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

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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 COVID-19 patients. 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.
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$_2$ (SpO$_2$/FiO$_2$), 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 (CXR$s$) 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
| Reference | Range  |
|-----------|--------|
| T 1  | 14–18 |
| T 2  | 14–18 |
| T 3  | 14–18 |
| T 4  | 14–18 |
| T 5  | 14–18 |
| T 6  | 14–18 |
| T 7  | 14–18 |
| T 8  | 14–18 |
| T 9  | 14–18 |
| T 10 | 14–18 |
| T 11 | 14–18 |
| T 12 | 14–18 |
| T 13 | 14–18 |
| T 14 | 14–18 |
| T 15 | 14–18 |
| T 16 | 14–18 |
| T 17 | 14–18 |
| T 18 | 14–18 |
| T 19 | 14–18 |
| T 20 | 14–18 |
| Mean | 14–18 |
| SD  | 14–18 |

**Table 2**

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

| Patient | Age  | Gender | Hemoglobin (g/dL) | White blood cells (x10^3/μL) | Neutrophils (x10^3/μL) | Lymphocytes (x10^3/μL) | Platelets (x10^3/μL) | C-reactive protein (mg/L) | IL-6 (pg/mL) | Ferritin (ng/mL) | Fibrinogen (mg/dL) | D-dimer (ng/mL) | PaO₂ (mmHg) | PaCO₂ (mmHg) | FiO₂ (%) | O₂ gradient (mmHg) | Ventilation (IV = invasive; NIV: non-invasive) |
|---------|------|--------|------------------|-----------------------------|-----------------------|------------------------|---------------------|-------------------------|-------------|----------------|-----------------|----------------|-------------|-------------|--------|------------------|-----------------------------|
| S 1     | 75   | F      | 8,4              | 18800                      | 13520                 | 1690                   | 207                 | 1766                    | 390          | 96             | 44              | 421            | 223         | 170         | 44     | 217              | 223                         |
| S 2     | 70   | M      | 10               | 26400                      | 25400                 | 80                     | 280                 | 335                     | 61           | 113            | 881             | 1855           | 67         | 50         | 65     | 180              | 192                         |
| S 3     | 74   | M      | 8,9              | 11800                      | 10960                 | 500                    | 500                 | 356                     | 2367         | 423            | 64955          | 124            | 48         | 65         | 151    | 151              | 280                         |
| S 4     | 68   | M      | 14,2             | 8220                       | 7350                  | 530                    | 413                 | 78                      | 17,3         | 6166           | 204            | 103           | 45         | 229        | 167    | 189              | 167                         |
| S 5     | 72   | F      | 9,2              | 7990                       | 5200                  | 2260                   | 265                 | 500                     | 59           | 507            | 1693           | 100           | 40         | 24         | 417    | 401              | 21                          |
| S 6     | 45   | F      | 7,2              | 20                         | 10                    | 10                     | 10                  | 286                     | 2001         | 619            | 4033           | 115            | 29         | 40         | 288    | 249              | 134                         |
| S 7     | 80   | M      | 12,1             | 9050                       | 8222                  | 500                    | 237                 | 238                     | 119          | 2893           | 829            | 86            | 36         | 30         | 287    | 320              | 83                          |
| S 8     | 75   | M      | 8,7              | 12400                      | 11420                 | 430                    | 92                   | 107                     | 4305         | 192            | 11790          | 113            | 54         | 50         | 226    | 196              | 176                         |
| S 9     | 69   | M      | 8,6              | 5600                       | 4790                  | 470                    | 179                 | 170                     | 143          | 2844           | 3334           | 106           | 59         | 100        | 106    | 96               | 533                         |
| S 10    | 65   | M      | 9,7              | 5330                       | 4650                  | 440                    | 188                 | 36                      | 3035         | 452            | 674            | 103            | 51         | 50         | 206    | 196              | 190                         |
| S 11    | 58   | F      | 11,5             | 11600                      | 10520                 | 650                    | 168                 | 267                     | 231          | 390            | 1817           | 130            | 39         | 70         | 186    | 141              | 320                         |
| S 12    | 77   | M      | 9                | 4905                       | 4030                  | 540                    | 176                 | 118                     | 234          | 849            | 3479           | 93             | 43         | 40         | 231    | 242              | 138                         |
| S 13    | 73   | M      | 10,4             | 8230                       | 7490                  | 610                    | 196                 | 103                     | 37,8         | 5855           | 7349           | 121            | 31         | 60         | 202    | 164              | 268                         |

**p value** 1: 0.057, 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

*p value* indicates the significance of the difference between groups. Table 2 shows the clinical and laboratory characteristics of severe COVID-19 patients at baseline. The table includes data on hemoglobin, white blood cells, neutrophils, lymphocytes, platelets, CRP, IL-6, ferritin, fibrinogen, D-dimer, PaO₂, PaCO₂, and FiO₂. The patients were treated either with or without tocilizumab, and the results are presented for each patient. The p values indicate the significance of the differences between groups.
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\textsubscript{2} and A-a O\textsubscript{2} gradient and a significant increase in SpO\textsubscript{2}:FiO\textsubscript{2} and
PaO\textsubscript{2}:FiO\textsubscript{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 signifi-
cantly 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 repli-
cation, but then SARS-CoV-2 infection may lead to an aberrant hyper-
inflammatory 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 addi-
tion to diffuse alveolar damage with edema, hemorrhage, and infil-
trating 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\textsubscript{2} gradient as measuring the difference be-
tween the alveolar and the arterial oxygen concentration increases in
conditions of V/Q mismatch, right-to-left shunt or alveolar

