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Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy

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A B S T R A C T

A hyperinflammatory syndrome (HIS) may cause a life-threatening acute respiratory distress syndrome (ARDS) in patients with COVID-19 pneumonia.

A prospective series of 100 consecutive patients admitted to the Spedali Civili University Hospital in Brescia (Italy) between March 9th and March 20th with confirmed COVID-19 pneumonia and ARDS requiring ventilatory support was analyzed to determine whether intravenous administration of tocilizumab (TCZ), a monoclonal antibody that targets the interleukin 6 (IL-6) receptor, was associated with improved outcome. Tocilizumab was administered at a dosage of 8 mg/kg by two consecutive intravenous infusions 12 h apart. A third infusion was optional based on clinical response.

The outcome measure was an improvement in acute respiratory failure assessed by means of the Brescia COVID Respiratory Severity Score (BCRSS 0 to 8, with higher scores indicating higher severity) at 24–72 h and 10 days after tocilizumab administration.

Out of 100 treated patients (88 M, 12 F; median age: 62 years), 43 received TCZ in the intensive care unit (ICU), while 57 in the general ward as no ICU beds were available. Of these 57 patients, 37 (65%) improved and suspended noninvasive ventilation (NIV) (median BCRSS: 1 [IQR 0–2]), 7 (12%) patients remained stable in NIV, and 13 (23%) patients worsened (10 died, 3 were admitted to ICU). Of the 43 patients treated in the ICU, 32 (74%) improved (17 of them were taken off the ventilator and were discharged to the ward), 1 (2%) remained stable (BCRSS: 5) and 10 (24%) died (all of them had BCRSS ≥ 7 before TCZ). Overall at 10 days, the respiratory condition was improved or stabilized in 77 (77%) patients, of whom 61 showed a significant clearing of diffuse bilateral opacities on chest x-ray and 15 were discharged from the hospital. Respiratory condition worsened in 23 (23%) patients, of whom 20 (20%) died.

All the patients presented with lymphopenia and high levels of C-reactive protein (CRP), fibrinogen, ferritin and IL-6 indicating a HIS. During the 10-day follow-up, three cases of severe adverse events were recorded: two patients developed septic shock and died, one had gastrointestinal perforation requiring urgent surgery and was alive at day 10.

In conclusion, our series showed that COVID-19 pneumonia with ARDS was characterized by HIS. The response to TCZ was rapid, sustained, and associated with significant clinical improvement.

1. Background

After the first epidemic of Coronavirus associated disease (COVID19) sustained by SARS-CoV-2 in Wuhan (China), the region of Lombardy in Northern Italy has become the second most affected area in the world [1,2]. The Spedali Civili of Brescia, a large university hospital with 1570 beds serving an area of nearly one million people in the east of Lombardy, is one of the 15 first-responder hub-hospitals admitting COVID19 patients [3]. In the first 14 days of epidemic, hospital admissions increased sharply and the hospital rapidly became overloaded with patients with pneumonia and acute respiratory failure. At the time of writing, after the first patient was admitted on February

