

Tocilizumab for Severe and Critical COVID-19 Pneumonia in Queens, NYC

Carlos Salama, MD,*† Emma Kaplan-Lewis, MD,*‡ Richard Durrance, MD,*† Linda Wong, MD,*†
Vasanthi Arumugam, MD,*† and Marilyn Fabbri, MD*†

Background: New York City was hard hit by COVID-19. Elmhurst Hospital is a public hospital in Queens where more than 1500 patients were hospitalized with COVID. During the pandemic, various treatments were used with hopes of reducing the need for mechanical ventilation and death.

Methods: We retrospectively reviewed charts of patients admitted from March 25 to April 3 with severe or critical COVID-19 pneumonia who received tocilizumab compared with a similar cohort who did not. Analyses were performed to determine differences in outcomes.

Results: There was no observed difference in need for mechanical ventilation, length of stay, or mortality rate. In the tocilizumab-treated group, mechanical ventilation rate was 55%, and 49% of patients died. In the control group, 54% required mechanical ventilation and 46% died. Tocilizumab was overall well tolerated, although alanine aminotransferase elevation was more common in the tocilizumab-treated group.

Conclusions: Tocilizumab failed to show short-term benefits in clinical outcomes in patients with hypoxic COVID pneumonia at our institution.

Key Words: COVID-19, tocilizumab, COVID pneumonia, cytokine release syndrome

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly led to a worldwide pandemic.¹ Areas across the United States with high population densities have been disproportionately impacted,² with New York City (NYC) leading the country, reporting 212,000 cases and 17,509 deaths as of June 17, 2020. In Queens County, where Elmhurst Hospital Center is located, 64,176 cases have been reported, with 5011 deaths.^{3,4} In the face of a devastating new disease that has transformed health care, clinicians have focused on identifying effective treatments with hopes of reducing the catastrophic loss of life.

Attention has been paid to the high levels of inflammation seen in patients with severe cases of COVID-19, and characteristic

laboratory patterns have emerged including lymphopenia, increased neutrophil-to-lymphocyte ratio, elevated C-reactive protein, ferritin, D-dimer, and proinflammatory cytokines interleukin-1 β and interleukin-6 (IL-6).^{5–8} Some of these markers, particularly the neutrophil-to-lymphocyte ratio and D-dimer, are predictive of worse clinical outcomes.⁸ It has been hypothesized that there is an exaggerated immune response to SARS-CoV-2 leading to release of high levels of proinflammatory cytokines and the resultant cascade of excessive inflammation. This process, termed cytokine release syndrome (CRS), is characterized by perturbations in the aforementioned laboratory parameters as well as worsening respiratory failure and progression of acute respiratory distress syndrome.⁹ The excessive inflammation observed in CRS can be targeted by various medications that suppress the immune system, including the IL-6 receptor blocker tocilizumab, which is Food and Drug Administration approved for treatment of CRS.

Reports from China demonstrated success using tocilizumab in patients with severe COVID-19, including a study of 15 patients who received this treatment, of whom 10 were noted to have clinical stabilization/improvement, whereas 3 died and 2 worsened.¹⁰ An additional study from China of 21 patients with severe COVID-19 treated with tocilizumab demonstrated decreased supplemental oxygen requirements in 75% of patients and discharge from the hospital in 90.5%.¹¹ Limitations in both of these studies include lack of a control group and small sample size. The Corimuno-Tocilizumab trial, which included 65 patients treated with tocilizumab plus standard of care compared with 64 patients who received standard of care alone, announced preliminary results demonstrating decreased need for ventilation and decreased mortality at day 14 in the tocilizumab arm¹²; however, final results are forthcoming.

Within weeks of COVID-19 hitting NYC, Elmhurst Hospital was converted into a COVID hospital. Because of the number of cases, the infectious disease service changed their consult-based practice to a rounding structure, with an infectious disease attending attached to each admitting team to more rapidly identify patients who might benefit from targeted treatments. We began treating patients with COVID-19 with tocilizumab at Elmhurst Hospital Center in late March 2020. The number of daily doses of tocilizumab was limited, so not every patient who was a potential candidate was given the drug. The following analysis is a description of our institution's experience with tocilizumab in patients hospitalized with severe COVID-19 pneumonia compared with clinically similar matched controls who did not receive tocilizumab.

