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Outcomes in patients with severe COVID-19 disease treated with tocilizumab: a case–controlled study

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Summary

Background: COVID-19 is an ongoing threat to society. Patients who develop the most severe forms of the disease have high mortality. The interleukin-6 inhibitor tocilizumab has the potential to improve outcomes in these patients by preventing the development of cytokine release storm.
Aims: To evaluate the outcomes of patients with severe COVID-19 disease treated with the interleukin-6 inhibitor tocilizumab.
Methods: We conducted a retrospective, case–control, single-center study in patients with severe to critical COVID-19 disease treated with tocilizumab. Disease severity was defined based on the amount of oxygen supplementation required. The primary endpoint was the overall mortality. Secondary endpoints were mortality in non-intubated patients and mortality in intubated patients.
Results: A total of 193 patients were included in the study. Ninety-six patients received tocilizumab, while 97 served as the control group. The mean age was 60 years. Patients over 65 years represented 43% of the population. More patients in the tocilizumab group reported fever, cough and shortness of breath (83%, 80% and 96% vs. 73%, 69% and 71%, respectively). There was a non-statistically significant lower mortality in the treatment group (52% vs. 62.1%, $P = 0.09$). When excluding intubated patients, there was statistically significant lower mortality in patients treated with tocilizumab (6% vs. 27%, $P = 0.024$). Bacteremia was more common in the control group (24% vs. 13%, $P = 0.43$), while fungemia was similar for both (3% vs. 4%, $P = 0.72$).
Conclusion: Our study showed a non-statistically significant lower mortality in patients with severe to critical COVID-19 disease who received tocilizumab. When intubated patients were excluded, the use of tocilizumab was associated with lower mortality.

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Introduction

The global pandemic caused by the novel coronavirus SARS-CoV-2 (COVID-19) has spread to over 185 countries, with more than 7.5 million infections and over 420 000 deaths globally. In the USA alone, over 113 000 people have died from this disease.[1] The majority of infected patients have only mild or no symptoms at all. Approximately 19% of patients develop severe or critical disease.[2] Higher risk of mortality has been reported among patients with advanced age, male gender and those with underlying comorbidities, such as hypertension, coronary artery disease, heart failure, diabetes mellitus and chronic lung disease.[3,4]

The case fatality rate (CFR) for COVID-19 has been reported to be around 2.3%. This number increases to 6–10% in the presence of chronic cardiovascular and pulmonary conditions.[2] In patients admitted to the intensive care unit (ICU) who require intubation, the CFR can range from 26% to 88%.[2,5–7]

One of the most accepted explanations for the development of severe COVID-19 disease is an overproduction of proinflammatory cytokines. Autopsy studies in patients who died of Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS) have suggested that aberrant host immune response results in an inflammatory cytokine storm and lethal disease.[8] Several studies in patients with severe COVID-19 disease have shown an increased plasma concentration of inflammatory cytokines, including interleukin (IL)-6, IL-2, IL-10, interferon gamma and tumor necrosis factor alpha.[9,10]

Studies have reported that patients with severe COVID-19 disease have experienced rapid resolution of fever and improvement in oxygenation after treatment with tocilizumab.[7,11] This is a recombinant humanized anti-human IL-6 receptor monoclonal antibody that binds to the IL-6 receptor with high affinity. Tocilizumab is currently FDA-approved in the USA for the management of rheumatoid arthritis and chimeric antigen receptor T-cell-induced cytokine release syndrome. No clinical study has reported the use of tocilizumab among hospitalized patients with severe COVID-19 infection in the USA.

We retrospectively analyzed the outcomes of severe COVID-19 disease among patients who received tocilizumab under compassionate use.

Methods

Study site

The study was conducted at Maimonides Medical Center, a 711-bed tertiary care teaching hospital in Brooklyn, NY, USA. The Maimonides Medical Center institutional review board approved the study. The need for informed consent was waived based on the study's retrospective nature and designation as minimal-risk research.