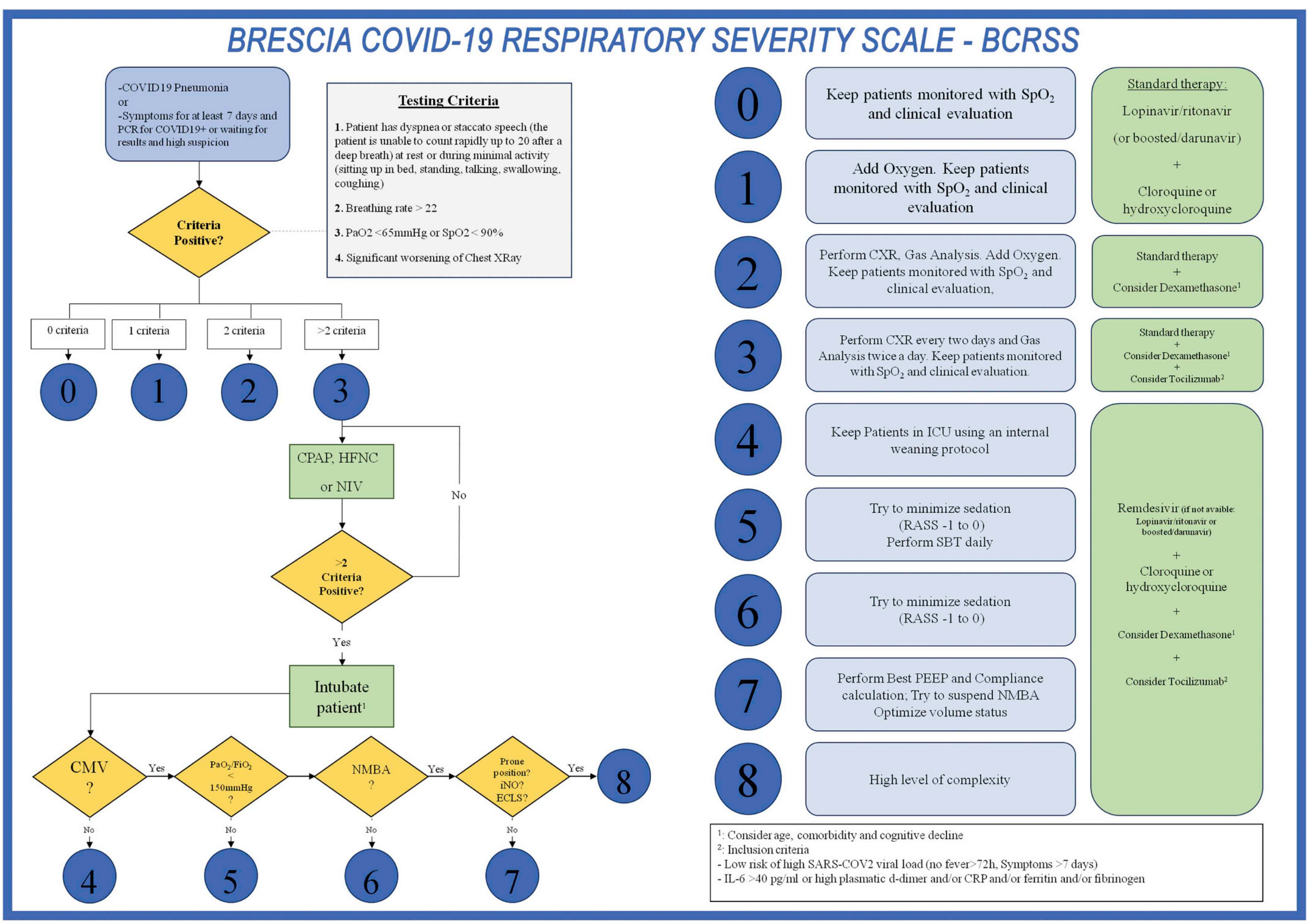

Fig. 1. Brescia COVID-19 Respiratory Severity Scale (BCRSS).
BCRSS is freely available at: https://www.mdcalc.com/brescia-covid-respiratory-severity-scale-bcrss-algorithm

23rd there are more than 500 hospitalized patients with COVID-19, of whom 55 are in the intensive care units (ICU).

The reason why a subgroup of COVID-19 patients with pneumonia develops rapidly progressing respiratory failure remains unknown, which makes the optimal therapeutic approach to these patients uncertain. The scarcely available evidence suggests that a hyperinflammatory syndrome (HIS) that resembles secondary hemophagocytic lymphohistiocytosis (sHLH) may have a pathogenetic role [4,5]. sHLH may be triggered by viral infections, and some cases have been linked to the Middle East respiratory syndrome due to coronavirus (MERS-CoV) [6–8]. The laboratory hallmarks of sHLH are cytopenia, elevated levels of ferritin, transaminases, triglycerides, lactate dehydrogenase (LDH) and D-Dimer, and low fibrinogen [9]. In Chinese reports, lower levels of lymphocyte count, higher levels of ferritin, LDH, transaminases and D-dimer were associated with a worse prognosis [10,11]. Patients with HIS may benefit from early identification and treatment with anti-cytokine targeted therapies [12]. Preliminary reports show higher IL-6 levels in COVID-19 patients with worse prognosis and Tocilizumab (TCZ), an anti-IL-6 receptor monoclonal antibody, has been used in 20 patients in China with encouraging results [13,14]. The aim of this report is to describe our experience with a series of 100 consecutive COVID-19 patients treated with TCZ in Brescia.

