Effects of Tocilizumab in COVID-19 patients: a cohort study

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Abstract

Background

Due to the lack of proven therapies, we evaluated the effects of early administration of tocilizumab for COVID-19. By inhibition of the IL-6 receptor, it has been proposed that tocilizumab may help to mitigate the hyperinflammatory response associated with progressive respiratory failure.

Methods

A retrospective, observational study was conducted on hospitalized adults who received intravenous tocilizumab for COVID-19 between March 23, 2020 and April 10, 2020.

Results

Most patients were male (66.7%), Hispanic (63.3%) or Black (23.3%), with a median age of 54 years. Tocilizumab was administered at a median of 8 days (range 1–21) after initial symptoms and 2 days (range 0–12) after hospital admission. On the day of administration, the median PaO_2/FiO_2 was 166 (range 33–523) and 50 patients (83.3%) had ARDS. By day 30, 36 patients (60.0%) demonstrated clinical improvement, 9 (15.0%) died, 33 (55.0%) were discharged alive, and 18 (30.0%) remained hospitalized. Successful extubation occurred in 13 out of 29 patients (44.8%). Infectious complications occurred in 16 patients (26.7%) at a median of 10.5 days. There was an increase in PaO_2/FiO_2 and an initial reduction in CRP that was not sustained beyond day 10.

Conclusions

Majority of patients demonstrated clinical improvement and were successfully discharged from the hospital alive after receiving tocilizumab. Similar to previous studies, infectious complications were not uncommon. A rebound effect with CRP was observed, which may suggest the need for higher or subsequent doses to adequately manage cytokine storm. Based on our findings, we believe that tocilizumab may have a role in the treatment of COVID-19, however randomized controlled studies are urgently needed.

Background

The rapid spread of the novel coronavirus disease led to a pandemic since the first reported case in Wuhan, China in December 2019. The Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2 is responsible for 145,942 deaths in the United State as of July 26, 2020 [1]. In Florida, we have seen an

increase in severe cases, which have accounted for over 5,000 deaths according to the Centers for Disease Control and Prevention [1].

COVID-19 is a rapidly progressing disease with hypoxemic respiratory failure as the primary cause of death [2]. Recent autopsy cases analyzing the etiology of severe lung injury in COVID-19 patients revealed histologic patterns of diffuse alveolar damage and perivascular T-cell infiltration in the presence of intracellular SARS-CoV-2 [3]. This severe lung injury is thought to be due to excessive immune upregulation in response to the virus, similar to what is seen in cytokine release syndrome (CRS) [4, 5]. Among the numerous cytokines that are released, interleukin-6 (IL-6) is thought to play a major role in causing acute respiratory distress syndrome (ARDS) [6, 7].

Tocilizumab, an antagonist of soluble IL-6 receptor, is now being evaluated for the management of COVID-19. Previously approved for the treatment of severe or life-threatening chimeric antigen receptor (CAR) T cell-induced CRS, its ability to down regulate the immune system may have positive implications for COVID-19 related CRS. [8]. Limited observational studies have demonstrated tocilizumab to be associated with improvements in inflammatory markers, clinical response, and survival [9–16]. During an unprecedented time when proven effective therapies remain lacking, we aimed to describe our experience using off-label tocilizumab for COVID-19.

Methods

Setting

We retrospectively analyzed hospitalized patients who received intravenous (IV) tocilizumab for COVID-19 within our large health care system in Miami, Florida between March 23, 2020 and April 10, 2020. Our health system is comprised of three acute care facilities with over 2,500 licensed beds, including 150 adult intensive care unit beds. This study was approved by the University of Miami Institutional Review Board and Jackson Health System Clinical Research Review Committee (CRRC) and a waiver of informed consent was granted.

