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Pulmonary vascular improvement in severe COVID-19 patients treated with tocilizumab

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ABSTRACT

As of October 2020 management of Coronavirus disease 2019 (COVID-19) is based on supportive care and off-label or compassionate-use therapies. On March 2020 tocilizumab - an anti-IL-6 receptor monoclonal antibody - was suggested as immunomodulatory treatment in severe COVID-19 because hyperinflammatory syndrome occurs in many patients similarly to the cytokine release syndrome that develops after CAR-T cell therapy. In our retrospective observational study, 20 severe COVID-19 patients requiring intensive care were treated with tocilizumab in addition to standard-of-care therapy (SOC) and compared with 13 COVID-19 patients receiving only SOC. Clinical respiratory status, inflammatory markers and vascular radiologic score improved after one week from tocilizumab administration. On the contrary, these parameters were stable or worsened in patients receiving only SOC. Despite major study limitations, improvement of alveolar-arterial oxygen gradient as well as vascular radiologic score after one week may account for improved pulmonary vascular perfusion and could explain the more rapid recovery of COVID-19 patients receiving tocilizumab compared to controls.

1. Introduction

Coronavirus disease 2019 (COVID-19), the illness caused by SARS-CoV-2 infection, has emerged as a novel complex disease with a variable clinical course from asymptomatic to life-threatening condition [1,2]. Management of COVID-19 is currently based on supportive care and off-label or compassionate-use therapies. Many treatments are under investigation and so far those showing most promising results are remdesivir and dexamethasone [3,4,40]. Among others, the Infectious Diseases Society of America (IDSA) and the National Institutes of Health are providing up-to-date recommendations for the treatment and management of COVID-19 patients that, particularly in critical cases, needs expertise [5,6]. Patients with severe disease requiring intensive care often present an hyperinflammatory syndrome, with elevated serum interleukin-6 (IL-6) levels as well as increase of other pro-inflammatory cytokines [7–10]. The "cytokine storm" described in COVID-19 patients shows some common features with chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome (CRS), the most common adverse event following CAR-T cell infusion [11,12]. In 2017 the Food and Drug Administration approved tocilizumab, a recombinant humanized anti-human IL-6 receptor monoclonal antibody, for the treatment of CAR-T cell-induced CRS [13]. Tocilizumab binds the IL-6 receptor with high affinity and prevents IL-6 from binding to the receptor, and had been already approved for the treatment of various inflammatory diseases (i.e. rheumatoid arthritis, systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, and giant cell arteritis). At the beginning of March 2020, Xu et al. firstly reported the use of tocilizumab in a case-series of 21 patients with severe or critical COVID-19 demonstrating the improvement of symptoms, arterial oxygen levels and lung opacities. Despite major limitations, the study came out very early in the COVID-19 pandemic and suggested the use of tocilizumab as a potential immunomodulatory treatment of severe

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and critical COVID-19 patients [14]. Then the following literature showed conflicting results, with the most recent study by the BACC Bay Tocilizumab Trial Investigators demonstrating that tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients [15]. However, the effect on severely ill patients admitted to the intensive care unit (ICU) remains unclear. Therefore, in this study we aimed at evaluating the clinical and imaging response after one week of treatment with tocilizumab in patients with severe COVID-19 requiring intensive care.

2. Material and methods

2.1. Setting and patients

This is a retrospective observational single-center study. Adult patients admitted to the Pneumology and Intensive Care Unit of the Careggi University Hospital, Florence, Italy, from March 11th to April 28th 2020, for COVID-19 pneumonia were included either as controls if treated only with standard-of-care (SOC) or as cases if treated with tocilizumab in addition to SOC. Patients with evidence of bacterial sepsis, an absolute neutrophil count below 500 per mm^3, thrombocytopenia (below 50000 platelets per mm^3), liver impairment (ALT above 2.5 times ULN), medical history positive for gastrointestinal perforation, and/or known hypersensitivity to tocilizumab were excluded from treatment with tocilizumab. SOC included supplemental oxygen therapy as needed, low-molecular-weight heparin (6000 UI q.d.), hydroxychloroquine 400 mg b.i.d., and lopinavir/ritonavir 400/100 mg b.i.d. (or darunavir/cobicistat 800/150 mg q.d. when not tolerated). Corticosteroids or remdesivir were not included in SOC at that time. The diagnosis of COVID-19 was made with a SARS-CoV-2 positive reverse transcription real-time PCR on nasopharyngeal swab or bronchoalveolar lavage fluid in accordance with World Health Organization interim guidance [16]. Tocilizumab was administered intravenously twice 12−24 h apart at 8 mg/kg (up to 800 mg). The study was approved by the Careggi University Hospital Ethical Committee (protocol 16859) and conducted in compliance with the Declaration of Helsinki Good Clinical Practice guidelines. The study was not funded by sponsors. All recruited patients provided informed written consent for treatment with off-label drugs, as provided for by local protocol.