2. Methods

Between March 9th and March 20th one hundred consecutive patients with severe COVID-19 pneumonia were treated with TCZ. Patients were treated “off-label” before the approval by the Italian Regulatory Agency (AIFA) on March 19th of a multicenter study on the efficacy and tolerability of TCZ in the treatment of patients with COVID-19 pneumonia (TOCIVID-19) [15]. Research was approved by the Ethics Committee of Brescia. Since the patients were unable to give their informed consent, the Ethics Committees waived the requirement, as in Italy relatives are not regarded as legal representatives of the patient in the absence of a formal designation [16]. Written informed consent was requested from all surviving patients as soon as they regained their mental competency. All investigations were conducted according to the principles expressed in the Declaration of Helsinki.

Selection of patients was based on disease severity and absence of contraindication to TCZ, including a suspected or confirmed bacterial infection, an active diverticulitis or gastrointestinal tract perforation, neutropenia (0.500 × 10ˆ3 cells/uL) and thrombocytopenia (50 × 10ˆ3 cells/uL).

Respiratory disease severity was assessed by a locally developed bedside respiratory severity scale, the Brescia COVID-19 Respiratory Severity Scale (BCRSS), a 9-category ordinal severity scale ranging from 0 (asymptomatic patient) to 8 (a critically ill patient with tracheal intubation, mechanical ventilation and advanced ICU management (Fig. 1). The BCRSS has been developed through multiple interactions by a multidisciplinary team of intensive care physicians, infectious disease specialists, pneumologists, internists, rheumatologists and immunologists to rapidly assess the patients' respiratory condition. BCRSS classifies the patients' severity based on the need for oxygen supplementation and ventilatory support, offering a step-up therapeutic approach for the use of antiviral and anti-inflammatory drugs. The scale was rapidly adopted at a regional level and used to define pragmatically the patient's response to treatment [17].

All patients receiving intravenous TCZ were treated with a standard pharmacological protocol, including antiviral drugs (lopinavir 400 mg + ritonavir 100 mg twice a day or remdesivir 100 mg/day), antibiotic prophylaxis (azithromycin, ceftriaxone or piperacillin/tazobactam), hydroxychloroquine 400 mg/day and dexamethasone 20 mg/day [18] and were receiving non-invasive ventilation (NIV) or mechanical ventilation with tracheal intubation (BCRSS score ≥3). Indication for TCZ was based on rapidly progressive respiratory failure, refractory to pharmacological therapy and ventilatory support.

Table 1
Clinical characteristics of the patients.

	Total (n = 100)		Improved or stable (n = 77)		Worsened or deceased (n = 23)	
Demographics and clinical characteristics						
Gender	88 M, 12 F		66 M, 11 F		22 M, 1 F	
Age	62 (57–71)		61 (54–68)		66 (63–74)	
Any Comorbidity	66 (66%)		47 (61%)		18 (78%)	
Arterial Hypertension	46 (46%)		33 (43%)		13 (57%)	
Diabetes Mellitus	17 (17%)		13 (17%)		4 (17%)	
Cardiovascular Disease	16 (16%)		10 (13%)		6 (26%)	
Chronic kidney disease	11 (11%)		6 (8%)		5 (22%)	
Chronic obstructive pulmonary disease	9 (9%)		6 (8%)		3 (13%)	
Malignancy	6 (6%)		4 (5%)		2 (9%)	
Obesity (BMI > 30)	31 (31%)		24 (31%)		7 (30%)	
Overweight (BMI 25–30)	34 (34%)		27 (35%)		7 (30%)	
Signs and symptoms						
Fever (>37.5 °C)	85 (85%)		67 (87%)		18 (78%)	
Cough	55 (55%)		43 (56%)		12 (52%)	
Dyspnea	73 (73%)		53 (69%)		20 (87%)	
Diarrhea	9 (9%)		8 (10%)		1 (4%)	
Days between onset of symptoms and hospital admission	6 (4–8)		7 (4–8)		5 (4–7)	
Days between hospital admission and TCZ infusion	5 (3–8)		5 (3–7)		5 (3–8)	
Days between the onset of symptoms and TCZ infusion	12 (9–14)		12 (10–14)		10 (8–13)	
	pre TCZ	**post TCZ**	**pre TCZ**	**post TCZ**	**pre TCZ**	**post TCZ**
BCRSS score	3 (3–7)	2 (1–4)	3 (3–6)	2 (1–3)	3 (3–7)	7 (6–7)

Data are expressed as median (1st Quartile - 3rd Quartile) or n (%). TCZ: tocilizumab; BMI: body mass index; BCRSS: Brescia COVID-19 Respiratory Severity Scale. Pre TCZ indicates 1–12 h prior to tocilizumab administration. Post TCZ indicates 10 days after tocilizumab administration.

