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Cytokine storm and immunomodulatory therapy in COVID-19: Role of chloroquine and anti-IL-6 monoclonal antibodies



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Severe acute respiratory syndrome coronavirus-2, the causative agent of coronavirus disease 2019 (COVID-19), was declared a pandemic by the World Health Organization on 11th March 2020 and is a major global health concern. How to treat patients with COVID-19 effectively is a common question for physicians worldwide. According to recent statistical data released by the Chinese Government, approximately 19% of cases of COVID-19 are severe or critical.

Huang et al. reported the clinical features and cytokine profile of critically ill patients with COVID-19 in Wuhan, China, and suggested that a cytokine storm (i.e. higher concentrations of granulocyte-colony stimulating factor, interferon gamma-induced protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 α and tumour necrosis factor α) could be associated with the severity of disease [1]. Another study from China reported that increased expression of interleukin (IL)-2R and IL-6 in serum appears to predict the severity and prognosis of patients with COVID-19 [2]. Additionally, pathological examination of a biopsy sample from a patient who died from COVID-19 revealed interstitial mononuclear inflammatory infiltrates in both lungs, dominated by lymphocytes [3]. Furthermore, peripheral blood flow cytometric analysis showed that overactivation of T cells accounted, in part, for the severe immune injury in this

patient [3]. Thus, cytokine storms should not be neglected in the treatment of COVID-19.

To date, therapeutic options for severe COVID-19 remain limited. Several antiviral drugs, such as lopinavir/ritonavir, have shown no benefits compared with standard care [4]. A new treatment strategy, in addition to antiviral therapy alone, is likely to be required to have a significant impact on clinical outcome. Immunomodulatory therapy to down-regulate the cytokine storm may provide insights into the treatment of COVID-19. Combined use of an immunomodulatory agent – to reduce the cytokine storm – with an antiviral agent may give physicians more time to provide supportive treatment for patients with COVID-19.

Corticosteroids are among the most commonly used drugs for immunomodulatory therapy of infectious diseases. However, the use of corticosteroids in the treatment of COVID-19 can cause host immune suppression and delay viral clearance. Recent study results have provided information to help handle this dilemma. A study at Xi'an Jiaotong-Liverpool University found that the use of corticosteroids did not influence viral clearance time, length of hospital stay or duration of symptoms in patients with mild COVID-19 [5]. Another retrospective cohort study conducted in China, which included 201 patients with COVID-19, found that treatment with methylprednisolone decreased the risk of death (hazard ratio 0.38, 95% confidence interval 0.20–0.72) among patients with acute respiratory distress syndrome (ARDS). Based on these findings, the use of corticosteroids is considered beneficial in severe cases of COVID-19 (especially in patients with ARDS), but not in mild cases [6]. According to treatment experiences in

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Table 1
Dosing regimen of chloroquine, hydroxychloroquine and tocilizumab for treatment of COVID-19.

Drug	Dosage	Duration
Chloroquine phosphate ^a	Only for adults aged 18–65 years Body weight >50 kg: 500 mg, twice per day Body weight ≤50 kg: 500 mg, twice per day, for Days 1–2 followed by 500 mg once per day for Days 3–7 Contraindications Cardiac diseases or conditions Precautions Pay close attention to drug–drug interactions and adverse reactions during the use of chloroquine	7 days
Hydroxychloroquine sulphate ^b	200 mg, three times per day Contraindications Retinopathy, G6PD deficiency, QT prolongation	10 days
Tocilizumab	First dose: 4–8 mg/kg (400 mg recommended) diluted with 0.9% sodium chloride injection into 100 mL Intravenous infusion time: ≥1 h Second dose: if the first dose is not effective, a second dose can be given after 12 h (same dose as before) Total number of administrations: ≤2 Maximum single dose: ≤800 mg Precautions Pay attention to anaphylaxis Contraindications Active infections such as tuberculosis	

G6PD, glucose-6-phosphate dehydrogenase.

^a This dosing regimen of chloroquine is provided in the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7) issued by the National Health Commission of China.

^b This dosing regimen of hydroxychloroquine was used in an open-label non-randomized clinical trial conducted in France to investigate the efficacy of hydroxychloroquine and azithromycin therapy in the treatment of COVID-19. Breastfeeding and pregnant patients and children were excluded from this clinical trial.