2.2. Clinical, laboratory and imaging monitoring

Physical examination, arterial blood gases test, laboratory parameters, and chest-X-ray (CXR) on day 0 (baseline time) and day 7 (after one week from baseline) were retrieved. We considered as baseline time the day of tocilizumab administration (within day 3 from ICU admission) for cases, and the second day after ICU admission for controls.

2.3. Data collection

Clinical and laboratory data were collected from hospital records and stored in a database after anonymization. Clinical and laboratory variables included gender, age, supplemental oxygen support, adverse events, outcome, hemoglobin levels, white blood cells, neutrophils, lymphocytes, and platelets counts, serum levels of IL-6, C-reactive protein (CRP), ferritin, fibrinogen, and D-dimer, fraction of inspired oxygen (FiO_2), partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), ratio of partial pressure of arterial oxygen to FiO_2 (PaO_2:FiO_2), ratio of arterial oxygen saturation to FiO_2 (SpO2:FiO2), and alveolar-arterial oxygen (A-a O_2) gradient. Adverse events were collected according to the common terminology criteria for adverse events (CTCAE) version 5.0. Chest-X-rays (CXRs) were performed at patient bedside by using portable machines. CXRs were reviewed by two independent radiologists and scored by evaluating both lung parenchyma and hilar vessels. Lung parenchyma was evaluated by applying the scoring method recently reported by Wong et al. and specifically developed for grading COVID-19 pneumonia: 0 for no involvement, 1 for less than 25 %, 2 for 25–50%, 3 for 50−75%, 4 for more than 75 % of parenchymal involvement on CXR [17]. Hilar vessels were scored by adapting the score previously used by Pistolesi et al. for acute respiratory distress syndrome (ARDS): 0 for normal, 1 for either increased density or dimensions, 2 for both increased density and dimensions [18, 19]. A final score was obtained by adding parenchymal and hilar scores (0–6), as summarized in Table 1.

Table 1
Chest X-ray scoring system.

Lung parenchymal score	
no involvement	0
<25 %	1
25−50%	2
50−75%	3
>75 %	4
Vascular score	
normal	0
either increased density or dimensions	1
both increased density and dimensions	2
Final score	
Lung parenchymal + vascular score	0−6

2.4. Statistical analysis

Data were expressed as mean ± standard deviation. Paired two-tailed Student's *t*-test was used for comparison of clinical, laboratory and imaging data obtained on baseline and day 7. Unpaired two-tailed Student's *t*-test was used for comparison of clinical and laboratory data of cases versus controls. A p value equal or less than 0.05 was considered as statistically significant. Intraclass correlation coefficient (ICC) was used to test the inter-reader agreement for CXR evaluation.

3. Results

3.1. Baseline features of recruited patients

In this retrospective study, we included 33 critical patients with SARS-CoV-2 infection who received SOC treatment. Twenty out of 33 (61 %) patients received tocilizumab in addition to SOC and 13 (39 %) only SOC treatment (control group). The main clinical features are summarized in Table 2. The PaO_2:FiO_2 and SpO_2:FiO_2 ratio were significantly lower, while the A-a O_2 gradient was significantly higher in the tocilizumab group compared with controls (Table 2). At baseline patients presented more commonly with low hemoglobin level, normal white blood cells, normal neutrophils, lymphocytopenia, and normal platelets counts. High serum levels of IL-6, CRP, ferritin, fibrinogen, or D-dimer were detected in all the cases at baseline (Table 2). Among the 20 patients who received tocilizumab, a total of 14 (70 %) were discharged home at 35 (±26) days after treatment, 5 (25 %) deceased at 23 (±18) days, while 1 (5%) was lost to follow-up. Among patients who received only SOC, 6 (46 %) were discharged home at 62 (±27) days after evaluation and 7 (54 %) deceased at 16 (±18) days. Hospitalization time from ICU admission to discharge home or death was 33 (±24) days for patients treated with tocilizumab and 38 (±33) days for patients of the control group.

