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RESEARCH ARTICLE

Laboratory parameters predicting mortality of adult in-patients with COVID-19 associated cytokine release syndrome treated with high-dose tocilizumab

BOTOND LAKATOS[1,2†*], BALINT GERGELY SZABO[1,2,3†], ILONA BOBEK[1], LASZLO GOPCSA[1], GABRIELLA BEKO[1], NOEMI KISS-DALA[1,3], BORISZ PETRIK[4], ZSOFIA GASPAR[4], BALAZS FERENC FARKAS[4], JANOS SINKO[1], PETER REMENYI[1], JANOS SZLAVIK[1] and ISTVAN VALYI-NAGY[1]

[1] National Institute of Hematology and Infectious Diseases, Szent Laszlo Campus, South Pest Central Hospital, Albert Florian ut 5-7., H-1097, Budapest, Hungary

[2] Department of Internal Medicine and Haematology, Department of Infectious Diseases, Semmelweis University, Albert Florian ut 5-7., H-1097, Budapest, Hungary

[3] School of PhD Studies, Semmelweis University, Ulloi ut 26., H-1085, Budapest, Hungary

[4] Faculty of Medicine, Semmelweis University, Ulloi ut 26., H-1085, Budapest, Hungary

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ABSTRACT

Large randomized clinical trials in severe Coronavirus Disease 2019 (COVID-19) patients have proven efficacy of intravenous tocilizumab. Our aim was to describe the laboratory parameters predicting in-hospital mortality of patients with tocilizumab administration in COVID-19 associated cytokine release syndrome (CRS).

We evaluated high-dose (8 mg/kg) intravenous tocilizumab administration in severe and critically ill COVID-19 adult patients fulfilling predefined strict CRS criteria. A single-centre, prospective, observational cohort study was carried out among consecutive adult (≥18 years of age) in-patients with COVID-19 between April 1 and December 31, 2020. The primary endpoint was 28-day all-cause mortality. The changes in laboratory parameters from baseline on day 7 and 14 after administration of tocilizumab were analysed.

In total, 1801 patients were admitted to our centre during the study period. One hundred and six patients received tocilizumab, and among them 62 (58.5%) required intensive care unit admittance while 25 (23.6%) deceased. At day 7 after tocilizumab administration, inflammatory markers (CRP, IL-6, ferritin) and lactate dehydrogenase (LDH) values were significantly lower among survivors. Subsequently, at day 14, differences of IL-6 and LDH levels has become more pronounced between subgroups. Restoration of absolute lymphocyte count (ALC) by day 7 and 14 was insufficient among patients who died.

In our cohort, administration of high-dose tocilizumab for COVID-19 patients with CRS demonstrated clinical and sustained biochemical parameter improvement in 76.4%. In this patient population high and increasing LDH, IL-6, and low ALC levels had a predictive role for mortality.

KEYWORDS

SARS-CoV-2, COVID-19, tocilizumab, interleukin-6, cytokine release syndrome

INTRODUCTION

Up to present day, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused around 150 million infections and more than 3 million deaths globally [1].

†The authors contributed equally to the work (*in equo loco*).

*Corresponding author.
E-mail: botond.lakatos@dpckorhaz.hu

Interleukin-6 (IL-6) is released in response to SARS-CoV-2 infection, stimulating inflammatory pathways as part of the acute phase response.

Tocilizumab is a monoclonal antibody acting as an inhibitor of the soluble and membrane-associated IL-6 receptors. To date, apart from systemic corticosteroids, tocilizumab remains the only medication that has been shown to improve survival in severe and critically ill COVID-19 patients, probably due to its anti-inflammatory effects [2]. Earlier randomised controlled trials have predominantly shown no benefit from IL-6 antagonists, as most of the patients included in these studies were not critically ill or the drugs were administered in a relatively early stages of the disease, generating heterogeneity [3–8]. In contrast, Report of the Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia (REMAP-CAP) trial confirmed that administering tocilizumab for critically ill COVID-19 patients requiring organ support for less than 24 h resulted in improved outcomes including better survival [9]. More recently, the RECOVERY platform trial reported that a mortality benefit was seen in hypoxemic patients with hyperinflammation receiving tocilizumab and systemic corticosteroids. This observation supports the idea that a benefit of IL-6 blockade with tocilizumab may be demonstrated in the presence of COVID-19 associated cytokine release syndrome (CRS) [10, 11].

