

Tocilizumab Accelerates Recovery in Patients With Severe COVID-19 Pneumonia on Venovenous Extracorporeal Membrane Oxygenation

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Keywords: COVID-19, respiratory failure, hyperinflammation, tocilizumab, interleukin 6, survival

Tocilizumab is known to improve outcomes in patients with severe coronavirus disease 2019 (COVID-19) pneumonia. However, little is known about its utility in patients with COVID-19 who require respiratory support with venovenous extracorporeal membrane oxygenation (V-V ECMO). We performed an observational cohort study of adult patients with COVID-19 admitted between March 1 and April 24, 2020 who required support with V-V ECMO due to acute respiratory failure. Patients who received tocilizumab 400 mg intravenous given once in addition to standard of care were compared to those who received standard of care alone. The primary outcome was time to hospital discharge. Twenty-nine patients with severe COVID-19 supported with V-V ECMO were evaluated, 22 of whom received tocilizumab and 7 who did not. Pneumothorax (18% vs. 86%, $p = 0.007$) and need for a thoracostomy tube (23% vs. 71%, $p = 0.03$), were significantly lower in the tocilizumab group. There was no difference in secondary bacterial infections between groups (73% vs. 100%, $p = 0.25$). The median length of ECMO support (16 vs. 64 days, $p = 0.04$), mechanical ventilation (36 vs. 127 days, $p = 0.02$), and hospital length of stay (40 vs. 138 days, $p = 0.008$) were all significantly reduced in patients who received tocilizumab (Table 3). Survival to hospital discharge did not differ between groups (95% vs. 86%, $p = 0.43$). Tocilizumab therapy was associated with significantly decreased hospital length of stay in patients on V-V ECMO. More data on COVID-19 targeted therapies in patients on V-V ECMO are needed.

Acute respiratory distress syndrome (ARDS) developed in approximately 30–40% of patients with coronavirus disease 2019 (COVID-19) during the first wave of the pandemic, leading to significant morbidity and mortality.^{1,2} Several institutions reported successful outcomes with the use of venovenous

extracorporeal membrane oxygenation (V-V ECMO) to support the most critically ill of these patients.^{3,4} However, little is known about the effects of concomitant antiviral or immunotherapies in this cohort because they were often excluded from clinical trials. Moreover, while there is a trend toward increased use of ECMO for patients with severe COVID-19, in-hospital mortality in these patients remains substantially high and appears to be rising, revealing an unmet need in their management.⁵

Tocilizumab, a monoclonal antibody inhibitor of the interleukin 6 (IL-6) receptor, was a commonly employed off-label immunotherapy from the outset of the pandemic based on the association of elevated IL-6 levels with more severe disease and increased mortality.^{6–9} The preponderance of observational data of tocilizumab in patients with COVID-19 suggested decreased duration of mechanical ventilation and improved survival but was subject to potential selection bias.^{10–12} Subsequently, randomized clinical trials confirmed the beneficial effect of tocilizumab on survival in large cohorts of patients with COVID-19.^{13,14} A meta-analysis of observational and randomized studies found greater reduction in in-hospital mortality in patients who received tocilizumab within 10 days of symptom onset or were admitted to the ICU, supporting potential benefit in the most critically ill patients if given early.¹⁵ However, data on tocilizumab specifically in patients on ECMO is limited to case reports.^{16–18} Although their respiratory function is supported, patients on ECMO still stand to potentially benefit from tocilizumab by reducing inflammation in the lungs and reversing immune cell exhaustion, which may expedite time to lung recovery.^{19,20} In addition, because tocilizumab is a systemic therapy, there may be additional benefit to the patient outside of its effects on the lung. Here, we report on our observations on the use of tocilizumab in COVID-19 patients on V-V ECMO.

Materials and Methods

Study Design

We performed a retrospective, observational cohort study of patients admitted to the NYU Langone Health (NYULH) Manhattan campus. The study was reviewed by the NYU Grossman School of Medicine Institutional Review Board, and a waiver of informed consent was granted due to its retrospective nature (i20-00611).