MATERIALS AND METHODS

This study was conducted by the infectious disease department at Elmhurst Hospital by reviewing patients admitted with COVID 19 pneumonia from March 25 to April 3 and was approved by the institutional review board.

Patients

Subjects were patients admitted to Elmhurst Hospital with a primary diagnosis of COVID-19 infection between March 25,

From the *Elmhurst Hospital Center, NYC Health and Hospitals, Queens; †Icahn School of Medicine; and ‡Office of Population Health, NYC Health and Hospitals, New York, NY.

Correspondence to: Carlos Salama, MD, NYC Health and Hospitals Elmhurst, 79-01 Broadway, Room D6-17, Elmhurst, NY 11373.
E-mail: csalama@yahoo.com.

Potential conflicts of interest: Dr Carlos Salama is the national principle investigator for the Genentech-sponsored clinical trial evaluating minority patients with Actemra looking at tocilizumab compared with placebo for COVID-19. Dr Carlos Salama received an honorarium from Genentech in 2020 for participating in a medical advisory board. Dr Emma Kaplan-Lewis is the site principle investigator at Elmhurst Hospital Center for the Genentech-sponsored clinical trial EMPACTA looking at tocilizumab compared with placebo for COVID-19. Dr Emma Kaplan-Lewis received an honorarium from ViiV pharmaceuticals in 2019 for participating in a medical advisory board. The other authors have no conflicts of interest to disclose.

Institutional Review Board approval was obtained from Mount Sinai Institutional Review Board (Number 00737).

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2020, and April 3, 2020. The criteria used to identify candidates for the off-label use of tocilizumab included radiographic evidence of bilateral pneumonia, elevated or rapidly rising inflammatory markers (CRP), and severe hypoxia, particularly those on nonrebreather face mask, continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BIPAP), and very recently (<48 hours) intubated patients. Presence of COVID-19 infection was determined by positive nasopharyngeal swabs tested with real-time reverse transcription polymerase chain reaction assay (PCR). Patients with a negative reverse transcription PCR were included if they presented with a classic COVID-19 clinical syndrome and the above criteria. A daily list was generated of potential candidates to receive tocilizumab, prioritizing those with better functional status. The comparator group was composed of patients who met criteria to receive tocilizumab and were admitted on the same dates as the treated patients but did not receive it because of a limited supply of the drug. On April 4, we temporarily stopped using tocilizumab while we assessed its efficacy in those who had received it.

The dose of tocilizumab used was a one-time dose of 400 mg. All patients received standard supportive medical care and therapy as per our hospital treatment protocol, including the placement of patients in a prone position, hydroxychloroquine and azithromycin, and consideration of therapeutic anticoagulation if there were no contraindications. In addition, some patients received corticosteroids at the discretion of the primary team.

Descriptive and biometric variables including age, sex, body mass index (BMI), number of days of symptoms before admission, and comorbidities were extracted from the electronic medical record by chart review. Patients were defined as having hypertension if hypertension was recorded in the medical history or progress notes. Diabetic patients were identified if a diagnosis of diabetes was noted in the medical history or progress notes or if the patients had a hemoglobin A1C of 6.5% or higher. Acute kidney injury (AKI) was defined as an increase in serum creatinine above normal levels after having a normal creatinine at admission.

Patients receiving anticoagulation were divided into those receiving anticoagulation for prophylaxis or treatment-level dosing. Patients receiving steroid treatment were defined as those receiving oral or intravenous steroids for a duration of 5 days or longer. Date of discharge was defined as the day they were discharged home, whether from Elmhurst Hospital or from another facility after being transferred for convalescent care.