Patient selection and data collection

We analyzed the information of adult patients hospitalized with severe to critical SARS-CoV-2 infection (COVID-19) who received tocilizumab between 8 March and 25 April 2020. The accepted method for diagnosis of COVID-19 was polymerase chain reaction (PCR) testing of a nasopharyngeal sample. Disease severity was defined based on the amount of oxygen supplementation required. Mild disease was defined as having an oxygen saturation above 95% on room air. Moderate disease referred to patients who required oxygen supplementation via nasal cannula up to 5 l/min to maintain an oxygen saturation of at least 95%. Severe disease was defined as requiring oxygen supplementation via face mask up to 10 l/min to maintain an oxygen saturation of 95% or higher. Very severe disease was defined by requiring a non-rebreather mask or high-flow nasal cannula to maintain an oxygen saturation of 95% or higher. Critical disease was defined by the need for intubation and mechanical ventilation. All interventions were done as part of regular patient care.

A control group of 97 patients with PCR-confirmed COVID-19 disease who had not received tocilizumab was included. Patients in the control group were required to be on supplemental oxygen that matched the treatment group. Individuals who died within 24 h of admission and those included in clinical trials with other biologic agents or convalescent plasma were excluded from the analysis.

Data were collected from the hospital's electronic medical record (Sunrise Clinical Manager). To ensure quality control, we performed manual data entry. The information collected included patients' demographics, presenting symptoms, comorbidities, home medications, initial vital signs, laboratory tests, treatment for COVID-19, and outcomes, including length of hospital stay, complications and mortality.

Endpoints

The primary endpoint was the overall mortality rate. Secondary endpoints were mortality in non-intubated patients only and mortality in intubated patients.

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 26.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were provided for all variables and presented as mean ± standard deviation for continuous variables and as number and percentage for categorical variables. Statistical tests of significance (Student's *t*-test for continuous variables and the χ^2 test or Fischer's exact test for categorical variables) were conducted to assess differences between the cohorts (treatment vs. control groups). A two-tailed *P* values ≤ 0.05 was regarded as statistically significant.

Results

Demographic and clinical characteristics

The demographic and clinical characteristics are shown in Table 1. A total of 193 patients were included in the study; 96 patients received the IL-6 inhibitor tocilizumab, while 97 patients served as the control group. The mean age was 60 years. Patients over 65 years of age represented 43% of the study population (37% in the treatment group vs. 49% in the control). Hypertension was present in 54%. Other comorbidities included diabetes (35%), atrial fibrillation (6%), heart failure (12%) and COPD (6%).

At presentation, more patients in the treatment group reported fever, cough and shortness of breath (83%, 80% and 96% vs. 73%, 69% and 71%, respectively). The average pulse oximetry oxygen saturation on admission was 84 ± 11 in the treatment group versus 88 ± 12 in the control group. The level of blood urea nitrogen was higher in the control group (25.9 ± 18.8 vs. 19.1 ± 10.7, $P = 0.002$). The initial CRP level was higher in the treatment group, but this was not statistically significant (17.1 ± 8.9 vs. 14.6 ± 9.6, $P = 0.074$). The admission values for