Patients

All patients who were hospitalized between March 1, 2020 and April 24, 2020 and received V-V ECMO for severe

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Submitted for consideration November 2021; accepted for publication in revised form January 2022.

Disclosure: The authors have no conflicts of interest to report. There was no funding associated with this research.

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DOI: 10.1097/MAT.0000000000001707

COVID-19 were evaluated for inclusion. COVID-19 diagnosis was confirmed by a positive SARS-CoV-2 polymerase chain reaction (PCR) nasopharyngeal swab. The decision to offer V-V ECMO was determined by a multidisciplinary team of a cardiothoracic surgeon and critical care physician, as previously described.³

The study group included patients who received one dose of tocilizumab in addition to routine care. Use of tocilizumab was considered for all patients. Enrollment into randomized clinical trials of IL-6 pathway inhibitors was prioritized. However, trial enrollment was low among our patients. Tocilizumab was given as a single intravenous dose of 400 mg. The control group included patients who refused tocilizumab, which in each case was documented in the electronic health record (EHR), or who were enrolled in a clinical trial of a non-tocilizumab IL-6 antagonist/placebo. Two patients who were enrolled in a clinical trial were confirmed to have received placebo and the third patient received a single dose of sarilumab 200 mg. For the purpose of this analysis, day zero was considered to be the date of chart documentation of either refusal of, or receipt of tocilizumab or alternative IL-6 antagonist/placebo. Patients included in this analysis may have been additionally enrolled in clinical trials of other COVID-19 therapeutics (such as remdesivir, convalescent plasma, etc.).

Study Variables

All data were manually collected from the EHR. Baseline demographics included age, sex, body mass index, and pre-existing comorbidities. Concomitant COVID-19-specific therapies included corticosteroids, remdesivir, convalescent plasma, and CytoSorb hemoadsorption. Laboratory variables collected included C-reactive protein (CRP), ferritin, absolute lymphocyte count, serum creatinine, and liver enzymes. Inflammatory markers were collected at day zero (receipt of tocilizumab or control date) and again after 7 days to evaluate for treatment effect. Lactate dehydrogenase and D-dimer were collected at these time points but were not compared because of the impact of the ECMO circuit on these variables, and many patients were not yet on ECMO at the time of tocilizumab administration, which would significantly bias the values. Serum IL-6 levels were collected but, ultimately, there were too many missing values to allow for comparison. A pre-ECMO SOFA score and P/F ratio were calculated using the worst value in the 24 hours preceding ECMO cannulation. Complications including pneumothorax, thoracostomy tube, need for thoracic surgery, ischemic or hemorrhagic stroke, acute kidney injury, acute liver injury, secondary infection, and hemophagocytic lymphohistiocytosis (HLH) were also collected. All complications were defined according to Extracorporeal Life Support Organization (ELSO) definitions, with the exception of HLH, which was defined according to diagnostic criteria outlined by the HLH-2004 trial.²¹

Management

The management of ECMO and mechanical ventilation for this patient population was consistent across the cohort and has been previously described.³ All patients received a tracheostomy within 3 days of ECMO cannulation. Additional critical care management, including mechanical ventilation

strategies, prone positioning, sedation/analgesia, anticoagulation, antibiotics, and prophylaxis was decided upon amongst a small group of critical care providers and was generally similar in all patients. Corticosteroids were frequently prescribed for the management of ARDS, but these patients pre-dated the release of the RECOVERY dexamethasone data.²² The majority of patients also received hydroxychloroquine/azithromycin based on hospital guidelines at the time. Other non-tocilizumab COVID-19 directed therapies were chosen on an individual basis and clinical trial availability.

Outcomes

The primary outcome was time to discharge from the hospital. Secondary outcomes included comparison of complications, duration of ECMO support, duration of mechanical ventilation, and comparison of changes in inflammatory laboratory markers.