To date, multiple laboratory parameters associated with poor outcome in COVID-19 have recently been described, although these parameters are inconsistent across studies [12–14]. Administration of tocilizumab influences clinical outcome in COVID-19 associated CRS but data is scarce on dynamics of laboratory parameters and their impact on survival. Small case series report that high IL-6 level after 24–48 h after tocilizumab administration is linked with worse outcome, in spite of the fact that SARS-CoV-2 viral specific antibody response does not seem to be impaired by IL-6 antagonism [12, 13]. Elevated levels of lactate dehydrogenase and lymphopenia have also been linked with higher mortality in COVID-19 patients, but laboratory changes and their impact on survival after tocilizumab administration are not well understood [14].

At our national COVID-19 centre, a standardized clinical protocol has been in practice since the beginning of the COVID-19 pandemic based on strictly revised CRS criteria to facilitate clinical indication of tocilizumab use on case-by-case evaluation. Our aim was to describe laboratory changes possibly predicting the outcome of high-dose tocilizumab therapy among adult patients with COVID-19 associated CRS.

METHODS

Study design and setting

A single-centre, prospective, interventional study was carried out among a cohort of consecutive adult (≥18 years of age at diagnosis) in-patients with COVID-19 and CRS, hospitalized at South Pest Central Hospital, National Institute of Hematology and Infectious Diseases (Budapest, Hungary) between 1 April and 31 December, 2020. Our centre is a tertiary referral institution and the main national COVID-19 hospital with more than 350 dedicated beds. The study was in accordance with the Helsinki Declaration and national ethical standards. The study protocol has been approved by the Institutional Review Board. As cytokine release syndrome is a potentially fatal complication of COVID-19, a randomized trial with a placebo arm was ethically not feasible.

An *off-label* emergency use of tocilizumab among other drugs in COVID-19 has been approved by the National Institute of Pharmacy and Nutrition of Hungary and the Institutional Review Board.

Patient eligibility and participant selection

All COVID-19 patients admitted to our centre during the study period were eligible for inclusion. Patients with an established COVID-19 diagnosis were prospectively screened for inclusion by daily case assessments using hospital electronic records. Participant selection has been performed by using *a priori* inclusion/exclusion criteria. Inclusion criteria were: 1) polymerase chain reaction (PCR) -based confirmation of SARS-CoV-2 infection from a respiratory specimen, in a clinically compatible case with cytokine release syndrome (defined below); 2) received standard-of-care (SOC, defined below) for more than 48 h after diagnosis; 3) received a minimum of 1 dose of tocilizumab (8 mg/kg intravenously). Exclusion criteria were: 1) the patient died within ≤48 h after diagnosis; 2) received SOC for less than 48 h after diagnosis; 3) patient data were not fully accessible through the hospital electronic database.

Data collection

Data were collected manually from hospital electronic records and written charts, and anonymously transferred to a standardized case report form by study physicians. Collected data were: 1) age and gender; 2) comorbidities; 3) need for intensive care unit (ICU) admission during hospitalization; 4) length of stay (LOS) and ICU LOS; 4) clinical and laboratory parameters at baseline and on days 7 and 14 after tocilizumab administration; 5) radiological parameters at baseline; 6) microbiological parameters of concomittant infections during follow-up; 7) antimicrobial and other immunomodulatory therapies and supportive care; 8) patient outcomes at the end of the follow-up period. All baseline characteristics were recorded on the day of COVID-19 diagnosis.

COVID-19 diagnosis, treatment, and patient follow-up

For COVID-19 case definition and severity, we adhered to the *European Centre for Disease Prevention and Control* (ECDC) and *World Health Organization* (WHO) criteria, respectively [15, 16]. Cytokine release syndrome (CRS) was diagnosed based on a compatible case presentation (persistent