Tocilizumab process

Tocilizumab was restricted to the Antimicrobial Stewardship Program (ASP) with pre-approval authorization for the management of highly suspected or laboratory-confirmed SARS CoV-2 infection. The approval process occurred in real-time seven days a week and incorporated multidisciplinary discussions between infectious diseases physicians, pulmonary/critical care physicians, hospitalists, and pharmacists. Since February 2020, we created an institution-specific clinical protocol to guide physicians on when to consider COVID-19 investigational agents. For tocilizumab, we recommended use if they met the following criteria: required ≥ 4 liters of nasal cannula to maintain a SpO2 > 93%, show signs of clinical deterioration, and have elevations in at least 2 biomarkers suggestive of cytokine storm **(see Appendix 1 supplemental material)** [17]. We recommended flat dosages of 400 mg (30–100 kg) and 600 mg (> 100 kg) based on the limited evidence and resource allocations during that time [11, 18].

Study participants

Eligible patients were hospitalized adults (age ≥ 18 years) with suspected or laboratory-confirmed SAR-CoV-2 infection and received at least one dose of IV tocilizumab. Any patients with high clinical suspicion and later confirmed as negative by qualitative real-time PCR were excluded. All patients received standard of care treatment for COVID-19 based on our institution-specific protocol, which at the time included hydroxychloroquine. Other therapies such as methylprednisolone, intravenous immunoglobulin, and convalescent plasma were recommended on a case-by-case basis. Universal dexamethasone was added after the completion of the study.

Outcomes and definitions

The electronic medical record was retrospectively reviewed to collect data on day − 1, 0, 1, 2, 3, 4, 5, 7, 10, 14 and 30 relative to tocilizumab administration. We recorded laboratory and respiratory parameters, clinical improvement (defined as ≥ 2-point reduction on the WHO COVID-19 ordinal scale), all-cause mortality, proportion of patients discharged, proportion of patients requiring oxygen support, proportion of patients requiring intensive care unit (ICU) care, proportion of patients successfully extubated (defined as not requiring re-intubation within the same hospitalization), and infectious complications within 30 days of tocilizumab. Infectious complications were defined as having a positive culture from a sterile site and treated by the medical team, we excluded suspected colonization or contamination. Oxygenation was assessed by calculating PaO_2/FiO_2 from the morning arterial blood gas (ABG) and corresponding FiO_2. For infrequent cases when an ABG was not available to measure the PaO_2, we used an estimation formula based on the corresponding SpO2, S/F = 64 + 0.84 * PaO_2/FiO_2 [19]. Acute respiratory distress syndrome (ARDS) was defined according to the Berlin Criteria [20]. Patient severity was assessed using the WHO ordinal scale for clinical improvement [21].

Statistical analysis

Descriptive statistics were used to analyze the data. Continuous variables were expressed as median and range while categorical variables were expressed as counts and percentages.

Results

A total of 63 patients were treated with tocilizumab during our study period. Three patients were excluded as they were empirically treated as “patients under investigation” per the US Centers for Disease Control and Prevention criteria but later confirmed to have a negative qualitative real-time PCR as well as an alternative diagnosis of infection. Patient characteristics are described in Table 1. Most patients were male (66.7%), Hispanic (63.3%) or Black (23.3%), with a median age was 54 years old (range 26–87). The most common comorbidities were hypertension (53.3%), obesity (38.3%), and diabetes (25.0%). The median time between symptom onset and hospitalization was 6 days (range 1–14). A majority of patients received hydroxychloroquine (86.7%). Of the 32 patients that received steroids, 28.1% received >

5 mg/kg/day of methylprednisolone equivalents, 15.6% received 2–5 mg/kg/day of methylprednisolone equivalents, and 56.3% received ≤ 2 mg/kg/day of methylprednisolone equivalents.

Tocilizumab was administered at a median of 8 days (range 1–21) after initial symptoms and 2 days (range 0–12) after hospital admission. Forty-seven patients received a flat dose of 400 mg and 13 patients received 600 mg. Only 3 patients received a second dose of tocilizumab. The median weight for our cohort was 91.5 kg (range 59–182) and the average dose of tocilizumab administered was 4.75 mg/kg.