TCZ was administered at a dosage of 8 mg/kg (max 800 mg) by two consecutive intravenous infusions 12 h apart. A third infusion, 24 h apart from the second was optional based on clinical response.

Clinical and laboratory data of all patients were collected at hospital admission, shortly before TCZ administration and 10 days after.

3. Results

One hundred patients were treated with TCZ (Table 1). The median age was 62 [IQR 57–71] and most patients were male (M/F: 88/12). Comorbidities were present in more than half of patients with hypertension being the most common one (46%), followed by obesity (31%), diabetes (17%) and cardiovascular disease (16%).

On admission the most common symptoms were fever (85%), dyspnea (73%) and cough (55%) with a median time from illness onset and hospital admission of 6 [IQR 4–8] days.

In all patients SARS-CoV-2 infection was confirmed by real time-PCR on nasopharyngeal swab and pneumonia was documented by chest x-ray or computed tomography. The most common radiological findings were bilateral pulmonary infiltration, ground glass opacities and consolidations.

All patients treated with TCZ had acute respiratory failure requiring ventilatory support (BCRSS ≥ 3). Fifty-seven patients were treated with NIV (BCRSS = 3): notably, these patients were treated in the general ward as no ICU beds and ventilators were available. Forty-three patients were treated in the ICU after tracheal intubation and mechanical ventilation with a BCRSS before treatment of 7 [IQR 5–8]. Eighty-seven patients (87%) received 2 infusions of TCZ, 13 patients (13%) 3 infusions.

At 24–72 h after TCZ administration, 58 patients (58%) showed a rapid improvement of clinical and respiratory condition, 37 (37%) stabilized compared to the rapidly declining pre-TCZ condition, and 5 (5%) worsened (of whom 4 died) (Fig. 2).

At 10 days, the respiratory condition was improved or stabilized in 77 (77%) patients, of whom 61 showed a significant clearing of diffuse bilateral opacities on chest x-ray and 15 were discharged from the hospital. Respiratory condition worsened in 23 (23%) patients, of whom 20 (20%) died.

Of the 57 patients treated outside the ICU, 37 (65%) improved and suspended NIV (BCRSS 1 [IQR 0–2]), 7 (12%) patients remained stable in NIV, and 13 (23%) patients worsened (10 died, 3 were admitted to ICU).

Of the 43 patients treated in the ICU, 32 (74%) improved (17 of them were taken off the ventilator and were discharged to the ward), 1 (2%) remained stable (BCRSS class 5) and 10 (24%) died (all of them had BCRSS ≥ 7 before TCZ).

At the time of TCZ administration, all patients presented lymphopenia (below 1 × 10ˆ3 cells/uL) and high levels of inflammatory markers, including CRP, fibrinogen, ferritin and IL-6. Ten days after, the lymphocyte count increased, especially in improved patients. CRP, fibrinogen and ferritin levels decreased toward the range of normality, while D-Dimer and IL-6 levels increased both in improved and worsened patients (Table 2).

During the 10-day follow-up, we observed three cases of severe adverse events: two patients developed septic shock and died, one had gastrointestinal perforation requiring urgent surgery and was alive at day 10.

4. Discussion

Trying to deal with an unprecedented sanitary emergency, a multidisciplinary team put efforts in the development of a standardized approach to manage patients with severe COVID-19 pneumonia and acute respiratory failure. We measured an extended panel of circulating biomarkers and used a disease-specific scale (BCRSS) to quickly classify respiratory severity, in order to provide a step-up approach for the use of antiviral and anti-inflammatory drugs. Besides lymphopenia, which has been consistently reported in patients with COVID-19, we found extremely high levels of CRP, ferritin, D-Dimer and triglycerides indicating that a HIS was present at the time when the respiratory condition was rapidly deteriorating [10,11]. Laboratory parameters did not fit completely with the definition of typical sHLH, which includes also hypofibrinogenemia, high AST levels and low platelet count. Hence, it remains uncertain whether the described biochemical pattern represents an incomplete form of sHLH confined to the lung or a peculiar hyperinflammatory and pro-coagulant state mediated by COVID-19 [5]. The COVID-19-associated HIS could be part of the spectrum of "hyperferritinemic syndromes", which includes many secondary auto-inflammatory conditions [19,20], and may have a genetic predisposition, like the majority of these diseases [21].

