Effects of cytokine blocking agents on hospital mortality in patients admitted to ICU with acute respiratory distress syndrome by SARS-CoV-2 infection: retrospective cohort study

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ABSTRACT

Background: The use of cytokine-blocking agents has been proposed to modulate the inflammatory response in patients with COVID-19. Tocilizumab and anakinra were included in the local protocol as an optional treatment in critically ill patients with acute respiratory distress syndrome (ARDS) by SARS-CoV-2 infection. This cohort study evaluated the effects of therapy with cytokine blocking agents on in-hospital mortality in COVID-19 patients requiring mechanical ventilation and admitted to intensive care unit.

Methods: The association between therapy with tocilizumab or anakinra and in-hospital mortality was assessed in consecutive adult COVID-19 patients admitted to our ICU with moderate to severe ARDS. The association was evaluated by comparing patients who received to those who did not receive tocilizumab or anakinra and by using different multivariable Cox models adjusted for variables related to poor outcome, for the propensity to be treated with tocilizumab or anakinra and after patient matching.

Results: Sixty-six patients who received immunotherapy (49 tocilizumab, 17 anakinra) and 28 patients who did not receive immunotherapy were included. The in-hospital crude mortality was 30,3% in treated patients and 50% in non-treated (OR 0.77, 95% CI 0.56-1.05, p=0.069). The adjusted Cox model showed an association between therapy with immunotherapy and in-hospital mortality (HR 0.40, 95% CI 0.19-0.83, p=0.015). This protective effect was further confirmed in the analysis adjusted for propensity score, in the propensity-matched cohort and in the cohort of patients with invasive mechanical ventilation within 2 hours after ICU admission.

Conclusions: Although important limitations, our study showed that cytokine-blocking agents seem to be safe and to improve survival in COVID-19 patients admitted to ICU with ARDS and the need for mechanical ventilation.

Key words: COVID-19; acute respiratory distress syndrome; tocilizumab; anakinra; intensive care unit; mechanical ventilation.

Background

Since February 20th, 2020 Italy has been overwhelmed by SARS-CoV-2 virus outbreak and several patients with interstitial pneumonia and respiratory failure requiring mechanical ventilation were admitted to our intensive care unit (ICU) [1]. Unfortunately, so far there are no validated therapies to prevent or treat the severe acute respiratory distress syndrome (ARDS) caused by this novel virus and, thus, the case-fatality rate in patients admitted to ICU is extremely high, ranging from 30 to 80% [2–7]. Therefore, along with the maintenance of vital functions by supportive treatments, effective therapies in COVID-19 are urgently needed and several trials are underway worldwide for evaluating the effects of new and old antivirals agents, hydroxychloroquine, convalescent plasma, specific immunosuppressive agents and others [8–10].

In the last weeks, the scientific community provided a tremendous improvement in the knowledge of mechanisms involved in COVID-19 pathobiology. Uncontrolled immune response characterized by systemic hyper-inflammation with an abnormal increase of circulating cytokines and chemokines (the so-called cytokine storm) is common in critically ill COVID-19 patients and seems to have a pivotal role in lung tissue damage, increase in vascular permeability and clots formation [11]. To reduce the burden of this hyperinflammatory state many authors postulated the use of drugs with selective (*e.g.*, anti-interleukin 1 and 6) and unselective (*e.g.*, steroids, immunoglobulins) block of inflammatory mediators. The assessment of serum levels of proinflammatory biomarkers and cytokines has become common in clinical practice for early recognizing COVID-19 patients at risk for clinical worsening and who could benefit by the use of specific immunosuppressive agents [12]. On February 25th 2020, we admitted the first patient with severe COVID-19 pneumonia to our ICU. Fifteen days later, based on the above mentioned pathophysiological considerations and the high mortality rate of patients, without any specific treatment showing real efficacy in improving clinical conditions, the use of tocilizumab (a recombinant humanized monoclonal antibody directed against both the soluble interleukin-6 receptor and the membrane-bound receptor) or anakinra (a recombinant interleukin-1 receptor antagonist), in case of shortage of intravenous tocilizumab, has been included in the local protocol for the management of COVID-19 as an optional treatment in critically ill patients with the need of non-invasive or invasive ventilatory support because of moderate to severe ARDS. Thereafter, on April 6th the first experience on the use of tocilizumab was published, with the same rational in the attempt of the use of cytokine-blocking agents, despite providing insufficient level of evidence and not fully positive results [13].