The clinical presentation of patients on the day of tocilizumab administration are described in Table 2. For disease severity, most patients scored a 4 (40.0%) or 7 (28.3%) based on the WHO COVID-19 ordinal scale. Most patients received oxygen supplementation via nasal cannula (31.7%) or invasive mechanical ventilation (40.0%). The median PaO_2/FiO_2 was 166 (range 33–523) and fifty patients (83.3%) had ARDS. For abnormal laboratory values, we observed neutrophilia, lymphopenia, elevated neutrophil-to-lymphocyte ratio, elevated aspartate aminotransferase (AST), along with increased interleukin-6 (IL-6), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), ferritin, procalcitonin, D-dimer, and troponin.

Outcomes for patients within 30 days from receiving tocilizumab are summarized in Table 3. A total of 36 patients (60.0%) achieved clinical improvement, 9 patients (15.0%) died, 33 patients (55.0%) were discharged from the hospital alive, and 18 patients (30.0%) remained hospitalized at 30 days. Fifty-two patients (86.7%) required ICU care of which twenty-nine (48.3%) were on invasive mechanical ventilation. Thirteen patients (44.8%) were successfully extubated within the 30 days. We identified 29 cultures in 16 patients (26.7%) who developed infectious complications post-tocilizumab. The median time to first infection was 10.5 days (range 2–28). The most common types of infection were respiratory (48.3%) and bacteremia (44.8%) **(see Appendix 3 supplemental material)**. We describe additional clinical measures pertaining to organ complications, modes of ventilation, and SOFA scores in the **Appendix 2 supplemental material**.

The progression of select laboratory and respiratory parameters within 14 days of tocilizumab are displayed in Fig. 1 and Fig. 2. We observed an initial reduction in CRP; however levels began to rise after day 10. The opposite effect was seen with D-dimer. We saw an increase in IL-6 as expected. Additionally, there were improvements in both lymphopenia and oxygenation as assessed by PaO_2/FiO_2. No clear trends were seen for lactate dehydrogenase, procalcitonin, troponin, or neutrophil-to-lymphocyte ratio (NLR).

Discussion

During the rapidly spreading pandemic, physicians were faced with the challenge of recommending investigational agents for the treatment of COVID-19. At our site, we chose to provide tocilizumab in patients with suspected CRS in order to reduce IL-6 levels, which has been associated with ICU admission,

ARDS, and death when in excess [7]. The first dose of tocilizumab was given at a median of two days from hospital admission and a majority of patients (66.7%) received tocilizumab while not on invasive mechanical ventilation. We aimed to provide early administration of tocilizumab in hopes of preventing progressive lung injury that would require invasive mechanical ventilation. Out of the 31 patients who received tocilizumab while not intubated, we observed only 9 patients who later required mechanical ventilation. In the future, we hope to evaluate the effects of tocilizumab on mechanical ventilation and the role of timing with clinical response.

Our patients presented with typical manifestations of COVID-19 and had signs and symptoms of cytokine release syndrome on the day of tocilizumab administration. Similar to previous reports, patients with more severe disease demonstrated transaminitis, along with abnormal blood counts such as neutrophilia, lymphopenia, and elevated NLR ratio [5, 22]. After receiving tocilizumab, we observed reductions in CRP, however unlike other studies, this effect was not sustained [10–12]. We believe our eventual rise in CRP beyond day 10 correlates with tocilizumab's elimination half-life of 11 to 13 days [23]. Sciascia et al. reported a sustained decrease in CRP for 14 days, but a large proportion of their patients received a second dose of tocilizumab (91% vs. 5%) along with higher doses (8 mg/kg). As such, tocilizumab's effect on CRP may be dose-dependent and that re-dosing after 10 days may be warranted. When analyzing other laboratory parameters, there were improvements in both ferritin and absolute lymphocyte count, which is in agreement to previous reports [11, 12]. And although serial IL-6 levels were only available for one third of our patients, we observed an increase shortly after tocilizumab administration; previous studies have explained this effect to be from the temporary accumulation of IL-6 from the inhibition of receptor-mediated clearance [10–12]. Furthermore, we observed an increase in D-dimer that peaked at day seven, and then decreased. Some have correlated D-dimer with the risk of developing pulmonary embolism in COVID but this was not investigated in our study. No clear trends were seen for LDH or procalcitonin, suggesting that these markers are non-specific to COVID-19.