Table 1. Baseline and clinical characteristics

	Total (N = 193)	Tocilizumab group (N = 96)	Control group (N = 97)	P-value
Characteristic or condition				
Age (years)	60.4 ± 13.8	58.8 ± 13.6	62.0 ± 14	0.11
Age >65 years, *n* (%)	82 (42.5)	35 (36.5)	47 (48.5)	0.09
Male gender, *n* (%)	137 (71)	74 (77.1)	63 (64.9)	0.06
Race or ethnic group, *n* (%)				
White	106 (54.9)	49 (51.0)	57 (58.8)	
Black	17 (8.8)	7 (7.3)	10 (10.3)	
Hispanic	34 (17.6)	16 (16.7)	18 (18.6)	0.42
Asian	19 (9.8)	10 (10.4)	9 (9.3)	
Coexisting conditions, *n* (%)				
Hypertension	104 (53.9)	53 (55.2)	51 (52.6)	0.71
Diabetes	67 (34.7)	29 (30.2)	38 (39.2)	0.19
Stroke	7 (3.6)	4 (4.2)	3 (3.1)	0.72
Atrial fibrillation	11 (5.7)	4 (4.2)	7 (7.2)	0.36
Heart failure	18 (9.3)	7 (7.3)	11 (11.3)	0.33
Asthma	13 (6.7)	4 (4.2)	9 (9.3)	0.15
COPD	11 (5.7)	8 (8.3)	3 (3.1)	0.11
Active smoker	2 (1.0)	2 (2.1)	0	0.24
Active medications				
ACEi/ARB	64 (33.2)	36 (37.5)	28 (28.9)	0.2
Anticoagulation	18 (9.3)	9 (9.4)	9 (9.3)	0.98
Betablockers	60 (31.1)	32 (33.3)	28 (28.9)	0.5
Presenting symptoms				
Fever	151 (78.2)	80 (83.3)	71 (73.2)	0.08
Cough	144 (74.6)	77 (80.2)	67 (69.1)	0.07
Shortness of breath	161 (83.4)	92 (95.8)	69 (71.1)	<0.001
Myalgia	37 (19.2)	24 (25)	13 (13.4)	0.04
Vital signs				
Oxygen saturation (%)	86 ± 12	84 ± 11	88 ± 12	0.01
Respiratory rate (breaths/min)	28 ± 8	30 ± 8	26 ± 8	0.003
Disease severity—oxygen requirement, *n* (%)				
Mild disease—no oxygen required	1 (0.5)	0	1 (1)	0.31
Moderate disease—nasal cannula	11 (5.7)	6 (6.3)	5 (5.2)	0.74
Severe disease—face mask up to 10 l/min	6 (3.1)	0	6 (6.2)	0.02
Very severe disease—non-rebreather/high flow nasal cannula	59 (30.6)	29 (30.2)	30 (30.9)	0.91
Critical disease—intubated patients	121 (62.7)	61 (63.5)	60 (61.9)	0.8
Laboratory values				
White blood cell count (K/ml)	8.7 ± 4.4	8.9 ± 4.4	8.5 ± 4.5	0.5
Lymphocyte count (%)	12.5 ± 9.1	12.4 ± 9.6	12.6 ± 8.7	0.89
C-reactive protein (mg/dl)	15.9 ± 9.3	17.1 ± 8.9	14.6 ± 9.6	0.07
Ferritin (Ng/ml)	1014 ± 1072	1023 ± 934	1004 ± 1204	0.9
D-dimer (Ng/ml)	1839 ± 1951	1672 ± 2137	2228 ± 1392	0.19
Troponin I (Ng/ml)	0.19 ± 1.16	0.10 ± 0.41	0.28 ± 1.59	0.29
Procalcitonin (Ng/ml)	1.54 ± 5.01	1.09 ± 1.93	2.02 ± 6.90	0.23

ACEi, angiotensin–converting–enzyme inhibitors; ARB, angiotensin receptor blockers.

white blood cell count, lymphocyte count, ferritin level, D-dimer and troponin I were similar in both groups.

Management for COVID-19

Management of COVID-19 is detailed in Table 2. Most patients in both groups received hydroxychloroquine and azithromycin (92% and 92% for the treatment group and 97% and 94% for the control group). Corticosteroids were given to 43% of patients in the treatment group versus 33% in the control group ($P = 0.16$). Full-dose anticoagulation was used in 59% and 48% in the treatment and control groups, respectively ($P = 0.2$). Remdesivir was used in 13% of patients in the treatment group versus 9% in the control group. Antibiotics for suspected bacterial infections were used in 94% in the treatment group and 89% in the control group. Vasopressors were used in 60% of patients in the treatment group versus 47% in the control group. Twenty-two percent of patients in the treatment group developed acute renal failure that required renal replacement therapy (RRT); this occurred in 13% of patients in the control group.