This cohort study aimed to evaluate the effects of the therapy with tocilizumab or anakinra on in-hospital mortality in patients requiring mechanical ventilation for severe COVID-19 pneumonia and admitted to ICU. We hypothesized that the use of tocilizumab or anakinra would be safe and associated with in-hospital mortality rate reduction in the analysis adjusted for the major factors related to poor outcome.

Methods

Design, population and protocol

This retrospective cohort observational study included consecutive adult patients (≥18 years) admitted to the ICU of University Hospital of Modena with ICU stay >24 hours, moderate to severe ARDS, requiring invasive or non-invasive mechanical ventilation and laboratory-confirmed SARS-CoV-2 infection from February 25th to April 6th. Moderate to severe ARDS was defined as new or worsening respiratory failure with bilateral opacities and PaO_2/FiO_2 ≤200 mmHg with positive end-expiratory pressure ≥5 cmH_2O not fully explained by cardiac failure, fluid overload, pleural effusions and lobar or lung collapse [14]. SARS-CoV-2 infection was defined as a positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of nasopharyngeal swabs or lower respiratory tract specimens. The study was approved by the Ethics Committee of Area Vasta Nord Emilia Romagna (n. 289/2020, 7 April 2020) who deemed informed consent unnecessary because of the retrospective design. The informed consent for off-label use of drugs is standard procedure in our Hospital with specific annotation on clinical charts. In unconscious patients, as for procedure, we communicate the off-label use to relatives and annotate it on clinical charts.

All the patients received standard ICU monitoring and supportive care, including mechanical protective ventilation, as recommended by the WHO guidelines [15] and specific therapies according to national [16] and local protocol for COVID-19 treatment including hydroxychloroquine, azithromycin if suspicion of bacterial respiratory superinfection, low molecular weight heparin for prophylaxis of deep vein thrombosis according to individual body-weight and renal function, and antiretroviral therapy with lopinavir/ritonavir or darunavir/cobicistat (removed on 22 March). The local protocol allowed the use of steroids (methylprednisolone 2 mg/kg/day) to prevent the onset of pulmonary fibrosis in patients who maintained a PaO_2/FiO_2 ratio <150 for at least 7 days of mechanical ventilation [17].

We compared the cohort of patients treated with cytokine-blocking agents (TOCI or ANA) with a control group composed by non-treated patients because admitted in ICU before the introduction of these cytokine-blocking therapies in our institutional protocol. Since March 5th, for the reasons described above (see Introduction), the local ICU management protocol included the option for off-label use of tocilizumab (TOCI) or anakinra (ANA), when intravenous TOCI was not available due to market shortage, in patients with moderate or severe ARDS and the need of mechanical ventilation (non-invasive or invasive). Patients with coexistent infection other than COVID-19, chronic use of steroids or other immunosuppressive agents, neutrophils <500/mmc or platelets <50.000 /mmc, gastrointestinal tract condition that might predispose to bowel perforation and severe hematologic, renal or liver impairment were excluded from this therapeutic option. Nevertheless, the decision for therapy with TOCI or ANA was left to the discretion of the treating team considering the benefit to risk ratio in the individual patient. TOCI was administered intravenously at the dosage of 8 mg/kg of body weight (up to a maximum dosage of 800 mg per infusion) in two doses, 12 hours apart. ANA was used intravenously at the dose of 400 mg/die for 14 days or until the patient was weaned from mechanical ventilation or adverse events related to therapy occurred. The TOCI and ANA schedules were based on dosages indicated for the treatment of cytokine release syndrome [18] and macrophage activated syndrome [19,20]. The standard supportive management in ICU did not change during the study period.

Data collection and analysis

Demographics, co-morbidities, medications, and laboratory values were collected by reviewing electronic medical records. The primary endpoint was in-hospital survival after ICU admission. Secondary endpoints were ICU mortality, ICU-free days censored at day 30, invasive and non-invasive ventilator-free days (VFDs) at day 30 after ICU admission, the incidence of secondary infections within hospital stay. All enrolled patients achieved the follow up period. The association between immunotherapy and in-

hospital mortality was estimated by multivariable Cox proportional hazards regression model including immunotherapy, variables with p<0.2 at unadjusted analysis (age, co-morbidities, SAPS II and invasive ventilation at ICU admission).