3.2. Effects of Tocilizumab on the respiratory status and inflammatory markers

Before treatment with tocilizumab, 15/20 (75 %) patients received invasive ventilation and only 5/20 (25 %) non-invasive ventilation (Table 2). An improvement on oxygen-support class was observed in 14 (70 %) patients treated with tocilizumab during a follow-up time of 30 (±24) days, including 9 patients receiving mechanical ventilation who were extubated after 13 (±9) days from treatment with tocilizumab. No

Table 2
Clinical and laboratory characteristics of severe COVID-19 patients at baseline.

	Patient	Age	Gender	Hemoglobin (g/dL)	White blood cells (x10^9/L)	Neutrophils (x10^6/L)	Lymphocytes (x10^6/L)	Platelets (x10^9/L)	C-reactive protein (mg/L)	IL-6 (pg/mL)	Ferritin (ng/mL)	Fibrinogen (mg/dL)	D-dimer (ng/mL)	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	FiO_2 (%)	PaO_2: FiO_2	SpO_2: FiO_2	Alveolar-arterial O_2 gradient (mmHg)	Ventilation (IV = invasive; NIV: non-invasive)
Reference range	–	–	–	14–18	4000–10000	1500–7500	500–5000	140–400	<5	<10	8–252	200–400	<500	–	–	–	–	–	–	–
	T 1	70	M	13,6	9500	8340	730	390	162	258,6	2478	639	727	119	50	70	170	138	223	IV
	T 2	70	M	11,6	13400	4770	8200	149	140	28,4	1090	613	1435	95	45	60	158	163	192	IV
	T 3	70	M	13,3	8620	7810	510	138	307	57,7	1058	846	28426	142	34	100	142	99	151	IV
	T 4	78	F	13,9	7570	5600	1250	287	46	18,9	1013	510	1076	103	40	80	129	123	216	NIV
	T 5	85	F	8,4	8970	8390	260	257	151	251,3	936	755	1176	147	43	80	184	124	410	IV
	T 6	85	M	11,1	11100	10260	460	224	78	4,4	468	567	68582	122	63	70	174	140	249	IV
	T 7	65	M	13,8	4140	5900	1020	214	131	270,2	2831	694	980	179	53	50	358	198	320	IV
	T 8	59	F	11,3	10400	8780	860	533	141	84,2	760	755	1370	108	48	50	216	198	196	IV
Patients treated with tocilizumab	T 9	57	M	12,9	7020	5300	1180	304	106	8,8	1073	584	467	129	39	80	161	123	96	NIV
	T 10	73	M	11,3	6190	5140	490	227	393	84,8	1399	933	1177	127	42	80	159	124	196	NIV
	T 11	58	M	10,1	5510	4850	350	185	223	32,7	700	619	109	83,8	37	60	140	162	141	IV
	T 12	58	M	13	9700	8620	610	298	364	72,3	1369	729	587	69,4	29	100	69	94	242	IV
	T 13	75	M	11,9	6960	6090	590	231	186	161,4	1610	918	26033	182	45	85	214	116	164	IV
	T 14	86	M	10,6	7410	6710	540	79	260	171,9	2740	390	82917	97,4	58	100	97	96	223	IV
	T 15	62	M	13	11000	9450	1140	402	166	3,5	751	651	899	88	56	55	160	173	192	IV
	T 16	58	M	12,2	4780	4380	240	193	104	21,8	3150	552	977	103	34	50	206	196	151	NIV
	T 17	64	M	12,9	11900	10460	710	430	264	80	1518	537	110200	121	44	100	121	98	216	IV
	T 18	45	M	10,9	6730	4580	1420	225	69	9,4	400	531	265	138	33	80	173	123	410	NIV
	T 19	77	M	13,2	8760	8050	340	596	22	94,2	1385	285	940	87,3	46	60	146	162	249	IV
	T 20	72	M	11,2	6610	6050	350	122	150	46,1	779	548	951	116	38	45	258	216	320	IV
Mean		68	–	12	8314	6977	1063	274	173	88	1375	633	16465	118	44	73	172	143	346	–
SD		11	–	1	2457	1967	1716	136	101	87,9	807	162	32282	30	9	18	61	38	136	–
	S 1	75	F	8,4	18800	13520	1690	–	207	–	1766	390	–	96	39	44	217	223	170	no
	S 2	70	M	10	26400	25400	80	280	335	61,1	1131	881	1855	90	67	50	180	192	183	IV
	S 3	74	M	8,9	11800	10960	500	–	171	35,6	2367	423	64595	124	48	65	191	151	280	IV
	S 4	68	M	14,2	8230	7350	530	413	78	17,3	6166	523	294	103	41	45	229	216	167	IV
Patients treated with standard-of-care	S 5	72	F	9,2	7990	5200	2260	265	0	–	599	507	1693	100	40	24	417	410	21	NIV
	S 6	45	F	7,2	20	10	10	10	286	200,1	3523	619	4033	115	29	40	288	249	134	IV
	S 7	80	M	12,1	9050	8222	500	237	110	81,9	2895	563	829	86	36	30	287	320	83	IV
	S 8	60	M	7,7	12400	11420	430	92	107	–	4305	192	11790	113	54	50	226	196	176	no
	S 9	69	M	8,6	5600	4790	470	179	170	143	2844	601	3334	106	59	100	106	96	533	IV
	S 10	65	M	9,7	5330	4650	440	188	36	–	3033	452	674	103	51	50	206	196	190	IV
	S 11	58	F	11,5	11600	10520	650	168	267	223	171	390	1817	130	39	70	186	141	320	NIV
	S 12	77	M	9	4900	4030	540	176	118	23,4	849	–	3479	93	43	40	231	242	138	no
	S 13	73	M	10,4	8230	7490	610	196	103	37,8	5855	659	7349	121	31	60	202	164	268	IV
Mean		68	–	10	10027	8736	670	200	153	91	2731	517	8479	106	44	51	228	215	205	–
SD		9	–	2	6683	6210	619	104	99	78	1894	171	17973	14	11	19	73	81	127	–
p value*		0,957	–	0,0005	0,302	0,244	0,436	0,128	0,576	0,921	0,008	0,104	0,439	0,243	0,0764	0,005	0,026	0,002	0,008	–