Outcomes

There was a non-statistically significant reduced mortality in the treatment group (52% vs. 62%, $P = 0.09$) (Table 3). When excluding intubated patients, those in the treatment group had a lower mortality (6% vs. 27%, $P = 0.024$). The length of hospital stay, excluding patients who remained hospitalized at the time

Table 2. Treatment for COVID-19

Medication, *n* (%)	Total (*N* = 193)	Tocilizumab group (*N* = 96)	Control group (*N* = 97)	*P*-value
Hydroxychloroquine	183 (94.8)	89 (92.7)	94 (96.6)	0.21
Azithromycin	180 (93.3)	89 (92.7)	91 (93.8)	0.09
Corticosteroids	73 (37.8)	41 (42.7)	32 (33)	0.164
Full-dose anticoagulation	104 (53.8)	57 (59.4)	47 (48.5)	0.2
Remdesivir	21 (10.9)	12 (12.5)	9 (9.3)	0.47
Vitamin C	28 (14.5)	18 (18.8)	10 (10.3)	
Zinc	30 (15.5)	9 (9.4)	21 (21.6)	0.004
Both	84 (43.5)	50 (52.1)	34 (35.1)	
Antibiotics for suspected bacterial infection	176 (91.2)	90 (93.8)	86 (88.7)	0.21

Table 3. Outcomes

Outcomes, *N* (%)	Total (*N* = 193)	Tocilizumab group (*N* = 96)	Control group (*N* = 97)	*P*-value
Overall mortality	98 (50.8)	43 (44.8)	55 (56.7)	0.09
Mortality in non-intubated patients (excluding patients still hospitalized)	11 (16.4)	2 (6.1)	9 (26.5)	0.024
Mortality in intubated patients (excluding patients still hospitalized)	86 (71)	41 (67.2)	45 (75)	0.34
Length of stay, excluding patients still hospitalized (days ± SD)	15.3 ± 9.9	14.5 ± 8.8	16.5 ± 10.8	0.329
Bacteremia	35 (18.1)	12 (12.5)	23 (23.7)	0.04
Fungemia	7 (3.6)	4 (4.2)	3 (3.1)	0.72
Renal replacement therapy (RRT)	35 (18.1)	22 (22.9)	13 (13.4)	0.08
Need for ECMO	1 (0.5)	1 (1)	0	0.49
Need for vasopressors	113 (58.5)	59 (61.5)	54 (55.7)	0.41

of submission, was lower in the treatment group; however, this finding was not statistically significant (15 vs. 17 days, $P = 0.32$).

Bacteremia was more commonly found in the control group (23.7% vs. 12.5%, $P = 0.04$), whereas fungemia was similar in both groups (4% vs. 3% $P = 0.7$). More patients in the treatment group required RRT; however, this was not statistically significant (23% vs. 13%, $P = 0.08$). There was no difference in the use of vasopressors (62% vs. 56%, $P = 0.41$).

Discussion

We analyzed the clinical characteristics and outcomes of 96 patients with severe to critical COVID-19 disease who received a single dose of the IL-6 inhibitor tocilizumab as part of their treatment. A group of 97 consecutive patients with confirmed severe to critical COVID-19 disease served as the control group.

Our study shows an overall mortality rate of 51%. This ranged from 16% in non-intubated patients to 71% in those who required intubation and mechanical ventilation. Patients in the treatment group had lower mortality than those in the control group; however, this was not statistically significant. When intubated patients were excluded, mortality was significantly lower in the treatment group.