To evaluate the independent association of TOCI and ANA with mortality, a second multivariable Cox proportional hazards regression model was built including the previous covariates with stratification of immunotherapies in the two different treatment arms. To further reduce the effects of confounding variables we performed a secondary analysis by using propensity score for patients matching. The individual propensity to be treated with TOCI or ANA was estimated by a multivariable logistic regression model that included the same covariates as the Cox regression; the nearest-neighbour method was applied to the propensity-score matching analysis. An additional sensitivity analysis included the same set of analyses was performed only in the population with invasive mechanical ventilation within 2 hours after ICU admission. Non-parametric and χ-2 tests were used as appropriate for the unadjusted comparison between controls and treated patients of demographic and baseline values, and outcomes. Cumulative survival analysis censored at day 90 was performed using the Kaplan-Meier method and the log-rank test was then used to examine differences in the curves between the groups. Patients discharged from the hospital before day 90 were considered survived. All tests were two-tailed with p<0.05 considered significant. SPSS version 22.0 package (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis.

Results

In the study period, ninety-nine COVID-19 patients were admitted to our ICU, of whom 94 met the inclusion criteria. Sixty-six patients (70%) received selective cytokine blockade therapy (immunotherapy group), 49 (52%) with 2 doses of TOCI and 17 (18%) with ANA for a median of 8 days (IQR 7-11). In 26 patients (53%) the first dose of TOCI was administered before ICU admission (median time 24 -IQR 12-48 hours) and in 23 (43%) after ICU admission (median time 6 -IQR 0-24 hours). ANA was started after ICU admission in all the patients (median time 4-IQR 0-24 hours) and was stopped in 9 (53%) patients for weaning from mechanical ventilation, in 4 (24%) for death during treatment and 3 (23%) patients completed the full therapy course.

Demographic and clinical characteristics at ICU admission were similar in patients who received and who did not receive selective cytokine blockade therapy with exception of percentage of patients undergoing invasive ventilation within 2 hours from admission (p=0.006) and PaO_2/FiO_2 (p= 0.029) that were larger in control patients, and interleukin 6 blood concentration that was higher (p= 0.019) in immunotherapy group (Table 1). Twenty-four out of the 44 patients in non-invasive ventilation within 2 hours after ICU admission were subsequently intubated during ICU stay (3 out of 7 in the control group (43%) and 21 out of 37 (57%) in immunotherapy group, p=0.48). Fifty-six patients [14 in the control group and 43 in the immunotherapy group (p =0.17)] received steroids during ICU stay for a median of 5 days (IQR 5-7).

Crude analysis showed that selective cytokine blockade therapy provided 20% absolute risk reduction of in-hospital mortality compared to controls (OR 0.77, 95% CI 0.56-1.05, p=0.069) (Table 2). The Kaplan Meyer analysis for cumulative in-hospital survival (Figure 1) shows a significative effect of immunotherapy as a protective strategy (p=0.036). Cox regression multivariable analysis indicated that age, SAPS II, and immunotherapy were related to mortality risk, with an improvement in survival by the use of TOCI or ANA (HR 0.40, 95% CI 0.19-0.83, p=0.015) (Table 3). The main cause of death in both groups was a multiorgan fail-

Table 1. Demographic and characteristics of the study populations.

	All patients (n=94)	Control (n=28)	Immunotherapy (n=66)	p
Age (median, IQR)	63 (56-70)	62 (55-68)	63 (57-71)	0.297
Sex, male (n, %)	75 (79.8)	22 (78.6)	53 (80.3)	0.848
Comorbidities (n, %)	67 (71.3)	22 (78.6)	45 (68.2)	0.309
Hypertension	47 (50)	14 (50)	33 (50)	
Body mass index >30	14 (14.9)	4 (14.3)	10 (15.2)	
Hyperlipidaemia	6 (6.4)	2 (7.1)	4 (6.1)	
Diabetes	15 (15.9)	6 (21.4)	9 (13.6)	
Any other	27 (28.7)	6 (21.4)	21 (31.8)	
SOFA (median, IQR)	4 (3-5)	4 (3-6)	4 (3-5)	0.849
SAPS II (median, IQR)	31.5 (27-37)	30 (25-38)	32 (27-37)	0.646
Ventilation at ICU admission (n, %)				0.006
Invasive*	50 (52.3)	21 (75)	29 (43.9)	
Non-invasive	44 (46.8)	7 (25)	37 (56.1)	
PaO_2/FiO_2 (mmHg, median, IQR)	100 (80-123)	113 (86-161)	96 (74-117)	0.029
D-dimer (ng/ml; median, IQR)	1985 (870-3700)	1915 (750-2660)	2085 (940-8650)	0.110
LDH (U/L; median, IQR)	762 (611-1031)	700.5 (588-1039.5)	774 (655-1031)	0.549
CRP (mg/L; median, IQR)	15.4 (6.2-22.7)	16.3 (7.5-26.2)	15.3 (6.1-21.1)	0.359
PCT (ng, ml; median, IQR)	0.3 (0.1-1.1)	0.4 (0.2-0.8)	0.3 (0.1-1.2)	0.351
IL6 (pg/ml; median, IQR)°	452.2 (207.2-1483.3)	242.9 (115.5-386)	541.6 (214.5-1526)	0.019
Lymphocyte count (cells/mcl; median, IQR)	0.64 (0.420.89)	0.56 (0.390.85)	0.66 (0.46-0.91)	0.215