The group of patients who received tocilizumab was compared with the control group with univariate analysis. Chi-square tests were used for categorical variables, and *t* tests were used for continuous variables. Multivariate analysis was performed by logistic regression in several models for mortality considering tocilizumab in the context of clinical and demographic data, treatments received, and oxygen requirement on admission. Finally, subgroup analysis of coagulation and inflammatory marker trends on deceased patients between the tocilizumab and control groups was performed. Statistical significance was defined as an alpha value less than 0.05. Statistical analysis was performed using SPSS Statistics for Windows Version 27 (IBM Corp, Armonk, New York) and Stata for Mac Version 16.1 (Stata Corp College Station, Texas).

RESULTS

Between March 25 and April 3, 2020, 69 patients were treated with a one-time 400 mg dose of tocilizumab in addition to standard care, whereas 46 patients received standard care alone. Of the study population, 95% were diagnosed with COVID-19 based on a positive COVID-19 PCR test and clinical features, whereas 5% had a negative COVID-19 PCR test and were diagnosed based on clinical features alone. Among both groups, the

majority (over 80%) were male. The tocilizumab-treated group was slightly younger, with a median age of 51 compared with 56 years in the control group; however, the 2 groups had no significant differences in comorbidities, duration of symptoms before hospitalization, or baseline oxygen requirements (Table 1).

None of the patients in either group received treatment with remdesivir, but 100% of patients in both groups received anticoagulation (mostly with enoxaparin), including therapeutic anticoagulation in 48% of the tocilizumab-treated patients and 37% of the controls ($P = 0.249$). There were similar rates of use of hydroxychloroquine, azithromycin, and systemic corticosteroid in both groups.

There was no significant difference between groups in baseline laboratories, but the postdose peak D-dimer was higher in the tocilizumab-treated group when compared with peak D-dimer during hospitalization seen in control patients (16,738 vs 9615 ng/mL; $P = 0.04$) (Table 2).

TABLE 1. Clinical Characteristics of SARS-CoV-2–Infected Patients Who Received Tocilizumab and Clinically Similar Patients Who Did Not

	Tocilizumab (n = 69)	No Tocilizumab (n = 46)	<i>P</i>
Age in years, median (IQR)	51 (42–57)	56 (49–63)	0.022
Sex n (%)			0.412
Male	56 (81.2)	40 (87)	
Female	13 (18.8)	6 (13)	
BMI (kg/m ²) (mean)	30.2	30.2	0.837
HTN, n (%)			0.935
Yes	22 (31.9)	15 (32.6)	
No	47 (68.1)	31 (67.4)	
Diabetes, n (%)			0.449
Yes	29 (42)	19 (41.3)	
No	40 (58)	27 (58.7)	
Pulmonary infiltrates on chest imaging	69 (100)	46 (100)	1.00
Oxygen requirement at baseline, n (%)			0.703
HFNC, CPAP, BIPAP, and ventilator	34 (49.3)	21 (45.7)	
NRB, NC	35 (50.7)	25 (54.3)	
Day of symptoms before hospitalization, median (IQR)	7.0 (4–7)	7.0 (5–8)	0.28
Anticoagulation			0.249
Treatment	33 (47.8)	17 (37.0)	
Prophylaxis	36 (52.2)	29 (63.0)	
Steroids			0.627
Yes	24 (34.8)	14 (30.4)	
No	45 (65.2)	32 (69.6)	
Hydroxychloroquine			1.00
Yes	69 (100%)	46 (100%)	
No	0	0	
Azithromycin			0.771
Yes	68 (99%)	45 (98%)	
No	1 (1%)	1 (2%)	

HTN indicates hypertension; HFNC, high flow nasal canula; NRB, nonrebreather; NC, nasal canula.

