REVIEW

Current and emerging immunomodulators for treatment of SARS-CoV2 infection (COVID-19)

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ABSTRACT

Introduction: SARS-CoV-2, the virus that causes COVID-19, elicits a variety of host responses ranging from asymptomatic or mild illness in most people, to severe disease and critical illness in a subset of patients with systemic inflammation and hypoxemic respiratory failure. Areas Covered: Heterogeneous clinical presentations are often driven by disparate responses of the host immune system, with severe disease associated with aberrant interferon signaling or cytokine storm syndrome. This manuscript examines current therapeutic approaches, including the use of immunomodulators such as corticosteroids, interleukin inhibitors, kinase inhibitors, fluvoxamine, and ivermectin, and also explores the ways that these therapies and others may be used to treat COVID-19 in the future. Expert opinion: Modulation of the immune response has become a mainstay of treatment of COVID-19, although the optimal mechanism has not yet been defined and there is considerable controversy regarding clinical management. As time progresses, the therapeutic approach to COVID-19 will undoubtedly change, particularly as we learn more about the pathophysiology of SARS-CoV-2 infection.

1. Introduction

During the first wave of the coronavirus pandemic, corticosteroids such as dexamethasone and prednisone were used sparingly in the treatment of COVID-19 owing to the suggestion that these drugs could enhance both viral shedding and progression of disease of other coronaviruses such as SARS-CoV and Middle East Respiratory Syndrome (MERS) [1,2]. The trajectory of the COVID-19 pandemic changed in the summer of 2020, however, with the publication of the manuscript, ‘Dexamethasone in Hospitalized Patients with COVID-19’ from the Randomized Evaluation of COVID-19 Therapy (RECOVERY) Trial, a large-scale, randomized trial of repurposed drugs [3].

In this landmark study, 2104 volunteers hospitalized with COVID-19 received dexamethasone while 4321 subjects received usual care [3]. In total, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization. A crucial finding of the study was that the incidence of death was lower in the dexamethasone group than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%). However, dexamethasone demonstrated no statistically significant benefit among those without hypoxia.

This study revolutionized the therapeutic approach to COVID-19 [4–6]. The finding that an inexpensive, widely available immunomodulator resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone ignited a hunt for other drugs that might work though similar mechanisms [7–9].

Rather than attempting to discover novel therapeutics, however, many clinical investigators elected to study existing drugs with known safety profiles [7]. This was a strategic decision necessitated by the devastating wrought by the global pandemic [10,11]. While basic scientists attempted to tease out the immunological underpinnings of severe COVID-19, and the role that inflammation may play in the emergence of viral resistance, clinical trialists began experimenting with a variety of immunomodulators, which will be discussed below [12,13].

2. Immunomodulators for hospitalized patients

2.1. Interleukin-6 inhibitors

SARS-CoV-2 infection produces a variety of responses in humans [14–17]. Those who require hospitalization are often found to have evidence of systemic inflammation associated with elevated blood levels of interleukin-6 (IL-6) [18]. It has been suggested that reducing IL-6 levels may ameliorate illness with either of two classes of Food and Drug Administration (FDA)-approved IL-6 inhibitors: anti-IL-6 receptor monoclonal antibodies (mAbs) (e.g. tocilizumab and sarilumab) and anti-IL-6 mAbs (i.e. siltuximab) [19–21]. The data, however, have been mixed for hospitalized patients [22].

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Tocilizumab is a recombinant humanized anti-IL-6 receptor mAb approved for patients with rheumatologic disorders such as giant cell arteritis and rheumatoid arthritis as well as cytokine release syndrome induced by chimeric antigen receptor T cell (CAR T-cell) therapy [23]. Given the finding that many patients with severe COVID-19 demonstrate signs of cytokine release syndrome, there has been intense interest in using this drug in patients hospitalized with COVID-19 [24].

A single-center propensity-score matched cohort study was performed evaluating consecutive hospitalized COVID-19 patients in 2020 [25]. Subjects were stratified according to the receipt of tocilizumab for cytokine storm and matched to controls using propensity scores; 274 patients screened and 132 were included in the matched dataset (tocilizumab = 66; no tocilizumab = 66). There were 18 deaths (27.3%) in the tocilizumab group and 18 deaths (27.3%) in the no tocilizumab group ($p = 1.00$). This small study did not support the use of tocilizumab for the management of cytokine storm in patients with COVID-19. Nevertheless, interleukin antagonist research continued [26,27].

