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Successful treatment of severe COVID-19 pneumonia with tocilizumab: A series of three cases

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Severe coronavirus disease 2019 (COVID-19) pneumonia associated with cytokine storm remains a challenge for clinicians. It is usually complicated by multiple organ dysfunction and despite optimal contemporary therapy leads to high mortality.

In this research letter, 3 consecutive patients are presented with severe COVID-19 pneumonia who between January and March 2021 were successfully treated with tocilizumab (a humanized antibody to the soluble interleukin-6 receptor) added to the standard therapy. This treatment was approved by the local ethics committee and subsequently all patients provided an informed written consent. On admission, all patients were moderately/severely ill with predominant respiratory failure and markedly elevated C-reactive protein (CRP) concentration (Table 1). Therapy with tocilizumab was initiated on day 1 in 2 patients and on day 6 in the 3rd one when he developed respiratory collapse requiring high flow oxygen therapy. All patients received two doses of tocilizumab and then their CRP concentration dropped on average by 71%. Following administration of tocilizumab combined with best known therapy, all patients were slowly and continuously improving. They all were

discharged home in a relatively good condition and at a short-term follow-up are mildly symptomatic or asymptomatic.

The decision to use tocilizumab was based on the promising results of randomized clinical trials (RCTs) published since March 2020 [1–10]. The largest and most recent study with the most spectacular outcomes is the RECOVERY trial [1]. Its results have only been published as a preprint to date. This trial included 4,116 participants receiving invasive ventilation (14%), non-invasive ventilation (41%) or usual oxygen therapy (45%). All enrolled patients had oxygen saturation < 92% and CRP concentration > 75 mg/dL. Median CRP in the RECOVERY trial was 143 [interquartile range 107–204] mg/L which is similar to our patients. Additionally, 82% of patients in the REVOVERY trial received systemic corticosteroids at randomization. The primary endpoint (all-cause 28-day mortality) was substantially reduced in the tocilizumab on top of standard care vs. standard care alone group (29% vs. 33%, p = 0.007), with consistent results in all predefined subgroups. Significant reductions in terms of secondary endpoints were also achieved in tocilizumab-treated patients (discharge from hospital alive within 28 days [54% vs. 47%], composite outcome of invasive mechanical ventilation or death [33% vs. 38%] and use of hemodialysis or hemofiltration [5% vs 7%]). Tocilizumab benefits were observed regardless of the level of respiratory support and were additional to the benefits of systemic corticosteroids, another class of anti-inflammatory agents. Also, the results of two moderate size RCTs indicated clinical benefits of tocilizumab. In the REMAP-CAP trial conducted in critically ill patients with COVID-19 pneumonia receiving organ support in intensive care units, treatment with the interleukin-6 receptor antagonist (tocilizumab [n = 353] or sarilumab [n = 48]) when compared with the control group (n = 402) improved clinical outcomes, including 90-day survival [2]. Similarly, the EMPACTA trial demonstrated superiority of tocilizumab (n = 249) over placebo (n = 128) on the primary composite endpoint of mechanical ventilation or death by day 28, but without any improvement in mortality [3]. This study included only patients who did not require mechanical ventilation at randomization. Importantly, several small/moderate size (all largely underpowered for assessment of hard clinical endpoints) RCTs indicated a neutral effect of tocilizumab on clinical outcomes [4–7], with some minor benefits seen in the CORIMUNO-19 study [5]. On the other hand, the TOCIBRAS trial was stopped early after inclusion of 129 participants due to a signal of increased mortality at 15 days related to tocilizumab therapy (11/65 [17%] vs. 2/64 [3%]) [8]. This observation may be a chance to find out when, considering the very low mortality in the standard care alone group. In all of the RCTs discussed above , adverse events were not more frequent in the tocilizumab vs.

placebo/standard care group [1–8]. Finally, an updated meta-analysis of all available RCTs performed by the ROCOVERY investigators shows all-cause mortality benefit in patients hospitalized for COVID-19 pneumonia and treated with tocilizumab added to usual care when compared with the usual care alone group (relative risk 0.87; 95% confidence interval 0.79–0.96; p = 0.005), with a substantial heterogeneity among the included trials [1]. Furthermore, it is suggested that tocilizumab may exert an additive beneficial effect in remdesivir-treated patients [9], as was used in the present case series.