* Unpaired two-tailed Student's *t*-test.

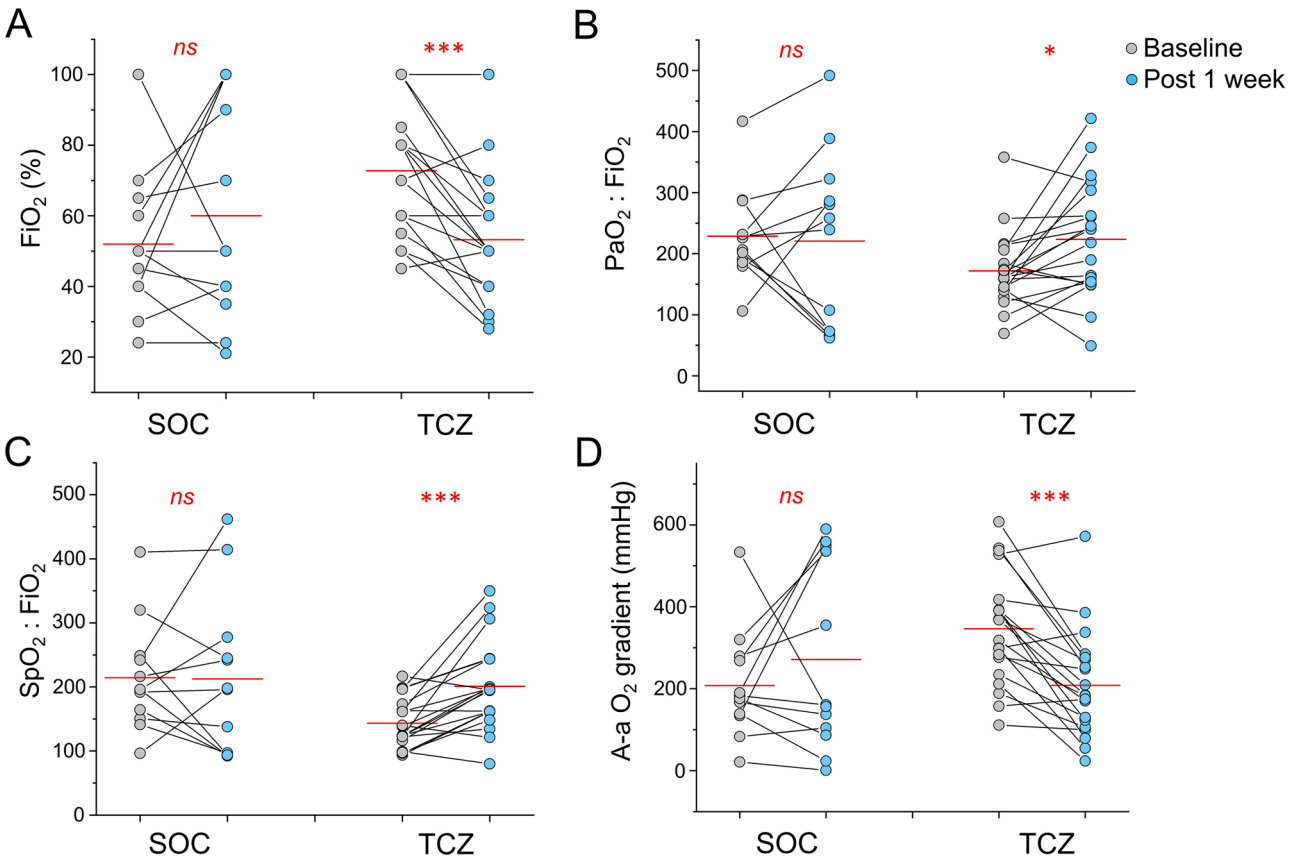

Fig. 1. Clinical course of severe COVID-19 patients at baseline and one week after standard-of-care (n = 13) and tocilizumab treatment (n = 20). (A) Fraction of inspired oxygen (FiO_2), (B) ratio of the partial pressure of arterial oxygen (PaO_2) to FiO_2, (C) ratio of the arterial oxygen saturation (SpO_2) to FiO_2, and (D) the alveolar-arterial (A-a) O_2 gradient at baseline (gray dots) and after one week (light blue dots) in severe COVID-19 patients undergoing standard-of-care (SOC) or receiving tocilizumab (TCZ) in addition to SOC. * $p < 0.05$, ***$p < 0.001$ calculated with paired two-tailed Student's *t*-test; ns not significant.

adverse events to the use of tocilizumab were reported. Among controls, an improvement on oxygen-support class was observed in 6/13 (46 %) patients, including 3 patients receiving mechanical ventilation who were extubated after 18 (±7) days from evaluation. At 28 days from ICU admission, mortality was 21 % (4/19) among patients treated with tocilizumab and 46 % (6/13) among controls. As opposed to controls, patients who received tocilizumab showed a significant reduction of the FiO_2 and A-a O_2 gradient and a significant increase in SpO_2:FiO_2 and PaO_2:FiO_2 after one week from treatment (Fig. 1). Likewise, in this group CRP, ferritin, and fibrinogen significantly decreased at one week (Fig. 2). D-dimer showed only a trend towards reduction (Fig. 2). No significant changes in inflammatory markers were observed in the control group after one week from baseline (Fig. 2).

3.3. Effects of Tocilizumab as assessed on CXR

The total radiographic score and the vascular score were significantly lower at one week after treatment with tocilizumab, while the lung parenchymal score remained unchanged (Fig. 3A). Fig. 3B shows the CXR before and after treatment with tocilizumab in a severe COVID-19 patient. In controls the total score and the lung parenchymal score significantly increased after one week, whereas the vascular score remained stable over time (Fig. 3A). Inter-reader agreement for CXR scoring was excellent for the vascular (ICC: 0.8; 95 %CI: 0.6−0.9) and the lung parenchymal scores (ICC: 0.8; 95 % CI: 0.6 to 0.9), and good for the total radiographic score (ICC: 0.7; 95 % CI: 0.4−0.8).