The RECOVERY study subsequently evaluated tocilizumab in patients with hospitalized with COVID-19 randomized, controlled, open-label trial [28]. Volunteers with hypoxia and evidence of systemic inflammation (C-reactive protein $P \geq 75$ mg/L) were randomized to standard care or with or without tocilizumab. A total of 4116 volunteers enrolled, including 3385 (82%) subjects receiving corticosteroids; 621 (31%) of the 2022 patients given tocilizumab and 729 (35%) of the 2094 patients randomized to standard of care died within 28 days ($p = 0.0028$). Those receiving tocilizumab were more likely to be discharged from hospital within 28 days ($p < 0.0001$). The RECOVERY study clearly demonstrated in a large-scale, randomized study that tocilizumab improved survival and other clinical outcomes in patients hypoxic patients with COVID-19 and signs of systemic inflammation [28].

Tocilizumab and the IL-6 antagonist sarilumab were evaluated in an international, multifactorial, adaptive platform trial, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) [29]. Adults with COVID-19 requiring intensive care unit (ICU) care were randomly assigned to receive tocilizumab, sarilumab, or standard care. A total of 353 patients were given tocilizumab, 48 received sarilumab, and 402 were in the control group. The median number of organ support-free days was 10 in the tocilizumab group, 11 in the sarilumab group, and 0 in the control group. The 90-day mortality rate revealed improved survival for those receiving either of the two IL-6 antagonists. While small studies showed minimal benefit (or, in some cases, harm), these large, randomized studies showed a clear benefit for a subset of patients [30,31].

Based on these studies, IL-6 inhibitors (tocilizumab and sarilumab) are now used by many clinical in hospitalized COVID-19 patients who require supplemental oxygen, high-flow oxygen, noninvasive ventilation, or invasive mechanical ventilation in conjunction with dexamethasone. Although the optimal patient population has not yet been defined, there appears to be a role for IL-6 inhibition in patients with a rapidly-escalating oxygen requirement and elevated inflammatory markers (C-reactive protein $>$7.5) if given within the first three days of hospitalization. There may also be a role for anti-IL-6 mAb therapy (i.e. sintuximab) but more data is necessary and for now, the drug should only be used within the confines of a clinical trial [19–21]. This work has shown the clear benefits of immunomodulation, and expanded the search for other drugs with anti-inflammatory properties. There is also considerable interest in IL-1 inhibition with the rheumatologic drug anakinra. However, the optimal COVID-19 patient population has not yet been defined.

### 2.2. Janus kinase inhibitors

Janus kinase (JAK) inhibitors interfere with phosphorylation of signaling molecules and activator of transcription (STAT) proteins that are implicated in cell signaling, growth, and survival [31]. JAK inhibitors, such as baricitinib and tofacitinib, have been suggested as treatments for COVID-19 because they can halt signal transduction that leads to immune activation and systemic inflammation [32,33].

Baricitinib was evaluated in a double-blind, randomized, placebo-controlled trial, Adaptive Covid-19 Treatment Trial (ACTT-2) [34]. The drug was administered with remdesivir to adults hospitalized with Covid-19. In total, 515 received combination treatment and 518 were in the control group. Patients receiving baricitinib had a median time to recovery of 7 days as compared with 8 days for those in the control group ($P = 0.03$), and 30% greater odds of symptomatic improvement at day 15 (odds ratio 1.3). Importantly, subjects receiving supplemental oxygen had a time to recovery of 10 days with combination treatment and 18 days with control and the four-week mortality was 5.1% in the combination group and 7.8% in the control group with fewer serious adverse events.

In another trial, the Study of Tofacitinib in Hospitalized Patients with Covid-19 Pneumonia (STOP-COVID), the JAK inhibitor tofacitinib was compared with placebo in hospitalized patients with COVID-19 [35]. A total of 289 volunteers underwent randomization; the incidence of death or respiratory failure after four weeks was 18.1% in the tofacitinib group. 

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**Article highlights**

*Severe COVID-19 is associated with misfiring of the human immune system.

*Systemic corticosteroids have become a mainstay of treatment for hospitalized patients with COVID-19 who require supplemental oxygen.

*Tocilizumab is an interleukin-6 receptor antagonist approved for patients with rheumatologic disorders and has improved outcomes in a subset of hospitalized COVID-19 patients with signs of systemic inflammation and increasing oxygen requirements.