fever for at least 72 h with or without deteriorating hypoxaemia) and simultaneous elevation of 3 out of 5 inflammatory markers: a serum ferritin level of ≥600 μg/L, a serum IL-6 level ≥3x and/or an LDH level ≥1x above the upper limit of normal (12.6 pg/mL and 480 IU/L at our centre, respectively), C-reactive protein level >100 mg/L, or an HScore of ≥250, as proposed by *Fardet* et al. [17]. Fever is defined as an axillary body temperature of ≥37.8 °C, measured with a digital thermometer. Hypoxaemia is defined as a resting O_2 saturation of ≤93% on room air (measured by finger pulse-oxymetry), or an arterial partial O_2 tension (PaO_2)/inspirational O_2 fraction (FiO_2) of ≤300 Hgmm (measured by arterial blood gas analysis), with or without dyspnea or tachypnea. Deterioration of hypoxaemia is defined as a novel increase of inspirational O_2 demand, necessitating a support through low or high flow nasal cannula, Venturi or noninvasive masking, or invasive mechanical ventilation.

Samples for respiratory SARS-CoV-2 PCR were taken by skilled nurses using nasopharyngeal (spontaneously breathing patients) or blind bronchoalveolar lavage (BAL) sampling (intubated patients). Disease onset was defined as the first day of symptom appearance attributable to COVID-19, as reported by the patient, or day of first PCR positivity if symptom onset could not be clarified. The day of first SARS-CoV-2 PCR positivity has been marked as COVID-19 diagnosis day. Testing of respiratory samples to confirm SARS-CoV-2 PCR negativity was initiated after the day of defervescence and clinical stability and were collected every other day. SARS-CoV-2 PCR negativity was confirmed on the day when two consecutive samples returned with negative results.

SOC included intravenous remdesivir (200 mg on the first day, and 100 mg thereafter, for a minimum of 5 days) with intravenous or oral dexamethasone (6 mg daily, for a minimum of 5 days), and on-demand oxygen therapy or respiratory support, intravenous fluid replenishment, antipyretics and bronchodilator drugs. If CRS was diagnosed at admission or ≤72 h, 2 doses of intravenous tocilizumab (8 mg/kg each) has been administered within 24 h. Empirical antibiotics were initiated as advocated by the *Infectious Diseases Society of America* (IDSA) community-acquired pneumonia guideline [18].

In-hospital follow-up consisted of daily visits of attending physicians. Patient care was facilitated by standardized written protocols and checklists, regularly updated since the start of the first wave based on growing scientific evidence. Physical examination, laboratory studies and arterial blood gas analyses were performed daily. Imaging studies (chest CT scans) were ordered on COVID-19 diagnosis day and repeated if disease progression or clinical instability was observed. Daily follow-up continued until the patients' death or hospital discharge. A post-discharge follow-up has not been routinely carried out.

Study outcomes

The primary outcome measure was 28-day all-cause mortality, defined as death within 28 days from COVID-19 diagnosis during hospital stay. Secondary endpoints were: 1) need for ICU admittance; 2) need for invasive mechanical ventilation; 3) rate and time to respiratory SARS-CoV-2 PCR clearance (during hospital stay or at discharge); 3) rate of any in-hospital infectious complication.

Statistical methods

Continuous variables were expressed as median±interquartile range (IQR), normality was tested by the *Shapiro–Wilk* test. Categorical variables were expressed as absolute numbers (n) with relative percentages (%). Statistical comparisons were done with *Mann–Whitney* U-test or *Fisher*'s exact test.

For all statistical tests, a 2-tailed *P*-value of <0.05 determined statistical significance. Data collection was carried out with Microsoft Office Excel 2016, tests were calculated using IBM SPSS Statistics 23. For reporting, we adhere to the *Strengthening the Reporting of Observational studies in Epidemiology* (STROBE) Statement.

RESULTS

During the study period, 106 adult COVID-19 in-patients with CRS receiving tocilizumab were included in the final cohort from 1801 patients screened (5.8%). Demographic and clinical characteristics at baseline are shown in Table 1. Median age of included patients was 64 ± 18 (27–85) years. Patients were mostly males (69.8%), prevalent comorbidities were diabetes mellitus (24.5%), chronic heart disease (23.6%) and chronic pulmonary disease (16.0%). Patients who passed more frequently had chronic heart and renal diseases (44% vs. 17.3%, $P < 0.01$ and 8.6% vs. 28%, $P = 0.01$, respectively), while other underlying conditions did not differ statistically between survivors and non-survivors. Baseline clinical characteristics, namely presence of fever and markers of oxygenation were balanced between the subgroups.

