

Early experience with anti-interleukin-6 therapy in COVID-19 hyperinflammation

Sir,

The current severe acute respiratory syndrome-coronavirus-2 pandemic has already caused >10 million cases worldwide. Acute respiratory distress syndrome (ARDS) secondary to coronavirus disease 2019 (COVID-19) is among the leading causes of mortality in these patients.^[1,2] Extensive release of pro-inflammatory cytokines, i.e., cytokine storm has been implicated in progression to ARDS and eventually a poor outcome. This cytokine storm is a part of hyperinflammatory syndrome associated with the COVID-19 infection and is characterized by multiorgan involvement, cytopenia, coagulopathy, and elevated levels of pro-inflammatory cytokines and inflammatory biomarkers such as interleukin-6 (IL-6), ferritin, lactate dehydrogenase (LDH), transaminases, C-reactive protein (CRP), triglycerides, D-dimer, and low levels of fibrinogen.^[1,2] Tocilizumab (TCZ), which is an anti-IL-6 receptor antibody, has shown promising results in the management of COVID-19-related cytokine storm.^[3-5] Herein, we present our experience and safety of using TCZ in four patients in our hospital.

All the four patients had confirmed COVID-19 on throat swab reverse transcription-polymerase chain reaction. Two of the patients had normal oxygen saturation at room air at presentation, whereas the rest two were hypoxemic at room air. These patients later progressed to Type 1 respiratory failure requiring noninvasive/invasive ventilation, indicating critical infection. All these patients had raised markers of hyperinflammation such as serum D-dimer, ferritin, LDH, CRP, and IL-6 levels [Table 1]. These patients received standard institutional care as per the existing guidelines in the form of antipyretics, steroids, therapeutic dose of anticoagulation (enoxaparin 1 mg/kg subcutaneous twice daily), and awake proning protocol. These patients were diagnosed to have cytokine storm syndrome based on their clinical deterioration and laboratory parameters. We used injection TCZ (dosage – 8 mg/kg) infusion over 1 h in these patients (maximum dose – 600 mg), and it was repeated

after 24 h if required. All these patients had a significant clinical improvement, reduction in inflammatory markers, and radiological improvement [Figure 1] post injection TCZ infusion [Table 1]. The clinical parameters included defervescence, improvement of oxygenation, and decreased FiO₂ requirement. The serum ferritin, LDH, and CRP showed gradual reduction post-anti-IL6 therapy, but D-dimer levels did not improve much. All the four patients were gradually weaned off the ventilator. None of these patients had any adverse reaction with the drug.

Cytokines such as IL-6, interferons, tumor necrosis factor, and chemokines are a group of small molecular proteins secreted by immune cells. They participate in immune reactions, but in viral infections such as COVID-19, there is an extraordinary release of pro-inflammatory cytokines and chemokines from infected macrophages, which causes massive immune response and further release of cytokines, eventually leading to cytokine storm.^[1,2] IL-6 is among the major cytokine involved in cytokine storm, and TCZ which is an IL-6 receptor antagonist has shown to improve hypoxemia and decrease fever, lung injury, and CRP levels in severe COVID-19 infection.^[3-5] It has also been shown to reduce mortality among these patients.^[3-5] Based on our initial experience, we believe that TCZ is safe and effective in patients with severe COVID-19 infection. The experience

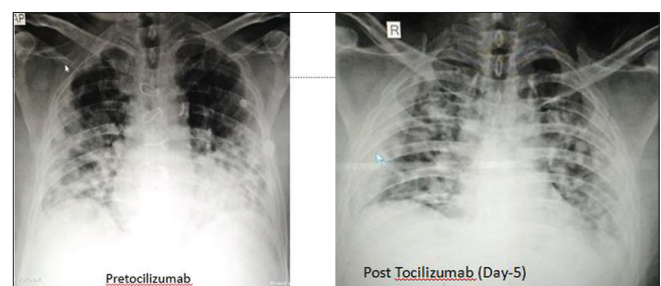


Figure 1: Chest radiograph showing air space opacities pre tocilizumab in bilateral mid and lower zones and clearing of opacities in radiograph five days after tocilizumab administration

Table 1: Demographic profile of patients with clinical and laboratory parameters pre- and post- Tocilizumab and follow-up

Demographic Profile	Patient-1			Patient 2			Patient 3			Patient 4		
	Age (Years)	Sex	Co-morbidities	Age (Years)	Sex	Co-morbidities	Age (Years)	Sex	Co-morbidities	Age (Years)	Sex	Co-morbidities
	67	Female	Primary Hypertension, Type-II DM	63	Male	-CAD post CABG, -Primary hypertension, -Type 2 DM	41	Male	Nil	66	Female	Primary Hypertension, -Type-II DM -Sick sinus syndrome on pacemaker -Bronchial Asthma
Parameters	Baseline	Pre	Post	After	Baseline	Pre	Post	After	Baseline	Pre	Post	After
FiO2 req (%)	30	80	60	30	65	75	60	50	Nil	30	85	75
PaO2/FiO2	170	80	100	220	100	95	115	140	300	233	63	89.3
Haemoglobin (g/dL)	11.3	9.1	9.7	11.3	16.7	14	13.3	13.3	13.7	11	10.8	11.4
TLC (cells/ μ L)	9000	6500	7400	11300	6900	4600	6500	5600	6400	7000	5300	10700
Neutrophil/Lymphocyte ratio	3.6	14	11	4	2.10	4.29	3.93	3.43	2	2.25	1.77	4.68
Platelet count (cells/ μ L) (lacs)	2.65	2.15	4.26	4.43	1.51	1.43	1.94	2.57	1.63	1.85	2.23	4.27
CRP (mg/L)(<5.00)	180	250	150	25	40.78	112.25	13	<5.00	32	146.93	18.6	<5.0
Serum Procalcitonin (<.05 ng/mL)	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
D-dimer (mcg/ml)	2.96	11.3	11.3	1.9	>20	0.95	1.19	1.76	0.33	1.09	0.36	0.7
IL-6 (<7.0 pg/mL)	250.9	Not repeated	Not repeated	Not repeated	2482	Not repeated	Not repeated	Not repeated	252.2	Not repeated	Not repeated	Not repeated
Ferritin (ng/ml)	350	1470	500	500	542	1013	724.7	356	410	735	482	802
CPK/CKMB	108/45	252/73	235/42	135/42	467/56	337/30	313/29	149/30	279/36	269/44	267/34	102/36
LDH (IU/L)	380	505	460	409	380	376	420	526	192	271	223	400
INR	2.93	1.05	1.05	0.93	0.93	1.18	1.25	0.93	0.84	0.9	0.8	1.0
ALT (U/L)	95	26	27	34	52	54	89	68	52	57	70	52
AST (U/L)	48	34	37	44	26	37	72	64	64	63	71	54

FiO - Fraction of Inspired oxygen, PaO₂ - Partial pressure of Oxygen, TLC- Total Leukocyte count, CRP- C-Reactive Protein, IL-6- Interleukin 6, CPK-Creatinine Phosphokinase, Creatinine Kinase-MB, LDH- Lactate Dehydrogenase, INR- International Normalised Ratio, ALT- Alanine Transaminase, AST-Aspartate Transaminase

of the use of TCZ has hardly been reported from India, and this article may be the first one in describing the initial experience of using this drug. It is pertinent to identify the features of cytokine storm and treat it to prevent the cascade of events, leading to acute and irreversible lung injury and finally a fatal outcome. However, a large study population is required to confirm its efficacy.

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Conflicts of interest

There are no conflicts of interest.

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