*Janus kinase (JAK) inhibitors interfere with cell signaling and signal transduction that leads to immune activation and have improved outcomes in some hypoxic hospitalized patients with COVID-19.

*The antidepressant fluvoxamine has shown promise for outpatient patients newly diagnosed with COVID-19.
and 29.0% in the placebo group (P = 0.04). Death from any cause occurred in 2.8% of the patients in the tofacitinib group and in 5.5% of those in the placebo group after four weeks. The key finding from this work, in which 89.3% of patients also received dexamethasone, was that tofacitinib led to a lower risk of death or respiratory failure than placebo after four weeks [35].

Guidelines from the United States National Institutes of Health (NIH) now recommend the use of the JAK inhibitor baricitinib or the IL-6 antagonist tocilizumab in conjunction with dexamethasone plus the antiviral remdesivir for recently hospitalized patients with COVID-19 in the setting of rapidly increasing oxygen needs and systemic inflammation. If these drugs are not available, the IL-6 inhibitor sarilumab may be used in place of tocilizumab and the JAK inhibitor tofacitinib may be used instead of baricitinib [18]. The successful use of these immunomodulators in hospitalized patients has led some investigators to believe that a similar approach is warranted for outpatients with COVID-19, especially those at high risk for hospitalization.

3. Immunomodulators for outpatients

There are no FDA-approved treatments for outpatients with newly diagnosed COVID-19. Monoclonal antibody therapy has demonstrated notable safety and efficacy for those at high-risk of hospitalization, but therapeutic options for low- and moderate-risk outpatients are lacking [36]. Moreover, the resources associated with antibody infusion limit its use in many locations. A number of antiviral treatments are under investigation, but there are no oral antiviral treatment options currently available to outpatients. In this setting of limited therapeutics, immunomodulators have emerged as a promising treatment option.

3.1. Fluvoxamine

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that was approved by the United States Food and Drug Administration (FDA) in 1994 for the treatment of obsessive-compulsive disorder and is now used to treat a variety of psychiatric conditions [37–39]. Beyond its neuropsychiatric effects, fluvoxamine has been noted to have anti-inflammatory properties that may benefit patients with newly-diagnosed COVID-19 [40].

In vitro experiments demonstrated that the drug limits uptake of the neurotransmitter 5-hydroxytryptamine (5-HT), also known as serotonin, by brain synaptosomes [41]. The therapeutic applications for fluvoxamine expanded, however, after it was observed that there is a close connection between the central nervous system and the human immune system and that depression might be related to aberrant immune activation. Down-regulation of inflammatory genes, such as intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), cyclooxygenases (COX), and inducible nitric oxide synthase (iNOS) supported a therapeutic role for fluvoxamine as an anti-inflammatory medication [42,43]. Fluvoxamine has also been shown to interact with the endoplasmic reticulum sigma-1 receptor (S1R) chaperone protein; fluvoxamine has a high affinity for S1R, which in turn dampens the immune response [44,45].

Based on these findings, a double-blind, randomized trial was performed to determine whether fluvoxamine prevents outpatient clinical deterioration and decreases the severity of disease [46]. One hundred fifty-two non-hospitalized adults with COVID-19 symptom onset within 7 days and oxygen saturation of 92% or greater were enrolled; participants were randomized to fluvoxamine (n = 80) or placebo (n = 72) for 15 days. Clinical deterioration occurred in none of the 80 patients in the fluvoxamine group and in 6 of 72 patients in the placebo group (P = .009).

Another prospective cohort study of 65 outpatient volunteers recently diagnosed with SARS-CoV-2 who received fluvoxamine were compared to 48 who declined the drug. Of the patients who received fluvoxamine, none were ultimately hospitalized; of those who declined (and received observation alone), six were eventually hospitalized (12.5%) [47]. This study was not randomized, but it provides additional support for further study of this drug in outpatients with COVID-19.

Perhaps most encouragingly, however, was the finding that fluvoxamine (100 mg twice daily for 10 days) reduced need for hospitalization defined as retention in a COVID-19 emergency setting or transfer to a hospital among high-risk outpatients in Brazil with newly diagnosed COVID-19 [48]. The proportion of patients observed in a COVID-19 emergency setting for more than six hours or transferred to a hospital due was lower for the fluvoxamine group compared with placebo (11% vs 16%). The finding established fluvoxamine, an inexpensive and widely available oral medication, as an important therapeutic option in the armamentarium against COVID-19.