Changes of COVID-19-specific laboratory parameters are shown in Fig. 1. At baseline, serum CRP ($P = 0.49$) and D-dimer levels ($P = 0.34$) did not differ statistically between the subgroups. At day 7, inflammatory markers (CRP 5 ± 7 vs. 17 ± 20 mg/L, $P < 0.01$; IL-6 189.0 ± 397.0 vs. 1,782.0 ± 5,683.3 pg/mL, $P = 0.01$; ferritin 715 ± 906 vs. 2,012 ± 2,176 μg/L, $P < 0.01$) and LDH values (606 ± 257 vs. 1,051 ± 604 IU/L, $P < 0.01$) were significantly lower among survivors, while at day 14, differences of IL-6 (86.0 ± 161.5 vs. 370.0 ± 8,739.3 pg/mL, $P < 0.01$) and LDH (483 ± 241 vs. 1,393 ± 1,276 IU/L, $P < 0.01$) levels became more pronounced between the subgroups. The absolute lymphocyte count by day 14 was also lower among patients who died (1.77 ± 0.88 vs. 1.04 ± 1.17 × 10^9/L, $P = 0.1$). Time from symptom onset, from respiratory PCR positivity and from admission to tocilizumab administration did not differ between the subgroups.

Outcome characteristics are shown in Table 2. In total, 28-day all-cause mortality was 23.6%. Sixty-two patients (58.5%) of the cohort needed ICU admittance, most of them

Table 1. Demographic and clinical characteristics of adult COVID-19 in-patients receiving high-dose tocilizumab, grouped by 28-day mortality

Parameter	Total (n = 106)	Survived (n = 81)	Died (n = 25)	*P value*
Age (years, median ± IQR, min–max)	64 ± 18 (27–85)	60 ± 16 (27–80)	69 ± 12 (38–85)	0.19
Male gender (n, %)	74 (69.8)	56 (69.1)	18 (72.0)	0.84
Comorbidities (n, %):				
–Chronic heart disease	25 (23.6)	14 (17.3)	11 (44.0)	**0.01**
–Chronic vascular disease	15 (14.2)	11 (13.6)	4 (16.0)	0.76
–Chronic pulmonary disease	17 (16.0)	10 (12.3)	7 (28.0)	0.06
–Chronic renal disease	14 (13.2)	7 (8.6)	7 (28.0)	**0.01**
–Chronic hepatic disease	3 (2.8)	3 (3.7)	0	0.32
–Diabetes mellitus	26 (24.5)	17 (21.0)	9 (36.0)	0.12
–Active oncological malignancy	11 (10.4)	10 (12.3)	1 (4.0)	0.23
–Active hematological malignancy	7 (6.6)	5 (6.2)	2 (8.0)	0.74
–Systemic autoimmune disease	2 (1.9)	2 (2.5)	0	0.43
–Chronic systemic corticosteroid treatment	6 (5.7)	4 (4.9)	2 (8.0)	0.56
–Chronic systemic immunosuppressive treatment	1 (0.9)	1 (1.2)	0	0.57
–Smoking	12 (11.3)	10 (12.3)	2 (8.0)	0.55
Clinical characteristics:				
–Fever (n, %)	99 (93.4)	76 (93.8)	23 (92.0)	0.39
–Horowitz index (mmHg, median ± IQR, min–max)	180 ± 99 (104–397)	190 ± 102 (104–390)	166 ± 50 (128–397)	0.08
–Need for oxygen supportation (n, %)	103 (97.2)	79 (97.5)	24 (96.0)	0.55
Laboratory characteristics (median ± IQR, min–max):				
–Blood absolute neutrophil count ($\times 10^9$/L)	5.9 ± 4.6 (1.4–34.2)	5.8 ± 4.2 (1.4–18.9)	6.8 ± 4.6 (1.6–34.2)	0.34
–Blood absolute lymphocyte count ($\times 10^9$/L)	0.9 ± 0.6 (0.3–9.3)	0.9 ± 0.5 (0.3–9.3)	0.6 ± 0.6 (0.3–1.7)	**0.01**
–Blood platelet count ($\times 10^9$/L)	214 ± 120 (13–510)	218 ± 113 (86–510)	182 ± 157 (13–382)	0.06
–Serum C-reactive protein (mg/L)	142 ± 156 (7–355)	130 ± 167 (7–355)	157 ± 96 (34–329)	0.49
–Plasma Interleukin-6 (pg/mL)	68.3 ± 120.6 (3.4–8,962.6)	50.2 ± 97.1 (3.4–5,041.9)	119.0 ± 454.5 (10.9–8,962.6)	**0.04**
–Serum ferritin (μg/L)	1,152 ± 1,181 (81–12,323)	1,053 ± 999 (81–12,064)	1,862 ± 1,864 (312–13,232)	**<0.01**
–Serum LDH (IU/L)	708 ± 386 (297–2,323)	656 ± 267 (399–1,615)	916 ± 445 (297–2,323)	**0.04**
–Plasma D-dimer (ng/mL)	1,027 ± 1,148 (203–122,027)	1,009 ± 1,061 (203–12,202)	1,103 ± 2,883 (380–58,515)	0.34
Time from symptom onset to tocilizumab (days, median ± IQR, min–max)	9 ± 4 (1–25)	9 ± 4 (2–21)	8 ± 7 (1–25)	0.26
Time from respiratory PCR positivity to tocilizumab (days, median ± IQR, min–max)	7 ± 5 (1–21)	7 ± 5 (1–21)	6 ± 7 (1–13)	0.53
Time from admission to tocilizumab (days, median ± IQR, min–max)	1 ± 3 (1–56)	1 ± 2 (1–56)	2 ± 4 (1–8)	0.48
Administration of tocilizumab within 7 days of symptom onset (n, %)	33 (31.1)	22 (27.2)	11 (44.0)	0.21