SOFA, simplified organ failure assessment; SAPS, simplified acute physiological score II, PaO_2, arterial partial pressure of oxygen; FiO_2, fraction of oxygen in inspired mixture; LDH, Lactate dehydrogenase; CRP, C-reactive protein; PCT, procalcitonin; IL6, interleukin 6; *within 2 hours after ICU admission; °measured in 65 patients, 10 controls, 55 Immunotherapy.

ure due to persistent and intractable hypoxemia (n=15, 75% in the Immunotherapy group and n=11, 79% in the controls). Baseline and mortality rate at day 30 were similar in patients treated with ANA and treated with TOCI. The Cox regression model with TOCI and ANA as separate covariates indicated that TOCI decreased (HR 0.31 - 95% CI 0.13-0.73, p=0.007) and ANA showed a trend in decreasing the risk of mortality (HR 0.46 - 95% CI 0.17-1.26, p=0.130). The multivariable analysis including 11 controls and 55 immunotherapy patients matched by propensity-score (well-balanced for all covariates) also indicated that the use of interleukin selective blockade agents is associated with reduced risk of mortality (HR 0.23- 95% CI 0.09-0.56, p=0.001).

The invasive ventilation free days (p=0.035), total ventilation (invasive and non-invasive) free days (p=0.,132) as well as ICU free days (p=0.07) at day-30 were larger in immunotherapy group. The rate of patients with new infections was similar in the 2 groups; the infections were sustained mostly by Gram-positive bacteria (65.8%) with respiratory tract (76.3%) and bloodstream (28.9%) as main sites of infection. As for viral infections, 4 patients in the control group and 5 in the immunotherapy group were treated by ganciclovir for cytomegalovirus reactivation; 1 patient who received ANA and 4 patients who received TOCI were treated with acyclovir for herpes simplex virus type 1 reactivation. No differences in secondary outcomes were observed between patients treated with ANA or TOCI. The sensitivity analysis in patients with invasive ventilation at ICU admission (21 patients in TOCI, 8 in ANA and 21 in controls) confirmed the potential association between selective cytokine blockade therapy and the reduced risk of in-hospital mortality.

Discussion

The results of this cohort observational study indicate that selective cytokine blockade with tocilizumab or anakinra in critically ill patients with moderate to severe ARDS pneumonia and need of mechanical ventilation seems to be well tolerated and to
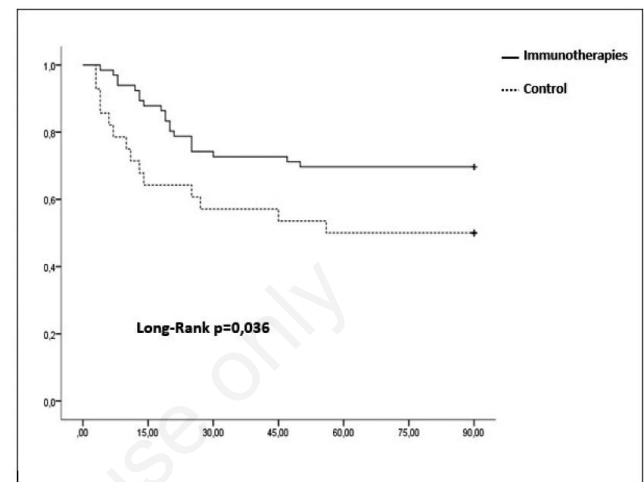

Figure 1. Kaplan Meyer Curves for survival probability at day 30.