![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\textsubscript{2}), (B) ratio of the partial pressure of arterial oxygen (PaO\textsubscript{2}) to FiO\textsubscript{2}, (C) ratio of the arterial oxygen saturation (SpO\textsubscript{2}) to FiO\textsubscript{2}, and (D) the alveolar-arterial (A-a) O\textsubscript{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.](image-url)
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 (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.
hypoxemia in COVID-19 patients is usually associated with increased A-a O₂ 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 O₂ gradient and the pulmonary 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 haemosis 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 immunomodulatory deregulation 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 O₂ 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 migrating 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. Secondly, 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. 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 (RDBPC) trial investigating the efficacy and safety of tocilizumab in patients hospitalized with Covid-19, N. Engl. J. Med. (2020), https://doi.org/10.1056/NEJMoa2028836 [Epub ahead of print].

World Health Organization, Laboratory Testing for Coronavirus Disease (COVID-19) in Suspected Human Cases: Interim Guidance, WHO, 2020. https://apps.who.int/iris/handle/10665/331501.

H.Y.F. Wong, H.Y.S. Lam, A.H. Fong, et al., Frequency and distribution of chest radiographic findings in patients positive for COVID-19, Radiology 296 (2) (2020) E27-E29.

M. Pistoletto, M. Miniati, E.N. Milne, C. Giuntini, The chest roentgenogram in adult respiratory distress syndrome. Comparison with the computed tomography, Chest 100 (1991) 762-769.

M.Z. Tay, C.M. Poh, L. Riazi, P.A. MacRae, L.F.P. Ng, The trinity of COVID-19: immunity, inflammation and intervention, Nat. Rev. Immunol. 20 (6) (2020) 363-374.

V. Castelli, A. Cimini, C. Ferri, Cytokine storm in COVID-19: ‘when you come out of the storm, you won’t be the same person who walked in’, Front. Immunol. 11 (2020) 2132.

J.M. Sanders, M.L. Monogue, T.Z. Jodlowski, J.B. Cutrell, Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review, JAMA 323 (18) (2020) 1824-1836.

M. Ackermann, S.E. Verleden, M. Kuehnel, et al., Pulmonary vascular endotheliitis, thrombosis, and angiogenesis in Covid-19, N. Engl. J. Med. 383 (2020) 120-128.

L. Carsana, A. Sonzogni, A. Naar, et al., Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study, Lancet Infect. Dis. 20 (10) (2020) 1135-1140.

K. Itoh, T. Ichikawa, Y. Watanabe, et al., Use of the alveolar-arterial oxygen gradient in the diagnosis of pulmonary embolism, Am. J. Med. 96 (1) (1994) 57-62.
Immunology Letters 228 (2020) 122–128

S.L. Archer, W.W. Sharp, E.K. Weir, Differentiating COVID-19 pneumonia from acute respiratory distress syndrome and high altitude pulmonary edema: therapeutic implications, Circulation 142 (2) (2020) 101–104.

M.J. Tobin, Basing respiratory management of COVID-19 on physiological principles, Am. J. Respir. Crit. Care Med. 201 (11) (2020) 1319–1320.

T. Kishimoto, IL-6: from its discovery to clinical applications, Int. Immunol. 22 (5) (2010) 347–352.

T. Hou, B.C. Tieu, S. Ray, et al., Roles of IL-6-gp130 signaling in vascular inflammation, Curr. Cardiol. Rev. 4 (3) (2008) 179–192.

R. Kerr, D. Stirling, C.A. Ludlam, Interleukin 6 and haemostasis, Br. J. Haematol. 115 (1) (2001) 3–12.

L. Nicolai, A. Leunig, S. Brambs, et al., Immunothrombotic dysregulation in COVID-19 pneumonia is associated with respiratory failure and coagulopathy, Circulation 142 (12) (2020) 1176–1189.

K. Middleton, J. Jones, Z. Lwin, J.I. Coward, Interleukin-6: an angiogenic target in solid tumours, Crit. Rev. Oncol. Hematol. 89 (1) (2014) 129–139.

F. Pan, T. Ye, P. Sun, et al., Time course of lung changes at chest CT during recovery from coronavirus disease 2019 (COVID-19), Radiology 295 (3) (2020) 715–721.

I. Rosas, N. Bräu, M. Waters, et al., Tocilizumab in hospitalized patients with COVID-19 pneumonia, medRxiv (2020), 2020.08.27.20183442. [preprint].

J.M. Galván-Román, S.C. Rodríguez-García, E. Roy-Vallejo, et al., IL-6 serum levels predict severity and response to Tocilizumab in COVID-19: an observational study, J. Allergy Clin. Immunol. (2020), https://doi.org/10.1016/j.jaci.2020.09.018, S0091-6749(20)31329-4. [Epub ahead of print].

I.M. Tleyjeh, Z. Kashour, M. Damaj, et al., Efficacy and safety of tocilizumab in COVID-19 patients: A living systematic review and meta-analysis, Clin Microbiol Infect. (2020), https://doi.org/10.1016/j.cmi.2020.10.036, In press.

J.H. Beigel, K.M. Tomashek, L.E. Dodd, et al., Remdesivir for the treatment of Covid-19 - Final Report, N. Engl. J. Med. (2020), Oct 8;NEJMoa2007764. [Epub ahead of print]. PMCID: 32445440; PMCID: PMC7266288MC.