There are mixed results on oxygenation progression after tocilizumab administration in COVID-19 patients. Both Xu et al. and Capra et al. reported improvements in oxygenation in a majority of their patients but Rimland et al. observed no improvement [11, 13, 24]. In our study, we observed an overall increase in PaO_2/FiO_2 within 14 days of tocilizumab. However, it is unclear whether this improvement is due to tocilizumab or reflects the natural course of ARDS. When compared to Sciascia et al., our oxygenation improvement was not as impressive and could be due to having more patients on invasive mechanical ventilation (48.2% vs. 7.9%) [12]. Furthermore, we observed successful extubation in 13 out of 29 patients (44.8%) within 30 days of tocilizumab administration. Rates of extubation for COVID-19 have only been recorded in a small study where 2 out of 3 patients were successfully extubated after tocilizumab [10].

We observed 36 patients (60.0%) achieving at least a 2-point reduction in the WHO COVID-19 ordinal scale and 33 patients (55.0%) discharged alive within the 30 days of receiving tocilizumab. Our discharge rate was higher than the 18% reported by Rimland et al. but lower than the 63% reported by Campochiaro et al. [24, 25]. We observed a 30-day mortality rate of 15%, which is comparable to prior studies ranging

between 13% and 27% [10, 12, 14–16, 24, 25]. So far, only a few studies have compared mortality associated with tocilizumab versus standard of care in COVID-19 patients. Campochiaro et al. found no significant difference in 28-day mortality (15% vs. 22%, p = 0.15) whereas Somers et al. identified a 45% reduction in the risk of death (aHR 0.55, 95% CI 0.33–0.90) in mechanically ventilated patients [14, 25]. Guaraldi et al. also found tocilizumab to be associated with a reduced risk of all-cause mortality after adjusting for age, sex, recruiting center, duration of symptoms, and SOFA score (aHR 0.38, 95% CI 0.17–0.83) [15]. Overall, these findings suggest a possile mortality benefit with tocilizumab, however it is important to recognize that many patients also received steroids, which has been independently associated with improved survival [27].

Historically, tocilizumab has been associated with secondary infections. In the rheumatoid arthritis population, a meta-analysis conducted by Navarro et al. found a 37.5% infection incidence in the tocilizumab group compared to 33.8% in the placebo group [28]. In the chimeric antigen receptor modified (CAR) T population, 133 patients who received tocilizumab had an infection incidence of 23% within 90 days [29]. In our COVID-19 study, we identified a higher proportion of infections within a shorter amount of time: 26.7% within 30 days. Additionally, Kimmig et al. found an even higher incidence of infection of 64.2% but they had a longer follow-up time at 8 weeks and a broader definition for infection, which also captured highly suspected infections [26]. Another study by Somers et al. found a two-fold higher incidence of infections in patients who received tocilizumab at 28 days (54% vs. 26%, p < 0.001) but more patients in the tocilizumab arm received steroids [14]. To date, the only study who excluded steroid use reported a 13% infection incidence at 28 days [25]. Taken altogether, tocilizumab may increase the risk of infections, however better designed studies taking into account confounding factors are needed.

Our study had several limitations. First, it was a retrospective study with a small sample size. Second, the flat doses of 400 and 600 mg for tocilizumab could have resulted in lower than optimal doses if extrapolating from FDA-approved (8 mg/kg) doses for CAR T cell-induced CRS [8]. Third, many patients received concomitant therapies that could impact clinical outcomes, such as IVIG and steroids. Fourth, many of our infections were diagnosed based on tracheal aspirates because bronchoscopies were infrequent at the time. The quality of the culture, in addition to the critical nature of the patient made diagnosis of pneumonia particularly challenging. Fifth, the study end point of 30 days precluded us from identifying long-term infectious complications post-tocilizumab. Lastly, this study was descriptive and not aimed to investigate predisposing risk factors for infectious complications or to determine tocilizumab efficacy.