Statistical Analysis

Continuous variables were summarized using median and ranges and categorical variables using frequency and proportions. Categorical variables were compared using Chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the Mann-Whitney *U* test. Odds ratios and 95% confidence intervals for complications were compared using unadjusted logistic regression. Change in laboratory variables post-tocilizumab was calculated as a percent change from day zero to day 7 and compared using a 1-way ANOVA for mean difference and treatment effects. Outliers were defined as any value exceeding 5 standard deviations from the mean and were removed from the analysis. A Cox proportional hazards model was constructed, first using an unadjusted comparison for tocilizumab, then adding additional variables previously shown to be associated with COVID-19 outcomes. Survival analysis was compared using a Kaplan-Meier analysis and log-rank test. All tests were two-tailed at a significance level of 0.05. Statistical analysis was performed using IBM SPSS Statistics version 25.

Results

Patient Characteristics

There were 30 patients who received V-V ECMO support for severe COVID-19 pneumonia. One patient who expired within 24 hours of cannulation was excluded leaving a final cohort of 29 patients. The majority of patients were male (86%) and the median age was slightly higher in the control group (39 vs. 46 years, $p = 0.18$). Obesity was the most common comorbidity (62%); all other comorbidities were infrequent and similar between groups. The median duration of symptoms before presentation to the hospital was 7 days (IQR, 5–10) in the tocilizumab group and 8 days (IQR, 8–14) in the control ($p = 0.06$). COVID-19 targeted therapies were also similar between groups, although remdesivir was numerically higher in the tocilizumab group (27% vs. 0%, $p = 0.29$). The majority of patients received methylprednisolone (79%) at a median dose of 1 mg/kg for a median duration of 10 days. The median pre-ECMO P/F ratio (84 vs 84, $p = 0.75$) was similar between

the tocilizumab and control groups, respectively. There was no difference between groups in median time to mechanical ventilation (2 vs. 3 days, $p = 0.90$), time to ECMO (6 vs. 4 days, $p = 0.44$), or time to tocilizumab or control (3 vs. 2 days, $p = 0.41$) from admission. There was no statistically significant difference in the percentage of patients who received tocilizumab or control before ECMO (77% vs. 43%, $p = 0.09$). All other patient characteristics are displayed in Table 1.

Effect on Inflammatory Markers

The mean CRP on day zero was 176.9 mg/L in the tocilizumab group and 246.5 mg/L in the control. The mean ferritin on day zero was 2210 ng/mL in the tocilizumab group and 4010 ng/mL in the control. The mean ALC on day zero was $0.9 \times 10^3/\mu\text{L}$ in the tocilizumab group and $0.7 \times 10^3/\mu\text{L}$ in the control. Tocilizumab significantly decreased the CRP (-83% vs. -54% , $p = 0.03$) and significantly increased the ALC ($+77\%$ vs. -13% , $p = 0.02$) over the first 7 days following administration (Figure 1). There was no significant difference in the effect on the ferritin (-16% vs. -45% , $p = 0.17$).

Complications and Outcomes

Pulmonary complications, including pneumothorax (18% vs. 86%; OR, 0.04; 95% CI, 0.003–0.40; $p = 0.007$) and need for a thoracostomy tube (23% vs. 71%; OR, 0.12; 95% CI, 0.02–0.80; $p = 0.03$), were significantly reduced in the tocilizumab group. The need for thoracic surgery (14% vs. 43%; OR, 0.21; 95% CI, 0.03–1.45; $p = 0.11$) and diagnosis of HLH (0% vs. 29%; OR, 0.71; 95% CI, 0.45–1.14; $p = 0.05$) were each numerically lower with tocilizumab but did not reach

statistical significance. Frequency of secondary infection was numerically higher in the control group, but also was not significant (73% vs. 100%; OR, 0.16, 95% CI, 0.008–3.41; $p = 0.25$). No other complications differed between groups (Table 2).