4. Discussion

COVID-19 is a biphasic disease. The first stage is that of viral replication, but then SARS-CoV-2 infection may lead to an aberrant hyperinflammatory response that overcomes the anti-viral immune response and appears to be critical in the pathogenesis [20]. Patients with severe COVID-19 may need intensive care and mechanical ventilation because of the acute onset of bilateral pulmonary infiltrates, severe hypoxemia, and lung edema in the context of ARDS as well as for the progression towards multi-organ failure [1]. These conditions are characterized by increase of biochemical markers of systemic inflammation and sustained by the release of pro-inflammatory cytokines [21]. These latter include elevated IL-6 levels typically found in patients with severe disease requiring intensive care who also show reduced frequency of granzyme A-expressing NK cells [7]. On this base, tocilizumab has been proposed as immunomodulatory therapy to mitigate the hyperinflammatory response associated with severe or critical COVID-19 [14,22]. In autopsied lungs of deceased COVID-19 patients, severe endothelial injury, diffuse vascular thrombosis with microangiopathy and occlusion of alveolar capillaries, together with angiogenesis are present in addition to diffuse alveolar damage with edema, hemorrhage, and infiltrating perivascular lymphocytes [23,24]. In line with these pathological observations, chest computed tomography demonstrated abnormal perfusion with proximal and distal pulmonary vessel dilation [25,26]. Vessel enlargement could be the result of an altered process of vaso-regulation leading to significant ventilation/perfusion (V/Q) mismatch [26]. The A-a O_2 gradient as measuring the difference between the alveolar and the arterial oxygen concentration increases in conditions of V/Q mismatch, right-to-left shunt or alveolar