Conclusion

In this study, we demonstrated the effects of off-label tocilizumab in 60 patients with COVID-19. We primarily used tocilizumab in patients presenting with signs of cytokine release syndrome and acute respiratory distress syndrome. Many patients achieved clinical improvement and were eventually discharged from the hospital. Interestingly, we observed a rebound effect with C-reactive protein suggesting the need for higher or subsequent doses. Similar to prior studies, infectious complications

after tocilizumab were not uncommon. Our results highlight the need for future studies investigating the safety, efficacy, and optimal timing of tocilizumab in COVID-19 patients. There are several ongoing clinical trials evaluating tocilizumab in patients with COVID-19: COVACTA (NCT04320615), CORON-ACT (NCT04335071), CORIMUNO-19 (NCT04331808), EMPACTA (NCT04372186) [30–33].

Abbreviations

COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; CRS: Cytokine release syndrome; IL-6: Interleukin-6; ARDS: Acute respiratory distress syndrome; CAR: Chimeric antigen receptor; IV: intravenous; CRRC: Clinical Research Review Committee; ASP: Antimicrrobial Stewardship program; SpO2: Saturation of peripheral oxygen; PCR: polymerase chain reaction; WHO: World Health Organization; ICU: Intensive care unit; PaO_2/FiO_2: Partial pressure of oxygen/fraction of inspired oxygen; ABG: Arterial blood gas; AST: Aspartate aminotransferase; CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase; NLR: Neutrophil-to-lumphocyte ratio

Declarations

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the University of Miami Institutional Review Board and Jackson Health System Clinical Research Review Committee (CRRC) and a waiver of informed consent was granted.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CA: Conceptualization, Methodology, Formal analysis, Data curation, Writing – Original Draft, Writing- Review & Editing, Visualization. KJD: Conceptualization, Methodology, Data curation, Writing – Original Draft, Writing- Review & Editing. ADV: Conceptualization, Methodology, Data curation, Writing – Original Draft, Writing- Review & Editing. MM: Conceptualization, Methodology, Data curation, Writing – Original Draft, Writing- Review & Editing. GH: Conceptualization, Methodology, Formal analysis, Writing- Review & Editing. YH: Conceptualization, Methodology, Writing- Review & Editing. JGZ: Conceptualization, Methodology, Writing- Review & Editing. VS: Data curation, Writing- Review & Editing. RB: Data curation, Writing- Review & Editing. SRM: Conceptualization, Investigation, Writing- Review & Editing. DC: Investigation. AFB: Investigation. LH: Investigation. JK: Investigation. AL: Investigation. AHR: Investigation. YR: Investigation. Susanne Doblecki: Writing- Review & Editing. DDLZ: Writing- Review & Editing. LMA: Conceptualization, Methodology, Writing- Review & Editing, Supervision.

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Tables

Table 1. Patient characteristics (N=60)

Age, median (range), years	54 (26-87)
Male, n (%)	40 (66.7)
Ethnicity	
Hispanic	38 (63.3)
Black	14 (23.3)
White	7 (11.7)
Asian	1 (1.7)
Comorbidities	
Obese (BMI >30)	35 (58.3)
Hypertension	32 (53.3)
Diabetes	15 (25.0)
Congestive heart failure	4 (6.7)
Coronary artery disease	1 (1.7)
Asthma	4 (6.7)
COPD	1 (1.7)
Obstructive sleep apnea	2 (3.3)
HIV	1 (1.7)
Transplant	1 (1.7)
Concomitant therapies	
Hydroxychloroquine	52 (86.7)
Corticosteroids	32 (53.3)
Inhaled nitric oxide	5 (8.3)
Intravenous immunoglobulin (IVIG)	4 (6.6)
Tacrolimus	2 (3.3)
Convalescent plasma	2 (3.3)
Plasmapheresis	1 (1.7)
Time from symptom onset to receiving tocilizumab, median (range), days	8 (1-21)
Time from hospital admission to receiving tocilizumab, median (range), days	2 (0-12)