The median length of ECMO support (16 vs. 64 days; $p = 0.04$), mechanical ventilation (36 vs. 127 days; $p = 0.02$), and hospital length of stay (40 vs. 138 days; $p = 0.008$) were all significantly reduced in patients who received tocilizumab (Table 3). Survival to discharge did not differ between groups (95% vs. 86%; $p = 0.43$). A Kaplan-Meier analysis of time to hospital discharge demonstrated a significantly reduced hospital length of stay in those who received tocilizumab (Figure 2, Log Rank test $p = 0.04$). Fourteen of 22 patients who received tocilizumab (64%) were discharged before the first control patient being discharged. A Cox proportional hazards model found that tocilizumab was not associated with a shorter hospital length of stay on unadjusted analysis (HR, 2.54; 95% CI, 0.99–6.50; $p = 0.05$) but did reach statistical significance (HR, 8.00; 95% CI, 1.74–36.77; $p = 0.008$) after adjusting for variables known to be associated with worse outcomes in COVID-19 (Table 4). Remdesivir was associated with a lower likelihood of hospital discharge (HR, 0.26; 95% CI, 0.08–0.89; $p = 0.03$). No other factors included in the model had a significant association with hospital length of stay.

Discussion

The management of patients with COVID-19 who develop severe pneumonia or ARDS is challenging.^{1,2} The use of ECMO as support for the most critically ill of these patients has proven successful but is accompanied with a prolonged time to

Table 1. Patient Characteristics

Variable*	Toci (n=22)	Control (n=7)	p value
Age (years)	39 (29–46)	46 (38–48)	0.18
Male sex, n (%)	19 (86)	6 (86)	0.97
Body mass index (mg/m ²)	32.6 (28.7–36.7)	28.3 (25.7–31.5)	0.17
Comorbidities, n (%)			
Obesity	15 (68)	3 (43)	0.38
Hypertension	4 (18)	1 (14)	1.00
Hyperlipidemia	5 (23)	1 (14)	1.00
Diabetes mellitus	3 (14)	0 (0)	0.56
Coronary artery disease	0 (0)	0 (0)	1.00
Chronic kidney disease	1 (5)	0 (0)	1.00
COPD	0 (0)	0 (0)	1.00
Asthma	2 (9)	0 (0)	1.00
Immunocompromised	3 (14)	0 (0)	0.56
Current smoker	2 (9)	1 (14)	0.61
COVID-19 therapies			
Corticosteroids	15 (68)	6 (86)	0.37
Remdesivir	6 (27)	0 (0)	0.29
Convalescent plasma	0 (0)	0 (0)	1.00
CytoSorb	5 (23)	4 (57)	0.16
Prone positioning	18 (82)	7 (100)	0.22
Duration of symptoms before hospitalization (days)	7 (5–10)	8 (8–14)	0.06
SOFA pre-ECMO	3 (2–4)	2 (1–4)	0.10
P/F ratio pre-ECMO	84 (75–107)	84 (79–117)	0.75
Time to mechanical ventilation (days)	2 (1–5)	3 (0–7)	0.90
Time to ECMO (days)	6 (4–8)	4 (2–9)	0.44
Time to tocilizumab or control date (days)	3 (1–5)	2 (1–4)	0.41
Time to corticosteroids (days)	8 (4–10)	5.5 (5–18)	0.91

COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; P/F, partial pressure of arterial oxygen/fraction of inspired oxygen; SOFA, sequential organ failure assessment; Toci, tocilizumab.

*All data reported as median (IQR), unless otherwise specified.