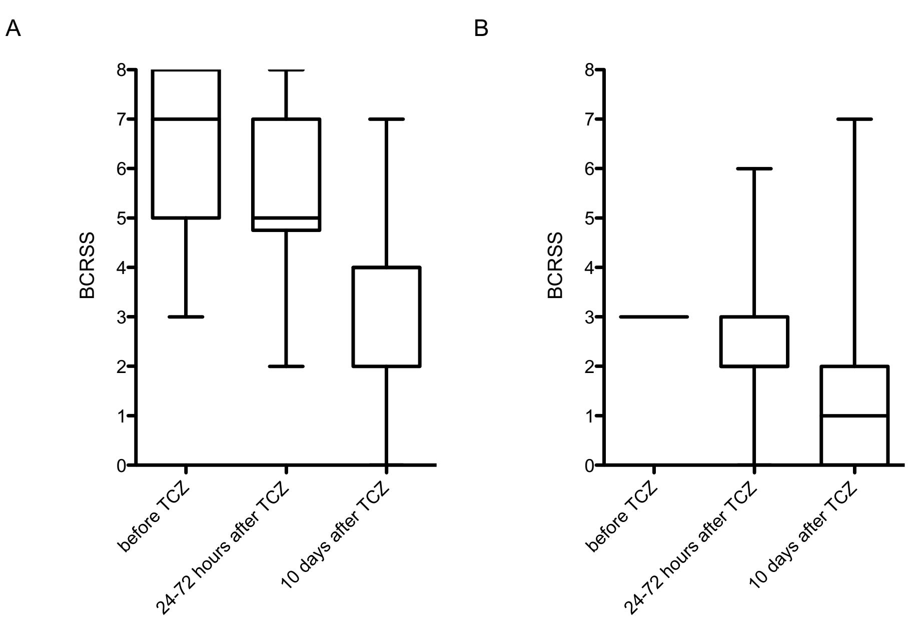

Fig. 2. Brescia COVID-19 Respiratory Severity Scale (BCRSS) trend over time after Tocilizumab administration in patients treated in the ICU (panel A) and in the general ward (panel B).

Table 2
Laboratory findings.