Table 2. Clinical presentation on day of tocilizumab administration

Disease severity	n (%)		
WHO Ordinal Scale 8 (deceased) 7 (invasive mechanical ventilation + organ support) 6 (invasive mechanical ventilation) 5 (non-invasive ventilation or high-flow oxygen) 4 (oxygen by mask or nasal prongs) 3 (hospitalized without oxygen therapy) 1-2 (not hospitalized)	 0 (0.0) 17 (28.3) 9 (15.0) 9(15.0) 24 (40.0) 1 (1.7) 0 (0.0)		
Temperature ≥38°C	28 (46.7)		
Heart rate ≥100 beats/min	34 (56.7)		
Respiratory rate ≥30 breaths/min	36 (60.0)		
Abnormal chest imaging	59 (98.3)		
Vasopressor use	18 (30.0)		
Renal replacement therapy	4 (6.7)		
Use of paralytics	9 (15.0)		
Proned	5 (8.3)		
Room air Nasal cannula Venti-mask Nonrebreather High-flow nasal cannula Non-Invasive Positive Pressure Ventilation Invasive mechanical ventilation	1 (1.7) 18 (30.0) 3 (5.0) 7 (11.7) 6 (10.0) 2 (3.3) 23 (38.3)		
ARDS Mild (201<PaO_2/FiO_2≤300) Moderate (101<PaO_2/FiO_2≤200) Severe (PaO_2/FiO_2 ≤100)	 13 (21.7) 21 (35.0) 16 (26.7)		
PaO_2/FiO_2, median (range)	166 (33-523)		
SOFA score, median (range)	3 (0-11)		
ICU care	45 (75.0)		
Laboratory parameters	Median (range)	Reference values	Number of patients with available data
White blood cell count, $x10^9$/L	9 (2.7-29.6)	4.0-10.5	51
Absolute neutrophil count, $x10^9$/L	**6.85 (1.8-26.8)**	2.0-6.0	49
Absolute lymphocyte count, $x10^9$/L	**0.8 (0.2-2.6)**	1.1-2.7	48
Neutrophil-to-lymphocyte ratio (NLR)	**7.56 (2.25-62)**	0.88-4[a]	48
Hemoglobin, g/dL	12.7 (9-15.9)	11.1-14.6	51
RDW-CV, %	14 (11.6-18.3)	11-15	51
Platelets, $x10^9$/L	240 (101-513)	140-400	49
Sodium, mmol/L	135 (123-148)	135-145	53
CO_2, mmol/L	24 (11-36)	22-30	53
AST, U/L	**70.5 (25-711)**	15-46	46
ALT, U/L	51.5 (6-242)	9-52	46
Total bilirubin	0.65 (0.2-2.4)	0.2-1.3	48
Creatinine, mg/dL	0.88 (0.4-4.58)	0.66-1.25	53
Interleukin-6, pg/mL	**133.9 (8.73-2160.69)**	none	26
C-reactive protein, mg/dL	**24.2 (3.2-45)**	0.0-0.9	49

Erythrocyte sedimentation rate, mm/hr	**50 (18-102)**	0-10	24
Lactate dehydrogenase, U/L	**1333 (477-5089)**	313-618	47
Ferritin, ng/mL	**1412.5 (45-29304)**	30-400	46
Procalcitonin, ng/mL	**0.40 (0.027-16.34)**	0-0.08	33
D-dimer, mcg/mL	**1.3 (0.4->20)**	0-0.49	33
Troponin, ng/mL	**0.104 (<0.012-7.21)**	0-0.034	15

