and severe COVID-19. This Editorial aims to present the background to the recent authorization of tocilizumab, a humanized therapeutic monoclonal antibody to the IL-6 receptor (IL-6R), for hospitalized patients with moderate and severe COVID-19 and future combination therapies.

Keywords: Editorial • IL6 Protein, Human • IL6R Protein, Human • Tocilizumab • Severe Acute Respiratory Syndrome Coronavirus 2 • COVID-19

There is no ‘cure’ for acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Prevention or amelioration of coronavirus disease 2019 (COVID-19) depends on the efficacy of vaccines [1,2]. However, no vaccine is 100% effective. Vaccinated, non-vaccinated, and immunosuppressed individuals will continue to be infected with SARS-CoV-2. Therefore, there is a priority to develop treatments that reduce the severity of COVID-19 in patients who require hospital admission. The US National Institutes of Health (NIH) identifies severe COVID-19 in patients with the following criteria: an oxygen saturation (SpO2) <94% at sea level on room air; a respiratory rate of >30 breaths/min; a ratio of the arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FIO2) of <300 mmHg; or pulmonary parenchymal infiltrates of >50% on lung computed tomography (CT) imaging [3].

For more than a year, clinical trials on potential therapeutic approaches to reduce patient mortality from moderate to severe COVID-19 in hospitalized patients have shown varied success compared to supportive care [4,5]. In 2021, there have been promising results for therapeutic approaches that reduce the local and systemic immunological and inflammatory effects of SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19. For example, in February 2021, data from the RECOVERY collaboration group controlled clinical trial (NCT04381936) showed that patients who were hospitalized with COVID-19, who were receiving either invasive mechanical ventilation or oxygen and treated with dexamethasone, had a significantly reduced 28-day mortality when compared with patients given usual care [8]. Dexamethasone reduces systemic inflammation, or the ‘cytokine storm,’ an exaggerated or unregulated immune response associated with excessive release of inflammatory cytokines, resulting in multi-organ damage and increased patient mortality [7].

In July 2021, the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group published the findings from a systematic review and meta-analysis of clinical trials, which included 10,930 patients, on the association between treatment with interleukin-6 (IL-6) antagonists and mortality in...
patients hospitalized for COVID-19 [8]. Meta-analysis showed that treatment with IL-6 antagonists, compared with usual care or placebo, resulted in a significantly lower 28-day all-cause mortality [8]. However, unlike dexamethasone, IL-6 and its receptor have a more specific role in the pathogenesis of COVID-19, which makes this cytokine a suitable candidate for targeted therapy for patients with the systemic effects of SARS-CoV-2 infection [9,10].

IL-6 is a proinflammatory cytokine produced by fibroblasts, lymphocytes, and monocyte/macrophages. In 2011, a humanized monoclonal antibody to the IL-6 receptor (IL-6R), tocilizumab (ACTEMRA®) (Genentech, Inc., San Francisco, CA, USA) was the first humanized therapeutic monoclonal antibody to IL-6R to be approved by the US Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, and Castleman’s disease [11,12]. In August 2017, tocilizumab was approved to treat chimeric antigen receptor (CAR) T-cell therapy-induced cytokine release syndrome (CRS) [13]. Observational studies have shown that serum levels of IL-6 are correlated with the severity of the clinical signs and imaging findings in patients with COVID-19 [14]. Tocilizumab is an inhibitor of the IL-6 pathway, and controlled clinical trials have now supported its effects on patients with moderate and severe COVID-19. In a meta-analysis of eight randomized trials of patients hospitalized with COVID-19, all-cause mortality was lower among patients who received tocilizumab when compared with placebo or standard of care [15]. In June 2021, the US FDA granted emergency use authorization (EUA) for tocilizumab to treat hospitalized patients with moderate and severe COVID-19, based on the findings from two main clinical trials [16,17].