Several authors have reported the potential benefits of tocilizumab in patients with COVID-19 disease.[7,11,12] Xu *et al.*[7] described their experience with this agent in 21 patients considered to have severe to critical COVID-19 disease. Their sample included two patients (10%) on mechanical ventilation and seven (35%) on oxygen supplementation via nasal cannula. Oxygen supplementation was de-escalated within 5 days from drug administration in 15 out of 20 patients (75%). All patients were discharged alive, and no significant adverse effects from the medication were reported. In another case series with 15 patients, three out of seven subjects (42%) classified as having critical COVID-19 disease died despite receiving tocilizumab. The rest of the patients were reported to have a fast recovery. One-third of the patients received more than one dose of the medication.[11] These authors highlight the potential benefit of tocilizumab when its use is implemented before the disease is too advanced. This is further underscored by the results reported by Capra *et al.*[13] In a cohort of non-intubated patients with COVID-19 disease, they found a lower mortality rate (8% vs. 57.9%) in those treated with tocilizumab.

Our findings correlate with these other reports. The use of tocilizumab did not affect the mortality rate in patients who were intubated. However, in the non-intubated population, the use of tocilizumab was associated with a lower mortality. None of the patients in our study received more than one dose of tocilizumab. Some authors propose using more than one dose of the medication in patients with persistently elevated inflammatory markers.[7,11]

In a case–control study with 20 patients treated with tocilizumab, Klopfenstein *et al.*[14] described a lower composite endpoint of mortality and ICU admission in the tocilizumab group. This difference was driven by a higher percentage of ICU admissions in the standard therapy group (44% vs. 0%, $P \leq 0.001$). When analyzed separately, the difference in mortality was not statistically significant.

In another study, Toniati *et al.*[15] reported their results on 100 consecutive patients treated with multiple doses of tocilizumab for severe to critical COVID-19 disease. They found a mortality of 18% in patients receiving non-invasive ventilation (severe and very severe disease). This is higher than the 6% found in our study. In those who were intubated, they reported a mortality of 24%. Only 15 patients were reported as being discharged (15%), suggesting that a significant number of patients might not have had a definitive outcome at the time of the analysis. In contrast to these findings, Colaneri *et al.*[16] found no difference

in ICU admission or mortality in patients with severe COVID-19 disease treated with tocilizumab. They conducted a case–control study with 21 patients treated with the drug and 21 propensity score-matched controls.

Some pitfalls of most of the previously reported studies are either a small sample size, lack of a control group or both. Our study represents the largest case–control study of patients with severe COVID-19 disease treated with tocilizumab in the USA.

A valid concern regarding the use of tocilizumab, and other biologic agents, is the risk of infections. Studies done in patients with rheumatologic disorders have reported a potential risk for developing serious infections with the use of tocilizumab.[17,18] Our study showed a lower rate of bacteremia in the treatment group and a similar rate of fungemia in both groups.

Limitations

Our study has several limitations that are inherent to its retrospective nature. First, the control and treatment groups were not matched. This could potentially explain the lack of benefit in intubated subjects. More patients in the treatment group were of male sex, reported more fever, cough and shortness of breath and presented with lower oxygen saturation. Despite these differences, patients with lower disease severity (non-intubated) did show better outcomes. Second, we excluded patients who received other biologic agents and convalescent plasma. This could represent a selection bias. However, our intention was to assess the outcomes with tocilizumab alone. Third, our treatment group received only one dose of tocilizumab, while other studies have reported the use of multiple doses. Currently, there is no consensus on the correct dose or timing of administration for tocilizumab.

Conclusions

Our study showed a non-significant trend toward lower mortality in patients with severe to critical COVID-19 disease treated with tocilizumab. When intubated patients were excluded, those who received tocilizumab had a lower mortality. Randomized clinical trials are needed to confirm these and other findings and provide more information regarding dosing, short- and long-term adverse effects, and proper timing of administration.

Conflict of interest: The authors declare that there is no conflict of interest regarding the publication of this article. .

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