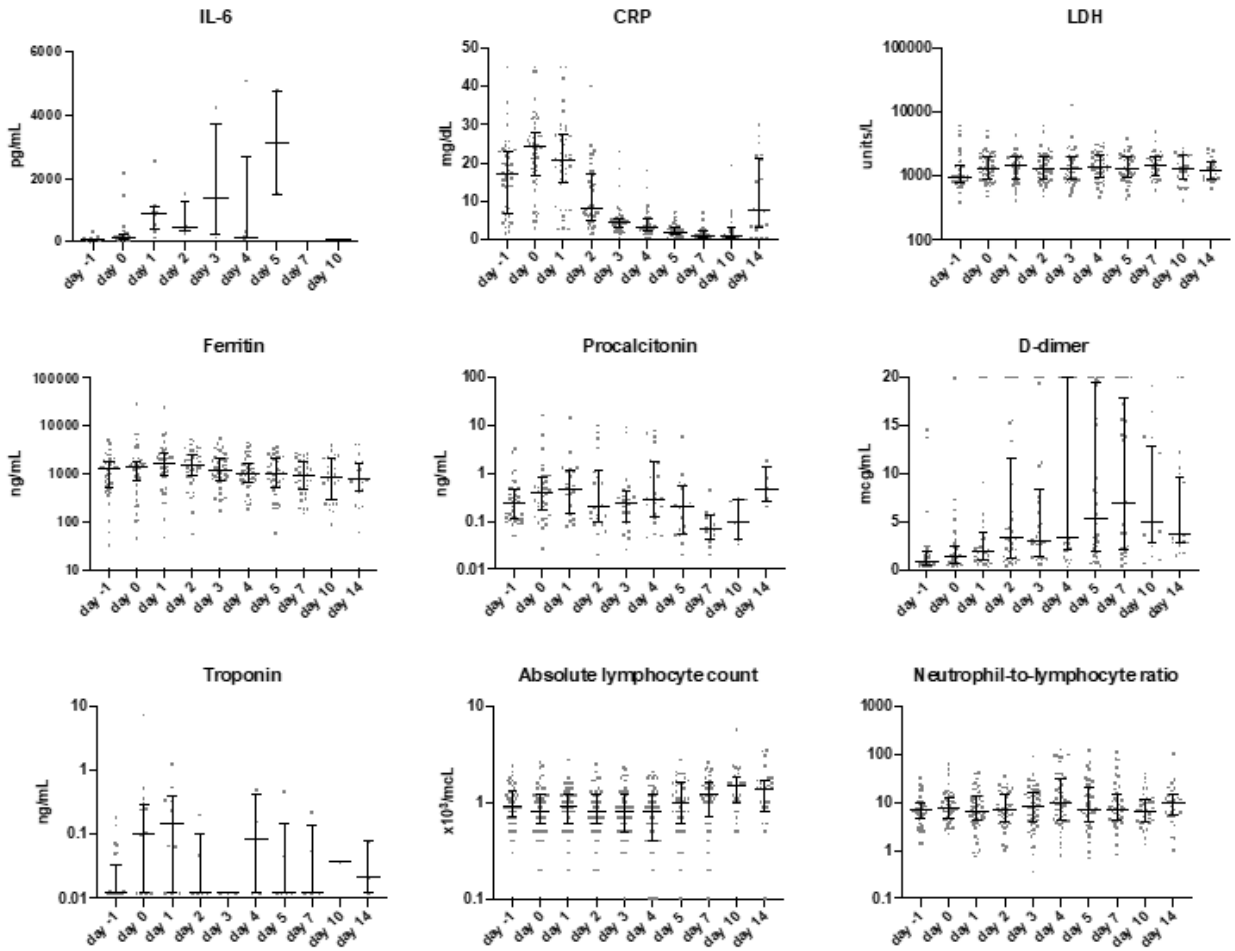
Note: abnormal medians highlighted in bold

[a]Luo H, et al. *Clin Lab* 2019;65(3).