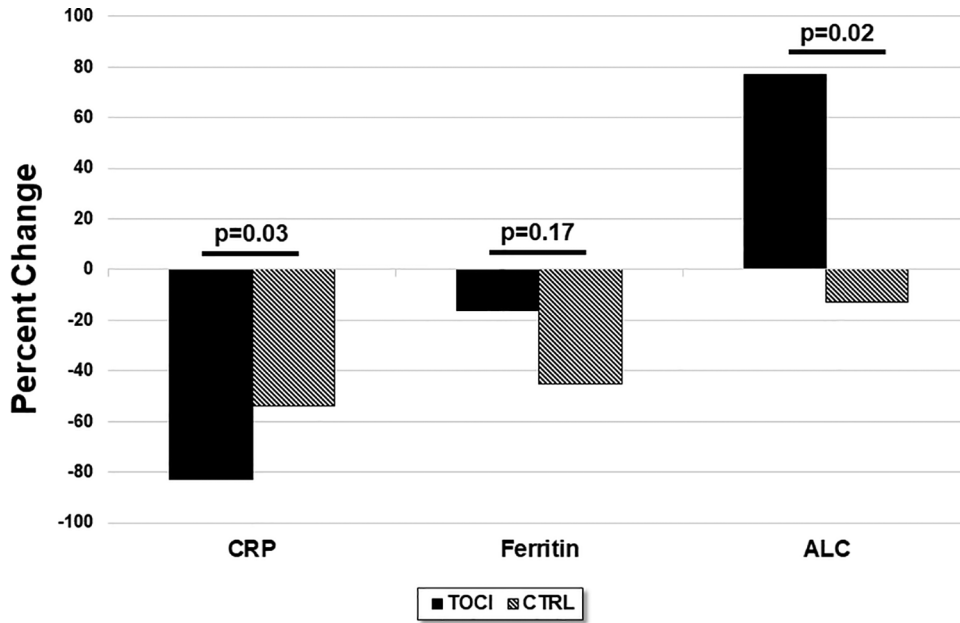


Figure 1. Effect of tocilizumab on inflammatory laboratory parameters. *Data presented as mean percent change from date of receipt of tocilizumab, or matched date, to day 7 post-tocilizumab. Mean between-group differences compared using a 1-way ANOVA.

recovery and hospital length of stay.^{3,4} Of all of the therapies investigated for COVID-19, only dexamethasone and tocilizumab have thus far demonstrated a reduction in the need for mechanical ventilation and mortality.^{13,14,22} However, patients supported with ECMO were underrepresented or absent from many large trials leaving gaps in the knowledge of management of these patients. Data specifically detailing the effect of tocilizumab in COVID-19 patients on V-V ECMO is limited to case reports.^{16–18} Here, we report significantly reduced duration of ECMO, mechanical ventilation, and hospital stay in patients on V-V ECMO who received tocilizumab compared with those who did not. The incidence of pneumothorax and need for thoracostomy tubes was also significantly reduced by tocilizumab, while secondary infections did not differ. These data suggest that tocilizumab may be associated with an accelerated recovery in patients with COVID-19 on V-V ECMO.

Tocilizumab has been extensively studied in randomized trials of patients with COVID-19 requiring supplemental oxygen or non-invasive ventilation and has demonstrated a significant reduction in progression to mechanical ventilation or death.²³ Data in patients on mechanical ventilation or V-V ECMO at the time of tocilizumab are less conclusive, but observational data and meta-analysis suggests that tocilizumab is still associated with a reduction in mortality in this subgroup.^{12,15} Whereas the benefit of tocilizumab in patients not on mechanical ventilation appears to be mitigating disease progression, it is unclear how it would benefit patients who have already progressed to the most severe respiratory failure. Two potential mechanisms have emerged that could potentially explain this: curtailing inflammatory damage to the lungs and/or reversing T cell exhaustion, hastening immune recovery. In preclinical models of acute lung

Table 2. Complications

Complication*	Toci (n=22)	Control (n=7)	Unadjusted OR	95% CI	p value
Pulmonary complications					
Pneumothorax	4 (18)	6 (86)	0.04	0.003–0.40	0.007
Thoracostomy tube	5 (23)	5 (71)	0.12	0.02–0.80	0.03
Thoracic surgery	3 (14)	3 (43)	0.21	0.03–1.45	0.11
Stroke	1 (5)	1 (14)	0.29	0.02–5.28	0.40
Acute kidney injury	11 (50)	3 (43)	1.33	0.24–7.41	0.74
Serum creatinine 1.5–3.0 mg/dL	8 (36)	1 (14)			0.38
Serum creatinine >3.0 mg/dL	3 (14)	2 (29)			0.57
Renal replacement therapy	1 (5)	2 (29)			0.14
Hemoconcentrator	4 (18)	2 (29)			0.61
Acute liver injury	9 (41)	2 (29)	1.73	0.27–10.97	0.56
HLH/cytokine storm	0 (0)	2 (29)	0.71	0.45–1.14	0.05
Secondary infection	16 (73)	7 (100)	0.16	0.008–3.41	0.25
Pneumonia	16 (73)	7 (100)			0.12
Bloodstream infection	3 (14)	2 (29)			0.57
Other infection	1 (5)	1 (14)			0.43

HLH, hemophagocytic lymphohistiocytosis; OR, odds ratio.
*All data reported as number (%).