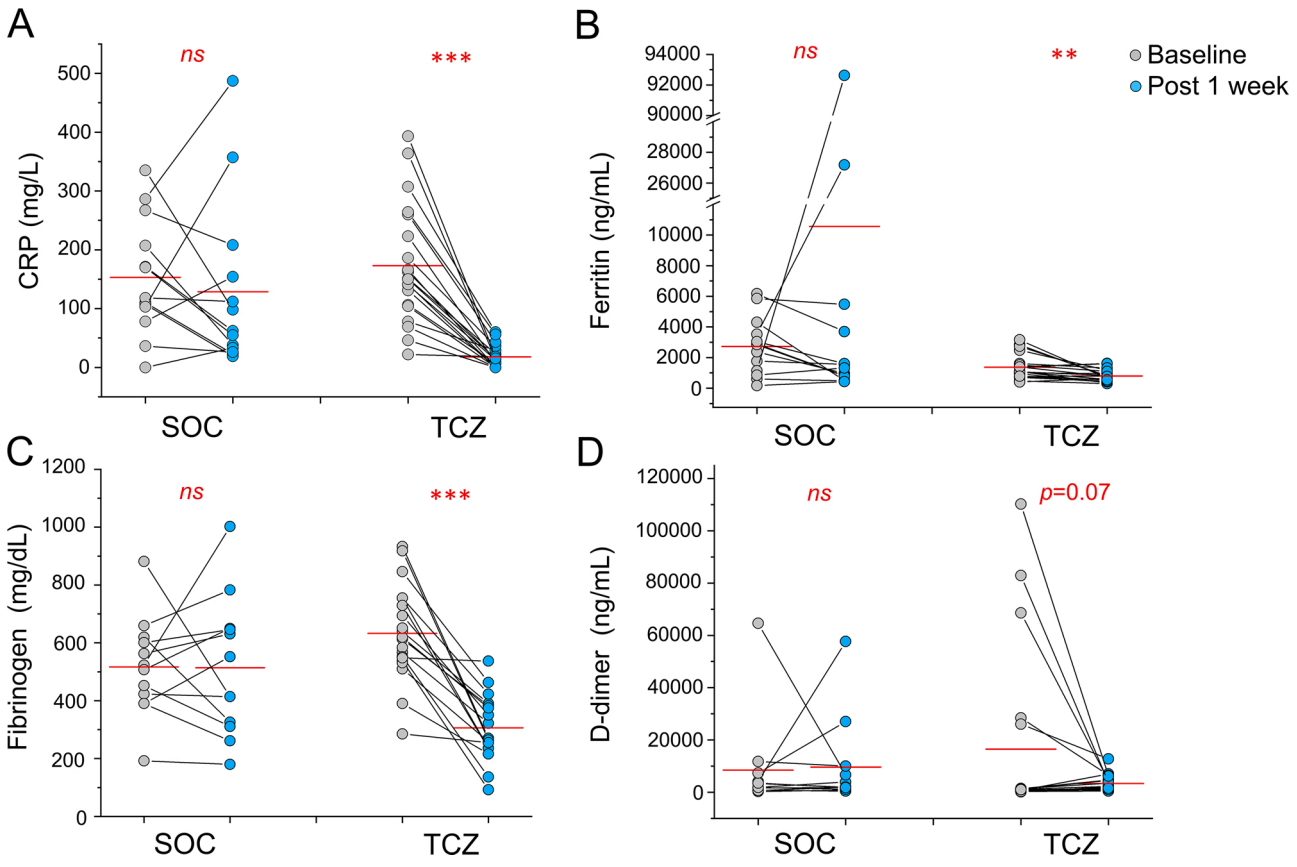

Fig. 2. Changes in inflammatory markers in severe COVID-19 patients at baseline and one week after standard-of-care (n = 13) and tocilizumab treatment (n = 20). (A) C-reactive protein (CRP), (B) ferritin, (C) fibrinogen and (D) D-dimer at baseline (gray dots) and after one week (light blue dots) in severe COVID-19 patients undergoing standard-of-care (SOC) or receiving tocilizumab (TCZ) in addition to SOC. * $p < 0.05$, ** $p < 0.01$, ***$p < 0.001$ calculated with paired two-tailed Student's *t*-test; ns not significant.

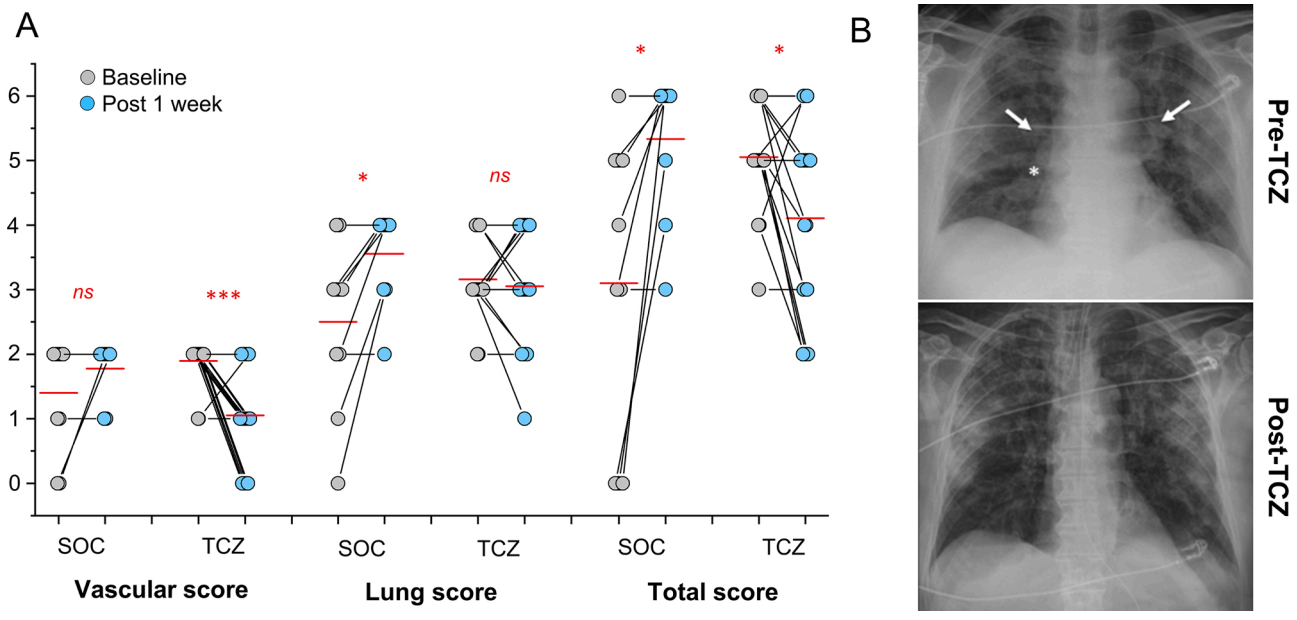

Fig. 3. Radiographic score in severe COVID-19 patients at baseline and one week after standard-of-care (n = 10) and tocilizumab treatment (n = 19). (A) Vascular score, lung parenchymal score and total radiographic score at baseline (gray dots) and after one week after (light blue dots) in severe COVID-19 patients undergoing standard-of-care (SOC) or receiving tocilizumab (TCZ) in addition to SOC. * $p < 0.05$, ***$p < 0.001$ calculated with paired two-tailed Student's *t*-test; ns not significant. (B) Representative chest radiographs of one severe COVID-19 patient prior (upper panel) and one week after (lower panel) treatment with tocilizumab. The vascular radiographic score improves both in terms of density (arrows) and dimension (asterisk) of hilar vessels.