TABLE 2. Comparison of Laboratory Results and Clinical Course

	Tocilizumab (n = 69)	No Tocilizumab (n = 46)	P
Peak D-dimer (ng/mL) baseline (mean)	2259	1900	0.085
Peak D-dimer (ng/mL) late hospitalization (mean)	16,739	9615	0.04
Peak baseline CRP (mg/L) (mean)	252	252.5	0.782
Peak CRP (mg/L) late hospitalization (mean)	207.4	241	0.013
CRP normalized			0.027
Yes	37 (54)	15 (33)	
No	32 (46)	31 (67)	
ALT baseline (mean)	64.9	69.0	0.539
Peak ALT during hospitalization (mean)	253.5	123.1	0.089
Need for mechanical ventilation during hospitalization, n (%)			0.939
Yes	38 (55.1)	25 (54.3)	
No	31 (44.9)	21 (45.7)	
AKI, n (%)			0.697
Yes	26 (37.7)	19 (41.3)	
No	43 (62.3)	27 (58.7)	
Death, n (%)			0.819
Yes	33 (48)	21 (46)	
No	36 (52)	25 (54)	
Survivor LOS from admission to discharge home in days (median)	13.0	15.0	0.126

LOS indicates length of stay.

Outcomes

There was no observed significant difference in need for mechanical ventilation during the hospitalization, development of AKI, length of stay, or mortality rate. In the tocilizumab-treated group, 28 (41%) patients subsequently required mechanical ventilation, in addition to the 10 patients who were already mechanically ventilated when they were dosed with tocilizumab, for an overall mechanical ventilation rate of 55%. Thirty-four (49%) patients in the tocilizumab-treated group died, 32 (46%) achieved hospital discharge, and 3 remained hospitalized at the time of this analysis. In the control group, 12 (25%) patients subsequently required mechanical ventilation, in addition to the 7 patients who were already mechanically ventilated at the start of observation, for an overall mechanical ventilation rate of 54%. Twenty-one (46%) patients died, 24 (52%) were discharged home, and 1 patient remained hospitalized (Table 2).

Change in Inflammatory and Coagulation Markers

In the analysis of the change in principal inflammatory (CRP) and coagulation (D-dimer) markers in the predose period, no significant difference was appreciated between the tocilizumab and control groups with respect to either CRP ($P = 0.78$) or D-dimer (0.09). As expected, postdose CRP was significantly lower in the tocilizumab-treated group with respect to controls ($P = 0.013$). Interestingly, postdose D-dimer was also significantly higher in the tocilizumab group with respect to controls ($P = 0.04$) (Table 2). However, neither one of these differences held up in the

subset of patients only requiring passive O₂ at the time of evaluation (Table 3).

When considering only deceased patients, CRP levels were significantly lower in both the predose ($P = 0.0164$) and postdose ($P = 0.0005$) periods in the tocilizumab group with respect to

TABLE 3. Characteristics and Outcomes of Patients With Oxygen Requirement of NRB or NC at Time of Tocilizumab Dose

	Tocilizumab (n = 35)	No Tocilizumab (n = 25)	P
Age in years, median (IQR)	51 (43–57)	52 (47–63)	0.443
Sex, n (%)			0.513
Male	27 (77.1)	21 (84.0)	
Female	8 (22.9)	4 (16.0)	
BMI (kg/m ²) (mean)	29.8	30.0	0.721
HTN, n (%)			0.174
Yes	11 (31)	4 (16.0)	
No	24 (69)	21 (84.0)	
DM			0.963
Yes	11 (31)	8 (32)	
No	24 (69)	17 (68)	
Days of symptoms before hospital admission, median (IQR)	7.0 (4–7)	7.0 (5–8)	0.491
Anticoagulation, n (%)			0.030
Treatment	13 (37.1)	3 (12.0)	
Prophylaxis	22 (62.9)	22 (88.0)	
Steroids, n (%)			0.513
Yes	8 (22.9)	4 (16.0)	
No	27 (77.1)	21 (84.0)	
Peak D-dimer baseline (ng/mL) (mean)	1343	962	0.225
Peak D-dimer late hospitalization (ng/mL) (mean)	15,293	4026	0.089
Peak CRP baseline (mean)	251.5	241	0.604
Peak CRP (mg/L) late hospitalization (mean)	183	216	0.102
CRP normalized			0.006
Yes	25 (71)	9 (36)	
No	10 (29)	16 (64)	
ALT baseline (mean)	70.7	78.4	0.341
Peak ALT during hospitalization (mean)	194.4	107.0	0.077
Required mechanical ventilation during hospitalization, n (%)			0.606
Yes	12 (34.3)	7 (28.0)	
No	23 (65.7)	18 (72.0)	
AKI, n (%)			0.778
Yes	6 (17.1)	5 (20.0)	
No	29 (82.9)	20 (80.0)	
Deceased, n (%)			0.853
Yes	12 (34.3)	8 (32.0)	
No	23 (65.7)	17 (68.0)	
Survivor LOS from admission to discharge home (median)	19.0	24.0	0.170