Table 3. Outcomes

Outcome*	Toci (n=22)	Control (n=7)	p value
ECMO duration (days)	16 (11–25)	64 (20–116)	0.04
Mechanical ventilation duration (days)	36 (25–46)	127 (37–155)	0.02
Hospital length of stay	40 (29–62)	138 (47–160)	0.008
Survival, n (%)	21 (95)	6 (86)	0.43

ECMO, extracorporeal membrane oxygenation; IQR, interquartile range.

*All data reported as median (IQR), unless otherwise specified.

injury, IL-6 has demonstrated both pro- and anti-inflammatory effects.^{24–26} However, data in adults with ARDS from etiologies other than COVID-19 have consistently demonstrated a correlation between elevated systemic or bronchoalveolar lavage fluid IL-6 levels with more severe disease and mortality.^{27–29} Similarly, IL-6 levels and CRP—the most prevalent measure of IL-6 activity—were significantly higher in COVID-19 patients who developed ARDS or died compared with those with mild disease.^{6–9,30} Moreover, elevated CRP levels have been reported in COVID-19 patients with pneumothorax with respect to controls.^{31,32} We found a significant decrease in CRP and lower incidence of pneumothorax in patients treated with tocilizumab, ultimately leading to faster weaning from ECMO and mechanical ventilation. These data suggest that tocilizumab may mitigate acute lung injury because of COVID-19 by preventing pulmonary complications that subsequently prolong hospital stay.

Perhaps equally as important as preventing lung injury is the ability of tocilizumab to reverse T cell exhaustion. Several studies have correlated the degree of lymphopenia with worse outcomes in COVID-19. Lymphopenia was accompanied by evidence of functional exhaustion of the immune response, characterized by downregulation of HLA-DR expression in monocytes, decreased cytotoxicity in CD8+ T cells, and natural killer (NK) cells, and increased expression of inhibitory markers on T cells.^{19,20,33} However, these deficits were partially restored following the addition of tocilizumab.^{19,20} We similarly

found a significant increase in ALC following administration of tocilizumab. This finding is in contrast to that of Fanelli et al¹⁸ who reported a blunted increase in ALC after receipt of tocilizumab in patients on ECMO compared with those who were not. Many of our patients received tocilizumab before going on ECMO potentially avoiding a diminished effect and arguing for prompt administration of tocilizumab when a patient starts to deteriorate. In our cohort of critically ill ECMO patients, the increase in ALC may allude to reversal of immune exhaustion, thus potentially explaining the reduction in lung damage and accelerated recovery in patients who received tocilizumab.

Our study has several practical limitations. First, the allocation of tocilizumab was not randomized and varied over time. However, it is unlikely that randomized trials of COVID-19 therapeutics will ever be conducted in patients on ECMO, or that enough patients on ECMO will be enrolled into larger clinical trials to result in a meaningful analysis. Thus, we feel that our observation supports the use of tocilizumab in patients with severe COVID-19 who were recently cannulated for ECMO or who are likely to progress to requiring ECMO. Second, the timing of administration of not only tocilizumab, but also corticosteroids and other COVID-19 therapeutics, was slightly different with respect to patient presentation, potentially influencing treatment effect. All but two patients (one in each group) received tocilizumab or control before or within 1 day of ECMO cannulation and the majority of patients received tocilizumab within 3 days of hospital admission. Randomized, controlled trials and meta-analysis highlight that early administration of tocilizumab yields greater benefit, suggesting that the improvement in recovery seen in our study may in part be related to timing of administration.^{14,15} Remdesivir, however, was associated with a prolonged length of stay in contrast to several clinical trials in non-ECMO patients. This was likely due to the late introduction of remdesivir to this cohort and not related to adverse effect of the drug. Moreover, remdesivir was only offered to patients who were COVID-19 positive on repeat PCR at the time the drug became available several weeks into the pandemic significantly biasing any assessment of its effect on recovery. Timing also impacted our ability to