3.2. Fluticasone

The glucocorticoid fluticasone is a potent immunomodulator, altering inflammatory pathways involving cytokines, leukotrienes, eicosanoids, and histamines in mast cells, macrophages, eosinophils, and lymphocytes [49–51]. When inhaled, fluticasone decreases local and systemic production of a variety of anti-inflammatory compounds, such as nitric oxide synthase, annexin-1, SLP1, IL-6, MOP-1 [52,53]. Fluticasone also increases apoptosis in white blood cells, including lymphocytes, eosinophils, mast cells, and macrophages, all of which have been implicated in the pathophysiology of COVID-19 [49,50,54]. Other inhaled corticosteroids, such as budesonide, exert similar effects and may also play a role in the treatment of COVID-19.

Although randomized trial data are lacking, inhaled fluticasone appears to be a promising therapeutic option based on findings of other corticosteroids (dexamethasone), which has been shown to serve as an important immunomodulator in hospitalized patients with COVID-19. Further studies are necessary, however, in order to clarify the optimal dose, duration, and method of administration for outpatients.
3.3. Ivermectin

Ivermectin has been in clinical use since 1981 and appears on the World Health Organization’s List of Essential Medicines for treating a range of parasitic infections in humans, including river blindness and lymphatic filariasis [55]. The drug has also been noted to have both antiviral and immunomodulatory properties, which make it appealing as a therapeutic option for COVID-19 [31,32]. Ivermectin has also received substantial media attention because of its use in veterinary medicine.

Ivermectin reduces the production of tumor necrosis factor (TNF)-alpha, IL-1 and IL-6 and numerous non-randomized, underpowered studies have demonstrated clinical efficacy in small studies [56]. However, the optimal dose, duration, and treatment population have not yet been identified and further studies are ongoing and it is not currently recommended as a treatment for COVID-19.

4. Expert opinion

COVID-19 disease has been broadly divided into an initial viral phase followed by an inflammatory phase. A number of immunomodulators have been investigated to address the inflammatory phase, and these drugs can be further separated into those used for outpatients and those used for hospitalized patients. In addition to the drugs mentioned above, a number of other immunomodulators are under investigation for hospitalized patients. On 17 April 2020 the NIH announced the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public–private partnership to develop a coordinated research strategy for prioritizing and speeding development of the most promising therapeutics and vaccines [9]. ACTIV-1 is a master protocol designed to evaluate multiple immunomodulators for moderately or severely ill patients infected with SARS-CoV-2.

ACTIV-1 has included three drugs thus far: abatacept, infliximab, and cenicriviroc. (Cenicriviroc has been removed from the study due to futility and will not be discussed further) [7]. Abatacept, a selective costimulation modulator, inhibits T cell activation by binding to cluster of differentiation 80 (CD80) and CD86, thereby blocking interaction with CD28 and full activation of T lymphocytes [57]. The rationale for studying abatacept is grounded in the working model of the coronavirus life cycle, which suggests that the virus initially infects and replicates in human epithelial cells in the nasopharynx. T cells are recruited to this site and activated, releasing interferon-gamma (IFNγ), which activates alveolar macrophages, creating an inflammatory signaling loop with T cells. As a therapeutic strategy, it is crucial to disrupt this pro-inflammatory signaling loop [58]. It is possible that abatacept will disrupt this loop. Infliximab is a monoclonal antibody that binds to tumor necrosis factor (TNF)-alpha and may also disrupt the signaling loop [59,60]. ACTIV-1 closed to enrollment on 30 December 2021; results are expected in mid-2022.

Outpatients are being evaluated in a separate NIH study, ACTIV-6. The platform protocol will enroll up to 15,000 participants around the United States in an outpatient setting with a confirmed polymerase-chain reaction (PCR) or antigen test for SARS-CoV-2 and is expected complete enrollment between December 2022 and March 2023 [8,9]. ACTIV-6 aims to provide a definitive answer about the therapeutic potential of fluvoxamine, fluticasone, ivermectin and other drugs for outpatients diagnosed with SARS-CoV-2. Because this is an adaptive trial, the study may change as the standard of care evolves. Results are expected in 2023. The therapeutic approach to COVID-19 will undoubtedly change as we learn more about the pathophysiology of SARS-CoV-2 infection. The fundamental underpinning of this strategy is an appreciation that symptomatic disease is driven by misfiring of the human immune system.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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