	Total (n = 100)			Improved or stable (n = 77)			Worsened or deceased (n = 23)		
	Hosp. Admis.	pre TCZ	post TCZ	Hosp. Admis.	pre TCZ	post TCZ	Hosp. Admis.	pre TCZ	post TCZ
White blood cell count (x10^3/uL)	6.0 (4.5–8.4)	8.8 (6.5–11.4)	11.3 (8.0–15.3)	5.7 (4.4–8.3)	7.9 (6.0–10.8)	10.9 (7.6–15.0)	7.0 (4.9–9.7)	9.7 (7.4–15.4)	13.8 (9.4–25.9)
Neutrophils (x10^3/uL)	4.9 (3.3–7.8)	6.7 (4.9–9.7)	8.9 (5.8–11.8)	4.4 (3.0–7.3)	6.1 (4.4–9.0)	7.9 (4.6–11.3)	6.1 (3.8–8.6)	9.5 (6.4–14.3)	11.4 (10.1–25.8)
Lymphocytes (x10^3/uL)	0.78 (0.51–1.10)	0.62 (0.41–0.84)	0.79 (0.61–1.16)	0.84 (0.53–1.2)	0.69 (0.43–0.86)	0.81 (0.61–1.30)	0.55 (0.46–0.83)	0.43 (0.32–0.72)	0.72 (0.52–1.10)
Platelets (x10^3/uL)	177 (141–224)	220 (174–294)	205 (142–289)	179 (139–224)	224 (181–296)	205 (154–297)	172 (145–219)	214 (141–266)	137 (102 – 323)
Haemoglobin (g/dL)	13.6 (12.8–14.8)	12.4 (11.1–13.6)	12.6 (11.3–13.8)	13.8 (12.8–14-8)	12.3 (11.1–13.3)	12.4 (10.9–13.5)	13.6 (12.6–14.7)	12.4 (11.4–14.7)	13.6 (12.4–14.5)
C-reactive protein (mg/L)	97 (38–159)	113 (45–169)	2 (1–5)	81 (38–138)	113 (43–170)	2 (1–4)	145 (57–205)	118 (71–164)	5 (5–7)
IL-6 (ng/L) [a]	NA	41 (10 – 102)	1812 (375–2600)	NA	16 (9–94)	1679 (335–2227)	NA	56 (25–157)	5000 (5000–5000)
Ferritin (ug/L)	1004 (268–3730)	1689 (981–3533)	1352 (806–2422)	905 (270–1705)	1568 (946–2664)	1308 (814–2397)	3733 (1937–5020)	3283 (988–4247)	1863 (790–6261)
D-Dimer (ng/mL)	525 (283–1100)	979 (456–3640)	2331 (887–3801)	383 (263–613)	746 (443–3444)	2210 (729–3257)	3854 (968–5250)	2407 (760–5250)	5250 (3328–5250)
Fibrinogen (mg/dL)	508 (421–627)	520 (436–714)	217 (150–285)	508 (458–653)	520 (473–713)	203 (148–274)	482 (352–587)	530 (350–765)	218 (168–316)
Aspartate aminotransferase (U/L)	55 (41–82)	47 (35–72)	43 (30–69)	53 (41–77)	46 (33–64)	41 (30–64)	61 (48–117)	52 (41–80)	69 (44–77)
Alanine aminotransferase (U/L)	39 (26–62)	43 (28–61)	75 (44–129)	39 (27–60)	39 (27–54)	76 (44–130)	40 (24–73)	59 (31–78)	63 (42–96)
Lactate dehydrogenase (U/L)	413 (281–542)	428 (293–537)	390 (319–531)	402 (285–513)	418 (288–481)	376 (317–504)	570 (247–764)	544 (365–749)	565 (406–870)
Triglycerides (mg/dL)	106 (91–135)	160 (113–219)	189 (164–220)	104 (92–129)	144 (102–207)	190 (163–219)	109 (88–153)	206 (147–233)	303 (228–432)
Cholesterol (mg/dL)	112 (89–134)	120 (107–139)	271 (220–355)	112 (94–127)	116 (107–126)	269 (215–336)	117 (87–156)	133 (123–141)	178 (175–222)
Creatine kinase (U/L)	161 (87–279)	105 (50–190)	87 (39–181)	172 (79–336)	104 (46–191)	85 (38–164)	152 (123–208)	116 (70–156)	167 (93–188)
Troponin T (ng/L)	18 (13 – 21)	11 (8–23)	25 (16–49)	18 (13–21)	10 (7–15)	19 (15–55)	18 (14–40)	23 (17–51)	42 (26–42)

Data are expressed as median (1st Quartile - 3rd Quartile). TCZ: Tocilizumab. Hosp. Admis. indicates hospital admission. Pre TCZ indicates 1–12 h prior to tocilizumab administration. Post TCZ indicates 10 days after tocilizumab administration.

[a] Interleukin-6 (IL-6): data available for 42 patients.

We treated with TCZ a series of 100 consecutive patients, the largest series until now, and found that the treatment was associated with a clinical improvement in more than three quarters of patients. CRP, ferritin and fibrinogen serum levels decreased toward the normal range and lymphocyte count increased, especially in patients whose clinical conditions improved. IL-6 serum levels increased, similarly to what was reported after TCZ administration in patients with Rheumatoid Arthritis and Castleman disease [22]. D-Dimer levels remained high, suggesting that TCZ was able to act only partially on the inflammatory cascade and might have had a minimal or no effect on down-modulating active coagulation [23].

These preliminary results are encouraging, considering that the response to TCZ was rapid, within 12 to 72 h, and sustained, as all patients with initial response continued to improve over the next ten days. Several acutely ill patients could be extubated and discharged to the ward or even discharged at home. It is worth emphasizing that, at the time of TCZ administration, ICU beds and ventilators were not available for many of these patients, leaving little time to save their lives [24].

In conclusion, our results should be considered preliminary, as they stem from an uncontrolled series and a causal inference cannot be established. TCZ efficacy needs to be validated in large clinical trials with randomized allocation of treatment. Given the dramatic spreading of the SARS-CoV-2 infection worldwide, we feel that our data would merit attention by colleagues caring for severe COVID-19 pneumonia and respiratory failure. Timely identification of the hyperinflammatory state and its treatment may be crucial in interrupting the cascade leading to irreversible lung damage and death. In these circumstances, Tocilizumab may be considered as rescue therapy if other treatments have failed or are not available.

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