NRB indicates nonrebreather; LOS, length of stay; NC, nasal canula.

controls, whereas D-dimer levels were significantly higher in the predose ($P = 0.015$) and postdose ($P = 0.0019$) periods in the tocilizumab group (Supplemental Table 1, <http://links.lww.com/IDCP/A33>).

In the rank sum evaluation of CRP change, no significant difference was seen in the predose versus postdose max CRP for the control group ($P = 0.276$), whereas there was a significant decrease in CRP in the tocilizumab group ($P = 0.0001$). Significant increase in D-dimer was appreciated in both the tocilizumab group ($P < 0.0001$) and the control group ($P = 0.008$) (Supplemental Table 2, <http://links.lww.com/IDCP/A34>).

Multivariate Analysis

On the multivariate analysis of clinical and demographic characteristics, no significant association was seen with respect to mortality, although patients with diabetes showed a tendency toward higher likelihood of death ($P = 0.13$) (Supplemental Table 3, <http://links.lww.com/IDCP/A35>). When considering all therapeutic modalities implemented, tocilizumab failed to show a significant difference in likelihood of intubation or mortality. However, those treated with full-dose anticoagulation had a greater likelihood of intubation ($P < 0.001$), AKI ($P = 0.008$), and death ($P = 0.022$) (Supplemental Table 4, <http://links.lww.com/IDCP/A36>). No difference in mortality was observed between those treated with tocilizumab versus usual care when considering different levels of respiratory support on admission (Supplemental Table 5, <http://links.lww.com/IDCP/A37>).

Lower O₂ Requirement Subgroup

In a subset analysis of less critically ill patients, we examined data from only those patients who were on either nasal cannula oxygen or nonrebreather mask at the time of consideration for tocilizumab dosing excluding those on high flow, CPAP, BIPAP, and mechanical ventilation. Comparing the treated group ($n = 35$) with the control group ($n = 25$), no statistical difference was seen in age, sex, BMI, comorbidities, duration of symptoms before admission, or proportion of patients treated with steroids. However, a larger proportion of patients in the tocilizumab-treated group were treated with therapeutic dose anticoagulation compared with the control group (37% vs 12% respectively; $P = 0.030$). There was no significant difference between groups in peak D-dimer or CRP before or after tocilizumab dosing, but the tocilizumab-treated patients were more likely to normalize their CRP (71% vs 36%; $P = 0.006$). No differences were seen in rates of intubation (34% vs 28%), development of AKI (17% vs 20%), or mortality (34% vs 32%) when comparing tocilizumab-treated patients to usual care (Table 3).

Adverse Effects

Among our entire cohort, tocilizumab was very well tolerated with minimal adverse effects. Three patients in the tocilizumab-treated group and 2 in the control group developed thrombocytopenia of less than 100,000/ μ L, and 1 tocilizumab-treated patient developed an absolute neutrophil count of less than 2000/ μ L. Peak alanine aminotransferase (ALT) showed a tendency toward higher values in the tocilizumab-treated group compared with the control group max during hospitalization (Table 2); 13 (19%) patients in the tocilizumab group had ALT elevations greater than 5 times higher than baseline, and 8 (11.6%) had elevations to greater than 10 times higher than baseline ALT, compared with only 2 such patients each in the control group. However, there was no clinically significant liver dysfunction in either group, and liver function tests tended to normalize quickly. There were more bloodstream infections in the tocilizumab-treated patients, with 7 bacteremias and 4 fungemias compared with 4 bacteremias and 1 fungemia in the control group, but this did not achieve statistical significance.