Table 2. Main outcomes in all population, controls and treated patients.

	All patients (n=94)	Control (n=28)	Immunotherapy (n=66)	p
Hospital mortality (n, %)	34 (36.2)	14 (50.0)	20 (30.3)	0.069
30-day mortality (n, %)	29 (30.9)	12 (42.9)	17 (25.8)	0.101
ICU mortality (n, %)	27 (28.7)	11 (39.3)	16 (24.2)	0.140
ICU-free days at 30 day (median, IQR)	16.5 (0-25)	0 (0-22)	18.5 (0-26)	0.072
Invasive ventilation free days at 30-day (median, IQR)	20.5 (0-28)	0 (0-26)	22.5 (0-29)	0.035
Ventilation-free days at 30-day (median, IQR)	16.5 (0-25)	0 (0-23.5)	18.5 (0-26)	0.132
Patients with new bacterial infections during hospital stay (n, %)	38 (40.4)	11 (39.3)	27 (40.9)	0.883

Table 3. Odds ratios and confidence interval obtained by unadjusted univariate and adjusted Cox regression analysis for in-hospital mortality. Data for survived and not survived during hospital stay are also reported.

	Survived (n=60)	Not survived (n=34)	Unadjusted OR (95% CI); p	Adjusted HR (95% CI); p
Age (median; IQR)	61 (54-67)	69 (62-75)	1.6 (1.01-1.11) 0.018	1.07 (1.02-1.12) 0.010
Comorbidities (n, %)	38 (63.3)	29 (85.3)	1.44 (1.09-1.89) 0.019	1.33 (0.51-3.51) 0.559
SAPS II score (median; IQR)	27 (24.5-32)	36 (34-43)	1.07 (1.03-1.11) 0.001	1.05 (1.01-1.10) 0.011
Invasive ventilation at ICU admission* (n, %)	23 (38.3)	27 (79.4)	1.83 (1.32-2.53) <0.001	2.38 (0.97-5.86) 0.059
Immunotherapy (n, %)	46 (76.7)	20 (58.8)	0.72 (0.48-1.07) 0.058	0.40 (0.19-0.83) 0.015

SAPS II, simplified acute physiological score II; *within 2 hours after ICU admission.

improve in-hospital survival rate. Based on recent reports [3,21], the pathobiology of interstitial pneumonia and acute respiratory failure by SARS-CoV-2 infection relies on the predominant role of hyper-inflammation in the context of a complex dysregulated immune function [22]. As observed by others [3,23], our patients showed a pronounced pro-inflammatory state at ICU admission with elevated serum CRP, D-Dimer, LDH and IL6 levels associated with lymphopenia. Subsequently to the poor outcome observed in the first reports on COVID-19 patients requiring ICU admission, the attractive hypothesis of controlling the exaggerated cytokine response by using different immunomodulating agents has been early proposed [24] and many randomized trials are ongoing.

TOCI and ANA, among immunomodulatory drugs, represent two treatment options in this context. TOCI, a selective interleukin-6 receptor antagonist, was approved for the treatment of autoimmune diseases and chimeric antigen receptor T-cell therapy-induced cytokine release syndrome [25]. Early reporting of clinical experiences with TOCI in COVID-19 patients have been published at the end of July 2020. The most of reported experiences deal with patients before ICU admission and/or mechanical ventilation [26]. As refers to ICU patients, in a retrospective analysis of 25 unmatched ICU patients, TOCI at the median dose of 5,7 mg/kg showed a significant reduction in invasive mechanical ventilation at day 14, although 90% of patients showed adverse events [27]. In a single-centre study including 100 unmatched COVID-19 patients with mechanical ventilation, the authors observed an improvement of the respiratory severity using a disease-specific scale and the decreasing of laboratory inflammation parameters after two intravenous administrations of 8 mg/kg of TOCI [28]. Two recent experiences, according with our results, report improvement in clinical outcomes of ICU patients affected by COVID-19 receiving tocilizumab [29,30]. In particular, one of these studies reports a decreased hospital mortality in treated patients, with similar associations in higher-severity subgroups [30].

As refers to ANA, it is a recombinant IL-1 receptor antagonist administered to treat autoinflammatory disorders and recently used in post-myocardial infarction remodelling and diabetes [31]. In the context of COVID-19 acute respiratory distress syndrome, a retrospective study was conducted on 29 patients treated with high-dosage ANA compared to 16 control ones; patients were non-invasively ventilated outside of the ICU. Compared with standard treatment, high-dose ANA was associated with a higher survival rate at 21 days and with a reduction in C-reactive protein and with progressive improvement in PaO$_2$/FiO$_2$. However, high-dose treatment was discontinued for adverse events in 24% of the treated patients [32].