hypoventilation [27–29]. Hypoxemia in COVID-19 patients is usually associated with increased A-a O_2 gradient, meaning either V/Q mismatch or intrapulmonary shunting [30]. In our study on severe COVID-19 patients admitted to the ICU and treated with tocilizumab, one week after treatment a significant decrease of both the A-a O_2 gradient and the vascular radiographic score was observed, without any modification of the lung parenchymal score. IL-6 has a well-known role in mediating endothelial dysfunction as well as in promoting haemostasis and coagulation thus contributing to a prothrombotic state [31, 32]. IL-6 increases megakaryocyte maturation and proliferation resulting in increased platelet production and enhanced platelet activation [33]. Excessive platelet activation has a central role in the immunothrombotic dysregulation that Nicolai et al. described in patients with severe COVID-19 [34]. Vascular injury and inflammation stimulate IL-6 synthesis by endothelial cells that in turn are activated by IL-6 [33]. In addition, IL-6 exerts pro-angiogenic effects that may account for new vessel formation, as described in COVID-19 pneumonia [23,24,35]. Thus, considering the role of IL-6 in promoting coagulation, the block of its receptor may be responsible of the rapid pulmonary vascular improvement in severe COVID-19 patients, while the parallel improvement of A-a O_2 gradient and vascular score on CXR may account for improved V/Q mismatch or intrapulmonary shunting. Viceversa, the lack of the lung parenchymal improvement on CXRs may be due to the fact that SARS-CoV-2 related pneumonia is often a migrant organizing pneumonia that needs at least more than a week to resolve [36].

To date among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel suggests against the routine use of tocilizumab [5,37]. A randomized double-blinded placebo-controlled (RDBPC) trial investigating the efficacy and safety of tocilizumab in patients with severe COVID-19 pneumonia found no difference in clinical status or mortality at day 28 between patients receiving tocilizumab versus placebo in addition to SOC, despite that median time to hospital discharge and duration of ICU stay were 8 days and 5.8 days shorter respectively in the tocilizumab compared to the placebo group [37]. The discrepancies between these results and our data could be due to various reasons. First, at variance with our patients, steroids were used in a large proportion of subjects recruited by Rosas et al. particularly in the placebo group, and this may account for a better outcome. Secondarily, our patients were selected by elevated levels of inflammatory markers, particularly IL-6 and this could have contributed to the results [37,38]. Finally, unlike Rosas et al. a second dose of tocilizumab (12-24 h after the first dose) was administered in our group of patients. On the other hand, our study is a retrospective observational single-center study and the risk of bias in selecting the control group cannot be excluded. More recently, the results of the RDBPC trial by the BACC Bay Tocilizumab Trial Investigators demonstrated that tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients, ruling out an exclusive role of IL-6 in COVID-19 immunopathogenesis at the initial stage [15]. Nonetheless, on severely ill patients, like in our study, tocilizumab might be beneficial at least by dampening the exuberant inflammatory response, occurring at a lower level in the moderately ill cases [38]. In this study we unveiled a potential effect of tocilizumab on vascular pulmonary pathology in COVID-19 that could be responsible of more rapid recovery in patients treated with tocilizumab than those not receiving it, but that do not account for improved survival as shown by recent meta-analysis [39].

In conclusion, we showed that in a subset of patients with severe COVID-19 presenting with systemic hyperinflammation, tocilizumab improved the A-a O_2 gradient and the pulmonary vascular radiologic score, thus promoting early vascular pulmonary recovery. Whether this effect might influence the long-term outcome of severe COVID-19 patients or be a transient early response to anti-IL-6 receptor treatment needs to be investigated.

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Declaration of Competing Interest

The authors declare no competing interest.

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