Based on the totality of the research evidence [10] and our clinical experience, we believe that tocilizumab is well tolerated and may be beneficial on top of standard therapy if early initiated in patients with COVID-19 pneumonia and both enhanced inflammatory response and a large extent of the involved lung tissue. However, further RCTs are necessary to define best tocilizumab responders.

Conflict of interest: None declared

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Table 1. Characteristics of patients severe COVID-19 pneumonia and respiratory failure treated with tocilizumab.

	Patient 1	**Patient 2**	**Patient 3**
Demographic data			
Age [years]	61	61	70
Gender	Male	Female	Male
Clinical characteristics and course, including respiratory status and support			
Body mass index [kg/m^2]	25	34	27
Comorbidities	Bronchial asthma, acute kidney injury (stage 1 according to KDIGO)	Hypertension, paroxysmal atrial fibrillation, history of pulmonary embolism, bronchial asthma, status post colon cancer surgery	Type 2 diabetes mellitus, diabetic neuropathy
Duration of symptom onset to hospital admission [days]	7	7	12
Clinical status on 7 level ordinal scale on hospital admission	4	4	4
Extent of the involved lung tissue on CT [%]	27*	78	75
Oxygen saturation on admission [%]	90 then deterioration to 75 on day 3	80	70
Minimal arterial pO_2 [mmHg]	49.5	45.1	50.3
Respiratory support	High flow oxygen through a nasal cannula [up to 60 L/min through 16 days]	Supplemental oxygen through a face mask [up to 17 L/min through 11 days]	Supplemental oxygen through a face mask [up to 17 L/min through 10 days]
Blood culture	All negative (obtained twice in all patients)		
Laboratory measurements on hospital admission			
Lymphocyte count [G/L]	0.35	0.75	0.95
CRP concentration [mg/L]	137.1	209.7	169
Procalcitonin concentration [ng/mL]	0.28	0.2	0.22
D-dimer concentration [ng/mL]	35200	768	Not available
Creatinine concentration [mg/dL]	1.44 (after patient hydration a decrease to	0.94	0.94

	0.83)		
Lactate dehydrogenase activity [U/L]	720	454	Not available
Cardiac troponin T	Negative	Mildly elevated (0.055 ng/L)	Negative
Pharmacotherapy during hospitalization			
Treatment with dexamethasone	Yes (6 mg IV once daily)	Yes (6 mg IV once daily)	Yes (6 mg IV once daily)
Treatment with remdesivir	Yes (initiated on day 3)	Yes (initiated on day 3)	Yes (initiated on day 1)
Anticoagulation	Prophylactic dose of enoxaparin	Rivaroxaban 20 mg/day	Prophylactic dose of enoxaparin
Treatment with tocilizumab	Initiated on day 6 at the dose of 600 mg IV which was repeated on day 7	Initiated on day 1 at the dose of 720 mg IV which was repeated on day 2	Initiated on day 2 at the dose of 640 mg IV which was repeated on day 3
Effect of tocilizumab administration on CRP concentration	After 2nd dose a decrease from 137 to 56 mg/L on the 2nd day	After 2nd dose a decrease from 209 to 40 mg/L on the 3rd day	After 2nd dose a decrease from 169 to 58 mg/L on the 3rd day
Antibiotic therapy	Ceftriaxone initiated on admission then on day 2 changed for piperacillin /tazobactam then on day 8 changed for meropenem for 7 days	Ceftriaxone initiated on admission and continued for 10 days	Ceftriaxone initiated on admission and continued for 10 days
Hospital discharge and follow-up			
Length of hospitalization [days]	28	13	14
Clinical status at the end of hospitalization	Discharged in a relatively good condition with the need of temporal low flow oxygen supplementation at home		
Length of follow-up [days]	53	26	31
Clinical status at the end of follow-up	Fully recovered without any respiratory failure	The need of temporary low flow oxygen supplementation at home	

*No control CT was performed after deterioration of the respiratory status as the patients was treated with high flow oxygen therapy and we were not able to transport him safely without tracheal intubation; CRP — C-reactive protein; CT — computed tomography; KDIGO — Kidney Disease: Improving Outcomes; pO_2 — partial pressure of oxygen; SpO_2 — oxygen saturation