(54 patients, 87.1%) required invasive mechanical ventilation as well. The rate of in-hospital infectious complications was statistically similar between survived and perished patients (8.6% vs. 24.0%, P = 0.07). Median time from admission to death was 13 ± 7 (5–27) days. Surviving patients reached respiratory SARS-CoV-2 PCR clearance in a higher rate (60.5% vs. 12.0%, P < 0.01). Experimental immunomodulatory therapies are detailed in Table 2, ruxolitinib was administered most frequently in the cohort (17.0%).

DISCUSSION

The present study on 106 adult patients receiving high-dose tocilizumab for COVID-19 associated CRS demonstrated high in-hospital survival (81/106, 76.4%) with sustained improvement of COVID-19 specific laboratory parameters.

Dysregulation of the immune system probably plays a crucial role in the clinical course of severe and critical COVID-19 [19]. Intervention in this pathological sequence

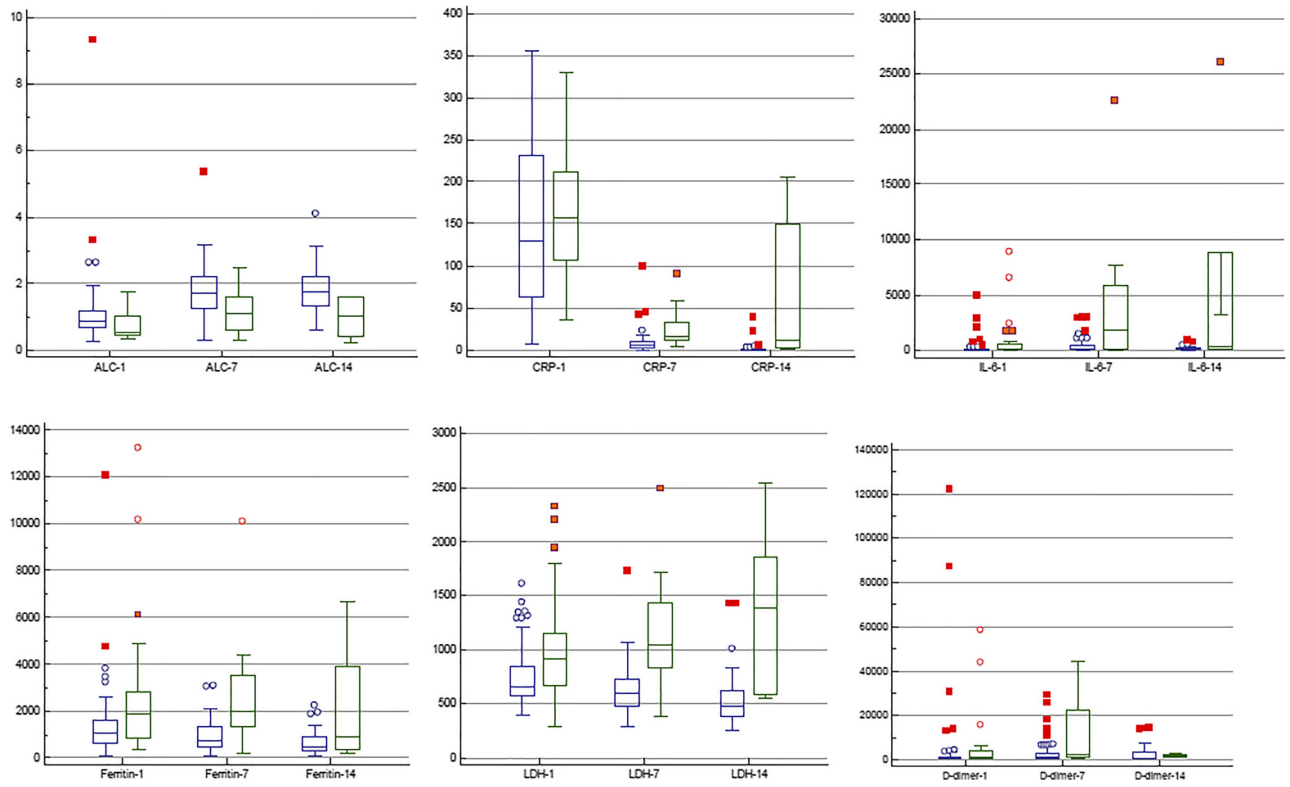

Fig. 1. Peripheral venous blood absolute lymphocyte counts (ALC, × 10^9/L), serum CRP (mg/L), plasma IL-6 (pg/mL), serum ferritin (μg/L), serum LDH (IU/L) and plasma D-dimer (ng/mL FEU) levels adult COVID-19 in-patients at baseline and days 7 and 14 after receiving tocilizumab, grouped by survival (survival: blue, death: green). Box middle lines represent medians, outer borders represent interquartile ranges, whiskers represent non-outlier min–max values. Blue circle: outlier, red square: extreme outlier

of events at the intracellular level could potentially abate overflow of cytokine production. The anti-inflammatory effect of systemic corticosteroids was demonstrated to be beneficial among hospitalized COVID-19 patients requiring oxygen support [2]. Data accumulated over one year of the current pandemic suggests that medications modulating the immune system may be a promising strategy to treat COVID-19 patients.