DISCUSSION

Among patients hospitalized at Elmhurst Hospital Center in the early peak of COVID-19 in NYC with severe or critical COVID-19 disease, tocilizumab improved inflammatory markers but failed to show clinical benefit. Although controls were slightly older, the cases and controls were otherwise well matched. No improvements were seen in the tocilizumab-treated patients with regard to need for mechanical ventilation, mortality, or length of stay. The ability of tocilizumab to rapidly and dramatically lower the CRP did not translate into a clinical or mortality benefit, as has been hypothesized. In addition, patients who initially responded with decreased CRP, but then clinically worsened, had re-elevations of CRP (data not shown). This may suggest that we underdosed our patients or that redosing may have been beneficial.

The Food and Drug Administration–approved dose of tocilizumab for CRS is 8 mg/kg, with some providers choosing to repeat doses if clinical improvement is inadequate.¹³ In our population, we dosed patients with 400 mg of tocilizumab with no repeat dosing, based on the initial study from China by Xu et al.¹¹ This would not have achieved the 8 mg/kg dose for most of our patients, potentially affecting the observed outcomes. Results achieved in the Xu et al study were dramatically better than what was seen in our study. One potential explanation is that a 400 mg dose of tocilizumab may result in a higher dose per kilogram in the Chinese population, which may have a lower BMI compared with the population at our institution. A second explanation is that their patients may have been less severely ill, as suggested by the fact that 35% of their patients were on nasal cannula oxygen at the time of study entry and might have improved with no treatment at all. This is supported by the lower baseline CRP levels in their study (75 vs 252 mg/L in the present study), suggesting that the study population was not as sick, although CRP may have been decreased by the use of methylprednisolone in their cohort. In addition, the lack of comparator arm in the study by Xu et al makes the efficacy of the treatment in patients requiring less oxygen difficult to interpret. Another single-arm study looking at the use of tocilizumab in patients with severe (but not critical) COVID-19 demonstrated only 11% mortality in their cohort of 63 hospitalized patients,¹³ as compared with our mortality rates of 49% and 46% in the tocilizumab and control groups, respectively. Both studies suggest that if tocilizumab is used earlier in the disease course, there may be greater potential for benefit.

In our attempt to treat patients with higher chances of immediate and short-term survival, we prioritized patients for tocilizumab who were not already in renal failure, hypotensive, or requiring prolonged mechanical ventilation.^{14,15} All patients in both groups were severely hypoxic, with most on nonrebreather mask, CPAP, and BIPAP. Although the goal for using tocilizumab was to prevent or shorten the duration of mechanical ventilation, we saw no improvements in outcomes among tocilizumab-treated patients. Even after subgroup analysis excluding patients with invasive and noninvasive ventilation, no benefits were seen in the tocilizumab group, in the need for mechanical ventilation, survival, or length of stay. With the mortality so high in advanced COVID-19, and those with mild hypoxia often improving without specific therapy, the challenge is figuring out whether an optimal time frame for tocilizumab treatment exists to achieve clinical benefit.

Difference Between Coagulation and Inflammation

One interesting observation is the magnitude and direction of change of the inflammatory marker (CRP) with respect to the marker of coagulopathy (D-dimer). Although CRP decreased as expected in response to treatment with tocilizumab, D-dimer