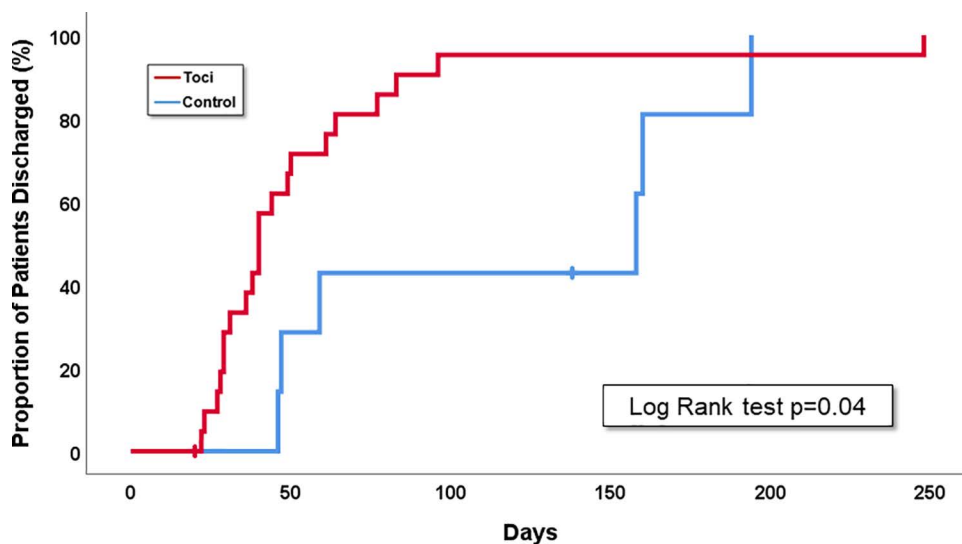


Figure 2. Time to hospital discharge. *Cumulative proportion of patients discharged estimated using a Kaplan-Meier survival model and compared using the Log-rank test. Toci, tocilizumab. [full color online](#)

Table 4. Cox Proportional Hazards Model for Hospital Length of Stay

Variable	Unadjusted		p value	Adjusted		
	Hazard Ratio	95% CI		Hazard Ratio	95% CI	p value
Tocilizumab	2.54	0.99–6.50	0.05	8.00	1.74–36.77	0.008
Corticosteroids				0.92	0.29–2.96	0.89
Remdesivir				0.26	0.08–0.89	0.03
Age				0.99	0.94–1.04	0.69
BMI				1.02	0.96–1.07	0.55
SOFA score pre-ECMO				0.89	0.60–1.31	0.55
Percent change in CRP at day 7*				1.00	0.99–1.00	0.63
Percent change in ALC at day 7*				1.01	0.99–1.03	0.35

BMI, body mass index; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; SOFA, sequential organ failure assessment.
 *Day 7 post-tocilizumab, or matched control, date.

compare other laboratory markers of interest, as many patients were not yet on ECMO at the time of receipt of tocilizumab. Third, the comparison of complications is biased by the prolonged length of ECMO and mechanical ventilation support in the control group. While it is unknown whether or not the increased complications were simply related to a longer length of hospital stay, our data support that tocilizumab was associated with a reduction in the risk of specific complications. Last, the decision to include a single patient who received sarilumab 200mg into the control may be controversial. The decision to include this patient was based on prior clinical data showing the ineffectiveness of this drug and dose. In addition, the drug manufacturer’s decision to not pursue further investigation of this dose after a planned interim analysis supported our decision to count this patient in the control arm.^{34–36}

In conclusion, we found significantly accelerated recovery in COVID-19 ECMO patients who received tocilizumab compared with those who did not. Tocilizumab significantly decreased CRP values and led to faster lymphocyte count recovery. These anti-inflammatory effects correlated with reduced pulmonary complications, namely the frequency of pneumothorax and need for chest tubes. Ultimately, patients who received tocilizumab had a shorter duration of ECMO, mechanical ventilation, and hospital length of stay. Tocilizumab should be considered early in the course for all patients with COVID-19 ARDS, even if they progress to the need for ECMO support. Future clinical trials of COVID-19 therapeutics should consider including patients supported with ECMO to better inform the management of this patient population, as they may still benefit from adjunctive therapies.

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