Initial reports showed that high levels of inflammatory cytokines (mainly IL-1β, IL-6, IL-10, IFNγ, IP-10 and MCP-1) in COVID-19 patients are associated with more severe disease, pulmonary inflammation, and multiple organ failure

Table 2. Outcome characteristics of adult COVID-19 in-patients receiving high-dose tocilizumab, grouped by 28-day mortality

Parameter	Total (n = 106)	Survived (n = 81)	Died (n = 25)	*P value*
Need for ICU admittance	62 (58.5)	38 (46.9)	24 (96.0)	**<0.01**
Need for invasive mechanical ventilation (n, %)	54 (50.9)	30 (37.0)	24 (96.0)	**<0.01**
Rate of respiratory PCR clearance (n, %)	52 (49.1)	49 (60.5)	3 (12.0)	**<0.01**
Rate of any in-hospital infectious complication (n, %)	13 (12.3)	7 (8.6)	6 (24.0)	0.07
Time to respiratory PCR clearance (n, %)	20 ± 13 (6–55)	21 ± 13 (6–55)	15 ± 7 (7–20)	0.10
LOS (days, median ± IQR, min–max)	20 ± 15 (1–65)	24 ± 17 (1–65)	8 ± 9 (1–22)	**<0.01**
ICU LOS (days, median ± IQR, min–max)	12 ± 13 (2–65)	16 ± 15 (3–65)	10 ± 8 (2–24)	**<0.01**
Immunomodulatory therapies given (n, %):				
–Ruxolitinib	18 (17.0)	13 (16.0)	5 (20.0)	0.64
–Baricitinib	4 (3.8)	4 (4.9)	0	0.25
–Intravenous immunoglobulin	9 (8.5)	7 (8.6)	2 (8.0)	0.91
–Reconvalescent plasma	2 (1.9)	0	2 (8.0)	0.05

[20, 21]. Most notably, IL-6 seems to play a crucial role, as in COVID-19 increased serum levels have been correlated with unfavorable outcomes such as respiratory failure, acute respiratory distress syndrome (ARDS) and death [22, 23]. Previous studies in the pre-COVID-19 era focused on cytokine release syndrome and secondary hemophagocytic lymphohistiocytosis with resembling pathophysiology and have already demonstrated the efficacy of IL-6 and IL-6R antagonists in these situations [24, 25].