Table 3. Outcomes within 30 days of receiving tocilizumab

Clinical improvement	36/60 (60.0)
Mortality	9/60 (15.0)
Time to death from receiving tocilizumab, median (range), days	6 (1-14)
Discharged alive	33/60 (55.0)
Hospital length of stay for those discharged, median (range), days	15 (0-32)
Required ICU care	52/60 (86.7)
Remained admitted to ICU at day 30 Step down to floor at day 30 Discharged from hospital alive by day 30 Died by day 30	13/52 (25.0) 5/52 (9.6) 25/52 (48.1) 9/52 (17.3)
Required invasive mechanical ventilation	29/60 (48.3)
Successful extubation, n (%) Duration of mechanical ventilation for those extubated, median (range), days	13/29 (44.8) 15 (6-35)
Infectious complications	16/60 (26.7)
Time to first infection, median (range), days Cultures drawn while in ICU, n (%) Cultures drawn while intubated, n (%) Receiving concominant steroids, n (%) Type of suspected infection, n (%) Respiratory Bacteremia Fungemia Urinary tract infection	10.5 (2-28) 26/29 (89.7) 25/29 (86.2) 10/16 (62.5) 14/29 (48.3) 13/29 (44.8) 1/29 (3.4) 1/29 (3.4)

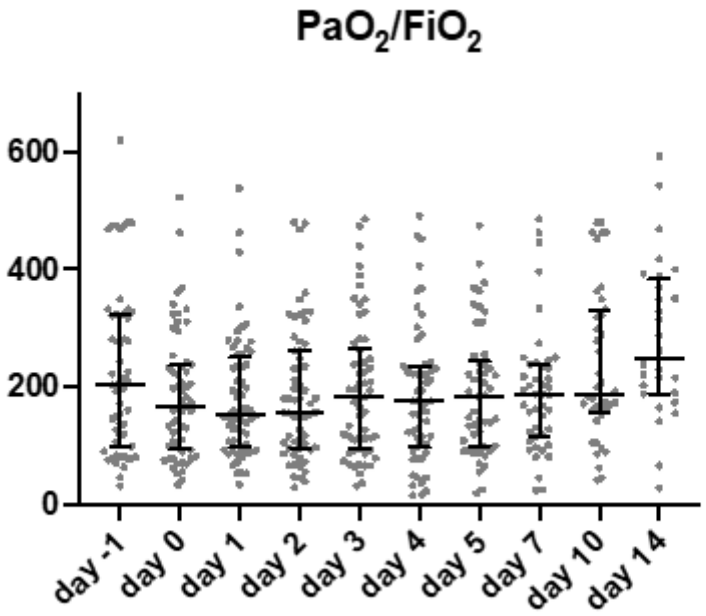
Figures



Median (n)	IL-6	CRP	LDH	Ferritin	Procalcitonin	D-dimer	Troponin	ALC	NLR
Day -1	63.1 (30)	17.3 (46)	968.0 (43)	1253.5 (40)	0.24 (37)	0.80 (38)	<0.012 (26)	0.9 (53)	6.9 (52)
Day 5	3140.0 (2)	2.1 (36)	1287.0 (39)	1017.5 (37)	0.20 (18)	5.3 (32)	<0.012 (6)	1.0 (46)	7.2 (45)
Day 14	--	7.7 (21)	1198.5 (22)	769.5 (20)	0.47 (6)	3.7 (21)	0.021 (3)	1.4 (27)	9.8 (27)

Figure 1

Progression of laboratory markers within 14 days of tocilizumab (results shown as median and IQR using Prism GraphPad version 8). Troponin: lower limit of detection <0.012 ng/ml; D-dimer: upper limit of detection >20 mcg/ml



Median (n)	PaO_2/FiO_2
Day -1	202.8 (55)
Day 5	184.3 (50)
Day 14	249.6 (28)

Figure 2

Progression of oxygenation within 14 days of tocilizumab (results shown as median and IQR using Prism GraphPad version 8).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.docx