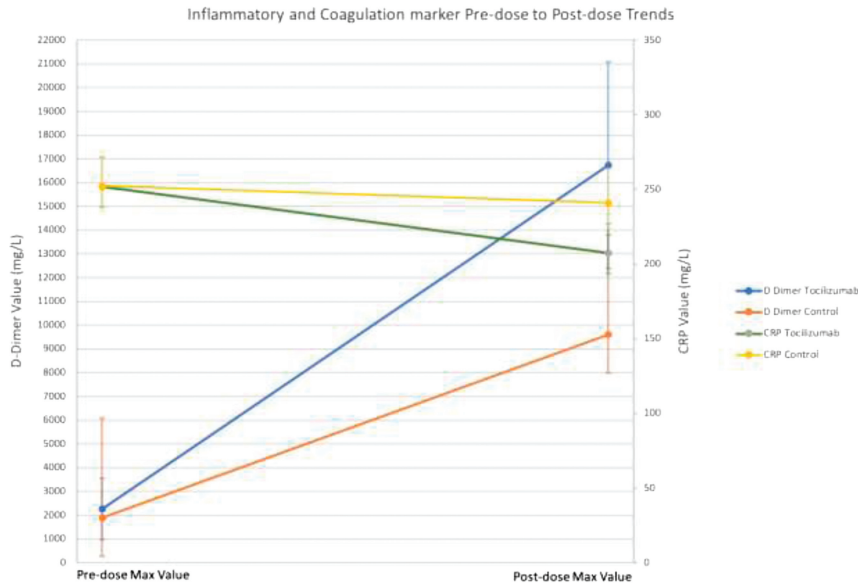


FIGURE 1. Inflammatory and coagulation marker predose to postdose trends.

increased (Fig. 1), particularly in patients who died. D-Dimer elevation after tocilizumab use in patients with COVID has been reported elsewhere, and it has been postulated that this elevation may be the result of a transient hypercoagulable state caused by the drug (vs due to late-phase COVID itself).¹⁶ Whether this potential effect can drive clinical complications such as embolic and clotting phenomena, and whether all patients receiving tocilizumab should receive a short period of anticoagulation, can only be answered by a randomized controlled trial. Nevertheless, this study has provided us with a unique opportunity to separate the inflammatory and coagulopathic aspects of COVID-19 disease. With the expected drop in CRP and rise in D-dimer appreciated in the tocilizumab-treated group, particularly among deceased patients, it seems that although inflammation can be tempered, the driving factor in disease progression and mortality seems to be related to the coagulopathic effect.

The caveat to the above conclusion is that there was greater mortality appreciated in those treated with full-dose anticoagulation. However, we recognize that at the time of this study, anticoagulation was only beginning to be appreciated as an important therapeutic modality. Hence, those that received full-dose anticoagulation may have been sicker than those receiving only prophylactic dosing. A more robust study in which a sufficient number of patients treated with and without both an IL-6 inhibitor and full-dose anticoagulation would be required to more clearly delineate this association.

Limitations

Limitations to this study include its retrospective nature, small sample size, and potential for bias in being unable to treat all patients meeting our treatment criteria. In addition, it is possible that the use of anticoagulation and systemic corticosteroids, 2 treatments that have now been shown to improve outcomes,^{17,18} may have confounded our results. Although our controls were well matched with respect to these treatments, and in fact, a higher percentage of the tocilizumab-treated patients received therapeutic anticoagulation (48% vs 37%) and systemic corticosteroids (35% vs 30%), this may imply that tocilizumab-treated patients may have been sicker and thereby chosen to receive these other treatments.

Tocilizumab failed to show short-term benefits in clinical outcomes in patients with hypoxic COVID pneumonia at our institution. However, we did witness that some patients had dramatic improvements after receiving this medication. The challenge is finding the right clinical scenario and timing of medication administration. Specifically, we wonder whether the drug may be efficacious if used earlier, at a higher dose, or with repeated dosing, particularly if there is no rapid clinical improvement or drop in CRP. In addition, one must consider whether the coadministration of corticosteroids with tocilizumab, as is done for CRS in (CAR)-T cell therapy and as guidelines in China suggest, would improve outcomes.^{19,20} Lastly, one must consider whether the use of IL-6 antagonists may have positive consequences on long-term lung function, which cannot be measured in a retrospective review such as ours. Long-term follow-up should be a secondary focus in any prospective trials to come.

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