To our knowledge, our study is the first to have evaluated the effects of the selective cytokine blockade on in-hospital mortality in ICU admitted patients requiring mechanical ventilation for ARDS due to COVID-19. Beyond the significant risk reduction compared to our controls, the in-hospital mortality (36.2% in all the patients and 54% in those with invasive ventilation at ICU admission) observed in our patients treated with selective cytokine blockade was also lower than mortality observed in other reports, even when only patients underwent invasive ventilation are considered. A large case series of ICU patients coming from Wuhan, China, showed an overall mortality rate at day 28 of 39% but increased to 97% in patients with invasive mechanical ventilation. Another retrospective study coming from Wuhan enrolled 52 critically ill ICU patients with a 28-day mortality rate of 61.5% [6]. In the Italian Lombardy ICU Network series, the hospital mortality rate of 1,715 patients admitted to ICU was 50.3% [33] and among 5,700 hospitalized patients in the New York Area, 373 patients needed ICU care with an ICU mortality rate of 78% [34]. Finally, the ICNARC report on COVID-19 updated on 1st May showed an ICU mortality of 62% in

3,508 patients with advanced respiratory support [35]. Remarkably, following previous reports, we did not observe any severe adverse event attributable with certainty to the use of TOCI or ANA [36]. The rate of secondary infections, mostly ventilator acquired pneumonia and catheter-related bloodstream infections by Gram-positive microorganisms, was high compared to non-COVID-19 patients admitted to our ICU (internal data from Prosafe-Giviti project https://giviti.marionegri.it), but the use of cytokine selective blockade therapy did not increase the risk in comparison with controls treated in our centre. Nevertheless, in our cohort, the incidence of adverse events by ANA and TOCI could have been underestimated because of frequent clinical and laboratory alterations occurring in critically ill patients with severe ARDS or other organ dysfunctions. In fact, in 5 patients treated with cytokine blocking agents and long ICU stay we observed late reactivation of herpes simplex virus type 1 and, besides, two COVID-19 patients treated with TOCI in other hospitals were transferred to our ICU for acute liver failure, without ARDS, due to herpes simplex virus type 1 reactivation (submitted for publication).

Our study had several limitations that are mainly due to the observational design and to the small size of the cohort studied. Although the use of propensity score for adjusting the multivariable analysis and for patients matching is considered an effective method in non-randomized trials, it is possible that some amount of unmeasured confounding factors still remains. Nevertheless, it is noteworthy the all the data analysis (unadjusted, adjusted without and with propensity score) pointed out the same signal with a potential benefit in terms of survival by using selective cytokine blockade. The change of intubation rules during the study period with more permissive use of non-invasive ventilation in patients with severe ARDS could have introduced a bias. However, the sensitivity analysis in patients with invasive ventilation at ICU admission (within 2 hours) confirmed the reduction in mortality by using TOCI and ANA (Table 3). Of note, evaluating together the results of patients treated with two different drugs represents a limitation of our study. Moreover, the small number of patients treated with ANA and the different timing of administration of the two drugs hinder more robust analysis on the potential different effect of TOCI and ANA on patient survival, even if Cox multivariable regression seems to indicate a greater effect when using TOCI.

Conclusions

In conclusion, our experience indicated that tocilizumab and anakinra appear to be safe and to improve survival in patients with moderate to severe ARDS by SARS-CoV-2 infection. The use of drugs able to provide a selective cytokine blockade may represent a promising therapeutic option in the treatment of mechanically ventilated COVID-19 patients even though, given our study's limitations, our results need confirmatory results from high-quality randomized controlled trials.

Acknowledgements

Abbreviations

ANA: anakinra;
ARDS: acute respiratory distress syndrome;
COVID-19:   coronavirus disease-19;
CRP: C-reactive protein;
FiO_2:   fraction of oxygen in inspired mixture ;
ICU: intensive care unit;
IL6:   interleukin-6;
LDH: lactate dehydrogenase;
PaO_2:   arterial partial pressure of oxygen;
PCT: procalcitonin;
TOCI: tocilizumab;
SOFA: simplified organ failure assessment;
SAPS II: implified acute physiological score II.

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