China, cautious use of corticosteroids is only recommended in certain critically ill patients (e.g. those with progressive deterioration of oxygenation indicators) at low-to-moderate doses (no more than 1–2 mg/kg/day methylprednisolone or equivalent) for a short duration (3–5 days), as stated in the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7) issued by the National Health Commission of China [7].

Recently, chloroquine and its derivative hydroxychloroquine have been used in the treatment of COVID-19. In February 2020, results from more than 100 Chinese patients with COVID-19 showed that chloroquine phosphate had good efficacy [8]. French doctors conducted an open-label non-randomized clinical trial, and this study reported that 20 patients with COVID-19 who received hydroxychloroquine treatment showed relatively good efficacy [9]. Both chloroquine and hydroxychloroquine are weak bases and are able to accumulate in acidic organelles (e.g. lysosomes); as such, they can increase endosomal/lysosomal pH and inhibit viral replication [10]. In addition to their antimalarial and antiviral effects, their anti-inflammatory properties have been demonstrated in the treatment of autoimmune diseases such as rheumatoid arthritis and lupus erythematosus. Chloroquine and hydroxychloroquine can inhibit major histocompatibility complex class II expression, antigen presentation and immune activation (reducing CD154 expression by T cells) via Toll-like receptor signalling and cGAS stimulation of interferon genes [11]. Thus, chloroquine and hydroxychloroquine can reduce the production of various pro-inflammatory cytokines, such as IL-1, IL-6, interferon- α and tumour necrosis factor, which are involved in the cytokine storm [11]. These immunomodulatory effects may synergize their antiviral effects in the treatment of COVID-19.

Immunomodulatory agents that directly target the key cytokines involved in COVID-19 may also help alleviate hyperinflammation symptoms in severe cases [12]. Elevated levels of the inflammatory indicator IL-6 in the blood have been reported to be predictive of a fatal outcome in patients with COVID-19 [13]. Tocilizumab, a specific monoclonal antibody that blocks IL-6, has been recommended for use in severe or critically ill patients with extensive lesions in bilateral lungs and a confirmed elevated level of IL-6 in the Diagnosis and Treatment Protocol

for Novel Coronavirus Pneumonia (Trial Version 7) issued by the National Health Commission of China [7]. A retrospective analysis on 20 severe cases of COVID-19 showed that treatment with tocilizumab led to a reduction in fever and lung lesion opacity, and recovered the percentage of lymphocytes in peripheral blood [14].

IL-6 can bind to transmembrane IL-6 receptors (mIL6R) and soluble IL-6 receptors (sIL-6R), and the resulting complex can combine with signal transducing component gp130 to activate the inflammatory response. Tocilizumab can bind specifically to sIL-6R and mIL-6R, and block signal transduction [15]. Tocilizumab is a good therapeutic option for cytokine release syndrome in chimeric antigen receptor T-cell immunotherapy. However, clinical experience with tocilizumab in viral disease is very limited. In a retrospective study on patients with juvenile idiopathic arthritis infected with influenza A, reduced fever and a reduced level of C-reactive protein were observed in patients who received tocilizumab compared with patients who did not receive tocilizumab [16]. Meanwhile, IL-6 inhibition by tocilizumab did not exacerbate or increase susceptibility to influenza virus infection [16]. However, there are well documented warnings on increased risk of opportunistic infections (including tuberculosis, fungal or other viral infections) caused by anti-IL-6 monoclonal antibodies during the treatment of rheumatoid arthritis [17]. High costs and safety risks may be a barrier for the wide use of tocilizumab in the treatment of COVID-19.

In early March 2020, Chinese clinicians investigated the use of other immunomodulatory agents, such as ulinastatin, for treatment of the cytokine storm for COVID-19 [18]. Ulinastatin is a serine protease inhibitor with anti-inflammatory properties (including inhibition of IL-6), and it has been used in the treatment of acute pancreatitis and sepsis in Japan and China [19]. Expert consensus from Shanghai was that ulinastatin is recommended in patients with exacerbated lung lesions [18]. Overall, certain immunomodulatory agents with good safety profiles may be considered for use in combination with antiviral drugs for the treatment of severe or critical cases of COVID-19 (Table 1).

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