Initial observational studies suggested that IL-6-targeted therapies, such as tocilizumab, may curb the dysregulated immune response in COVID-19 patients resulting in improved outcomes, such as lower risk of death or need for mechanical ventilation [26–33]. However, these studies were limited by several factors, such as lack of control groups, small patient populations or absence of adjusted analyses. Of note, dosing and criteria of tocilizumab administration were used differently and did not follow strict and homogenous CRS definitions, resulting in different and hardly comparable subpopulations and results for these treatment arms [4–6].

However, the recently published, so far the largest trial has demonstrated significantly reduced mortality among patients with elevated C-reactive protein levels (>75 mg/L) and documented need for supplementary oxygen. A benefit of tocilizumab was clearly demonstrated in addition to systemic corticosteroids [11]. This observation supports the hypothesis that IL-6 blockade may only be favorable in the presence of CRS.

Furthermore, large observational studies showed that if patients received tocilizumab within 24–48 h from the introduction of intensive support care, an improved survival could be recognized [10]. Importantly, this observation was confirmed by the recent report of *Gordon* et al. in the aformentioned multifactorial adaptive platform trial [9].

The findings of our study are consistent with the clinical observations of the above mentioned trials. Therefore, we postulate that administration of tocilizumab may add benefit in a restricted group of patients presenting in the definite ascendent phase of hyperinflammation reflected in laboratory parameters, in line with clinical deteroriation, most notably a persistent febrile state with or without hypoxaemia. Supposedly, neither too late nor too early administration of IL-6 blockade yields efficient intervention in hypercytokinaemia. Furthermore, we might postulate that low dose tocilizumab (<8 mg/kg) may not be sufficient to provide optimal effect in patients with COVID-19 associated CRS. In a recent retrospective study, lower doses of tocilizumab administration (400 mg for 30–100 kg and 600 mg over 100 kg) was related to a rebound of CRP levels, suggesting the need for higher and/or repeated doses of tocilizumab [34].

Laboratory parameters measured regularly in our study provided valuable data to predict mortality. Of note, CRP levels measured at baseline and on day 14 was not different between survivor and non-survivor patients. Baseline IL-6, ferritin and LDH levels were lower in the survival group, whereas ALC levels were higher, which is in line with previous observations [35, 36]. On days 7 and 14 LDH levels were significantly higher among patients who later perished, and showed progressive increase suggesting escalating lung injury. Also, levels of IL-6 also remained significantly higher on days 7 and 14, raising the concern that administration of IL-6 blockade was too late. Lower ALC levels at day 14 reflect delayed and defective immune response contributing to this poor outcome, as described earlier [37]. Notably, observations of our study suggest that LDH, IL-6 and ALC levels may have a predictive role for an unfavorable outcome in COVID-19 associated CRS patients treated with tocilizumab.

There are several limitations of our study. First, the lack of a matched control group. This could be explained by the fact that since the early beginning of the pandemic available data suggested an important role of IL-6 blockade in COVID-19 associated CRS. Therefore, based on local experience in stem cell transplant-associated CRS patients as well, we administered tocilizumab to practically all patients fulfilling criteria for this condition. Second, recommendations on antiviral medications for the treatment of COVID-19 changed vastly during the study period based on best available evidence. Third, administration of systemic corticosteroids has become part of routine clinical practice only since 1 September 2020, when national guidelines implemented positive findings of corticosteroid trials. Fourth, a relatively small number of subjects were included in the analysis.

CONCLUSION

In spite of limitations, findings from our cohort support the role of high-dose tocilizumab administration in COVID-19 associated CRS patients, and suggest that LDH, IL-6 and ALC levels may have a predictive role for mortality in this setting.

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