In April 2021, the results of the REMAP-CAP clinical trial (NCT02735707) were published [18]. This international, open-label, randomized trial included 803 patients with severe COVID-19 admitted to the intensive care unit (ICU), who required either respiratory or cardiovascular support [18]. Treatment with the IL-6 receptor (IL-6R) antagonists, tocilizumab and sarilumab, improved patient outcomes and survival [18]. However, all patients were enrolled within 24 hours of admission to the ICU, >80% were also treated with glucocorticoids, and 33% were also treated with remdesivir [18]. Intravenous remdesivir (GS-5734) is an inhibitor of viral RNA-dependent RNA polymerase, which has been shown in a double-blind, randomized, placebo-controlled trial (NCT04280705) to be superior to placebo in reducing recovery time in hospitalized adults with COVID-19 [19]. Sarilumab is a humanized monoclonal antibody that inhibits the binding of IL-6 to the soluble and membrane-bound α receptor and has previously been approved for the treatment of adults with moderate to severe rheumatoid arthritis [20,21].

On May 1st, 2021, the findings from the controlled, open-label Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial (NCT04381936) of 4,116 patients with suspected or confirmed COVID-19, conducted in the UK, were published [22]. Of the 4,116 patients treated with tocilizumab, 3,385 (82%) were also treated with corticosteroids [22]. The findings showed that the addition of one to two doses of tocilizumab to usual care significantly reduced the 28-day mortality rate compared with usual care alone (31% versus 35%) (relative risk 0.85; 95% CI, 0.76-0.94) [22]. Subgroup analysis showed that hospitalized patients with COVID-19 with systemic inflammation and hypoxia had improved survival and clinical outcomes with combined treatment with tocilizumab and dexamethasone [22]. The findings from the RECOVERY trial provide the most compelling support for the addition of tocilizumab to current combined treatments for patients with severe COVID-19 [22].

However, current recommendations on the use of tocilizumab in patients with COVID-19 vary. Therefore, it is clear that further clinical trials on the use of IL-6 antagonists are awaited, including on tocilizumab. The National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel currently recommends combining tocilizumab with dexamethasone in recently hospitalized patients with COVID-19 who require high-flow oxygen therapy or more advanced supportive care or who have increased inflammatory markers [23]. In the UK, the National Health Service (NHS) guidelines recommend using tocilizumab as an adjunctive treatment in addition to dexamethasone in patients with severe COVID-19 [24]. Also, the Infectious Diseases Society of America (IDSA) recommends the addition of tocilizumab to the current standard of care, and glucocorticoids, for hospitalized adults who have progressive, severe, or critical COVID-19 and increased levels of systemic inflammatory markers [25].

An estimated 70 monoclonal antibodies are currently in clinical development or undergoing clinical trials to treat COVID-19 [26]. The FDA has granted four EUAs for clinical use as combination antibody ‘cocktails,’ and more of these will likely undergo clinical trials. [26]. The FDA has granted four EUAs for clinical use as combination antibody ‘cocktails,’ and more of these will likely undergo clinical trials. For example, in November 2020, the US FDA gave EUA approval for the combination monoclonal antibody therapy of casirivimab and imdevimab (REGN-COV2), as a cocktail therapy, for mild to moderate COVID-19 in patients at increased risk for progression to severe COVID-19 [27]. The combination of bamlanivimab and etesevimab, which attach to two different sites of the spike proteins of SARS-CoV-2, was granted EUA from the FDA in February 2021 for clinical use in non-hospitalized patients who have mild to moderate COVID-19 and are at increased risk for developing severe disease or hospitalization [27].
Clinicians who currently manage hospitalized patients with severe COVID-19 should be aware that the efficacy of targeted monoclonal antibody therapies to IL-6 and IL-6R may be reduced in immunosuppressed patients and patients with new SARS-CoV-2 variants of concern (VOC) [28]. Recent clinical trials that have supported the authorization of the therapeutic monoclonal antibody, tocilizumab, have also shown that the future of successful management of hospitalized patients with severe COVID-19 will rely on the use of personalized combination therapies.

Conclusions

IL-6 and its receptor are now recognized as potential therapeutic targets in patients with severe systemic effects of COVID-19 due to SARS-CoV-2 infection. In June 2021, following the results from clinical trials, the US FDA granted EUA for tocilizumab, a humanized therapeutic monoclonal antibody to IL-6R, to treat hospitalized patients with moderate and severe COVID-19. Further clinical trials will provide safety and efficacy data on targeting IL-6 and IL-6R and provide rationales for more personalized combination treatments to control the systemic effects of SARS-CoV-2 infection in hospitalized patients with moderate and severe COVID-19.

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