Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Utilizing tocilizumab for the treatment of cytokine release syndrome in COVID-19

To the Editor

Coronavirus disease 2019 (COVID-19) was detected in China in December 2019 [1]. Effective treatments are under study particularly those modifying a dysregulated host immune response known as cytokine release syndrome (CRS). CRS has been seen with other strains of coronavirus leading to acute respiratory distress syndrome (ARDS). Interleukin 6 (IL-6) is one of the cytokines associated with ARDS related to COVID-19 and it's inhibitor, tocilizumab, is on the forefront of investigational treatment [2].

We present 9 patients with confirmed COVID-19 by detection of SARS-CoV 2 via reverse-transcriptase polymerase chain reaction in two community hospitals treated with tocilizumab (Table 1). The criteria for tocilizumab use (Table 2) was based on publicized clinical trial protocols and the package insert and was tailored to our needs [3]. The mean age was 60 years (37–88 years). The mean body mass index was 29.9 kg/m2 (17.8–38 kg/m2). All patients presented 7–10 days after symptom onset except Patient 4 who was transferred into our facility. All patients except one were admitted or transferred to the Intensive Care Unit (ICU). Average length of ICU stay was 10 days with 5 patients requiring ventilation. A lower subcutaneous dose of tocilizumab was given to 3 patients. Death occurred in 2 patients. Patient 7 underwent cardiac arrest after tocilizumab therapy, making it impossible to interpret the effect of tocilizumab. Clinical improvement was observed in 7 of the remaining 8 patients with either decreasing oxygen requirements or successful extubation. Most patients noted an improvement in inflammatory markers within 7 days.

This case series highlights characteristics of patients with presumed CRS and COVID-19. Most patients received one or two doses of tocilizumab within 48 h of respiratory decompensation. Reports have discussed uncertainty in dosing tocilizumab [4,5]. Within our patients, some received a lower subcutaneous dose of tocilizumab, suggesting that a lower dose might be enough to manage the CRS. Trials have proposed that a repeated dose of tocilizumab be given to critically ill patients with elevated IL-6 due to the limited response seen with one dose [4,5]. Within our patients there was no difference between those who received one or two doses and reflects reports of improvement in inflammatory markers and oxygen requirements within 1 week of tocilizumab administration [4,5]. The timing of administration in relation to disease course remains uncertain. It is unknown if earlier administration of tocilizumab triggered by rising inflammatory markers could prevent or decrease severity of respiratory decompensation.

Corticosteroids were administered with tocilizumab in 3 patients and have been used in prior studies for its potential steroid sparing effect [5]. There are concerns regarding the risk of infection as well as theoretically delaying viral clearance [2,5]. Our patients were screened for infections prior to and after treatment. In our evaluation, three patients were treated with antibiotic therapy for presumed hospital acquired pneumonia at various points throughout their hospital stay. Viral clearance was not assessed in our patients.

To conclude, while administration of tocilizumab in patients with COVID-19 exhibiting signs of CRS appeared to show clinical improvement, the ideal setting and dose of administration requires further study.

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Table 1
Patient Demographics.

Patient	Age	Sex	Ethnicity	Co-morbidities	Days from symptom onset to hospital admission	qSOFA	ICU LOS (days)	Length of intubation (days)	Days from symptom onset to tocilizumab administration	Total doses of tocilizumab	Dose and route of tocilizumab	Other anti-virals, antibiotics and anti-inflammatory agents used	Disposition	Total hospital LOS
1	37	M	Hispanic	None	4	0	10	Not intubated	9	1	400 mg, IV	Azithromycin, ceftriaxone, hydroxychloroquine	Home with self-care	13
2	55	F	Caucasian	Asthma, GERD, HTN, migraines	7	1	15	11	14	1	162 mg, SC	Cefepime, ceftriaxone, hydroxychloroquine, linezolid, vancomycin	Home with family care	21
3	67	F	Caucasian	HTN, GERD	7	0	11	9	14	1	400 mg, IV	Azithromycin, hydroxychloroquine	Rehab	22
4	54	M	Asian American	HTN, obesity	10	1	3	Not intubated	14	1	162 mg, SC	Azithromycin, hydroxychloroquine	Home with self-care	8
5	65	M	Caucasian	Obesity	17	2	23	14	10	2	400 mg, IV, 162 mg SC	Azithromycin, ivermectin, hydroxychloroquine, linezolid, meropenem	Still hospitalized	N/A
6	88	M	African American	Dementia, HLD, HTN	3	3	11	Not intubated	4	2	400 mg, IV	Azithromycin, cefepime, hydroxychloroquine, methylprednisolone, vancomycin	Expired	12
7	69	F	African American	Diabetes	10	3	6	6	5	1	162 mg, SC	Azithromycin, cefepime, ceftriaxone, hydroxychloroquine, vancomycin	Expired	6
8	42	M	Caucasian	Obesity	7	1	11	10	10	1	800 mg, IV	Azithromycin, hydroxychloroquine, ivermectin, meropenem, methylprednisolone	Still hospitalized	N/A
9	63	M	Caucasian	Cardiac	7	1	Not in ICU	Not intubated	8	2	400 mg, IV	Azithromycin, hydroxychloroquine, methylprednisolone	Home with self-care	13

Key: ICU - Intensive care unit, HTN - Hypertension, GERD - Gastroesophageal reflux disease, HLD - Hyperlipidaemia, qSOFA - Quick sequential organ failure assessment, LOS - Length of stay, IV – Intravenous, SC – Subcutaneous, N/A – Not applicable.

Table 2
Tocilizumab administration criteria [3].

Inclusion criteria for using an IL-6 inhibitor
SARS-CoV-2 infection confirmed by PCR
Positive Imaging on chest X-Ray or CT scan
PaO2/FiO2 < 350 while on room air in upright position **OR** PaO2/FiO2 < 280 on supplemental oxygen and immediately requiring high flow oxygen device or mechanical ventilation
Signs of Cytokine release syndrome with any of the following
● Serum ferritin > 1000 mcg/mL and rising since last 24 hours
● Single ferritin > 2000 mcg/mL in patients requiring immediate high flow oxygen device or mechanical ventilation
● Lymphopenia defined as < 800 lymphocytes/μL **AND** 2 of the following extra criteria
○ Ferritin > 700 ng/mL and rising since last 24 hours
○ -Increased LDH > 300 IU/L and rising since last 24 hours
○ D-Dimer > 1000 ng/mL and rising since last 24 hours
○ CRP above 70 mg/dL and rising since last 24 hours and absence of bacterial infection
Exclusion criteria: Pregnancy, immunocompromised state, malignancy, active TB, bacterial infection, fungal infection
Key: PCR – Polymerase chain reaction, CT – Computed tomography, CRP – C-reactive protein, TB - Tuberculosis

Declaration of Competing Interest

The authors report no conflicts of interest.

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