Incidence of Secondary Bacterial Infections Following Utilization of Tocilizumab for the Treatment of COVID-19 – A Matched Retrospective Cohort Study

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Abstract

Introduction: Immunosuppressive agents are theorized to target the cytokine storm syndrome in COVID-19. However, the downstream effects regarding susceptibilities to secondary infection risk remains unknown. This study seeks to determine risk differences for secondary infections among COVID-19 patients who did and did not receive tocilizumab. **Methods:** We conducted a matched retrospective cohort study from two large, acute care hospitals in Western Connecticut from March 1, to May 31, 2020. We collected variables using manual medical record abstraction. The primary exposure variable was any dose of tocilizumab. The primary outcome was any healthcare-associated bacterial or fungal infection as defined by the National Healthcare Safety Network. We performed a Kaplan–Meier analysis to assess the crude difference in cumulative probability of healthcare-associated infection (HAI) across exposure groups. We also performed a multivariable Cox regression analysis to determine the hazard ratio for HAI by exposure group while controlling for potential confounders. **Results:** The Kaplan–Meier analysis demonstrated no difference in the cumulative probability of HAI across groups. The adjusted hazard of HAI for patients given tocilizumab was 0.85 times that of patients not given tocilizumab (95% confidence interval = 0.29, 2.52, $P = 0.780$) after controlling for relevant confounders. **Conclusions:** Tocilizumab did not increase the incidence of secondary infection among COVID-19 patients. Larger, randomized trials should evaluate infection as a secondary outcome to validate this finding.

Keywords: Coronavirus, COVID-19, IL-6, SARS-CoV-2, secondary infection, tocilizumab

INTRODUCTION

Coronavirus-19 (COVID-19) is a novel viral infection that surged early in 2020 with limited evidence of effective treatment strategies.[1] The virus may result in asymptomatic to mild cases but is also capable of causing severe disease with high mortality in others. The late phase of infection is characterized by pathological hyper-activation of the immune system and significantly elevated inflammatory cytokines such as interleukin-6 (IL-6).[2-4] This cytokine release syndrome (CRS), or "cytokine storm," often leads to rapid clinical deterioration and death and requires swift management with medication to suppress the immune system.[4]

Tocilizumab (Genentech, San Francisco, USA) is a humanized recombinant monoclonal antibody and IL-6 receptor antagonist that has historically been used to treat rheumatoid arthritis.[5] Considered off-label for the treatment of COVID-19, rheumatologists and other clinicians suggest it may be a useful tool to combat CRS.[6-11] However, most of the evidence to support this approach is anecdotal or derived from small case studies.[12-15] A search of the U. S. National Library of Medicine clinical trials registry identified 23 protocols registered to study tocilizumab in COVID-19 patients.[16] However, all either were in the preparation or recruitment phase or had been withdrawn completely. Reports from clinical trials of tocilizumab in patients with rheumatoid arthritis documented an increased risk of serious infection in patients who received the medication.[17-22] The few studies that evaluated tocilizumab

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Access this article online

Quick Response Code:

Website:
www.jgid.org

DOI:
10.4103/jgid.jgid_358_20

in COVID-19 patients documented secondary infections as well, though most did not compare groups statistically.[13,15,23]

Given the mechanism of action and existing evidence, it is a logical concern that tocilizumab may place patients at higher risk for secondary healthcare-associated infection (HAI). However, no studies to date have assessed the incidence of HAI in COVID patients that received tocilizumab compared to those who did not. The primary objective of this study was to determine the difference in the incidence of secondary healthcare-associated bacterial and fungal infections among patients with COVID-19 given exposure to tocilizumab. We hypothesized that patients who received tocilizumab during their inpatient treatment for COVID-19 had a greater rate of HAI than those who did not receive tocilizumab after controlling for relevant confounders. This study can provide moderate evidence to support clinical decision making for COVID treatment while awaiting the results of clinical trials.

METHODS

Study design and sampling

To meet our objective, we conducted a matched retrospective cohort study. We selected patients from two large, acute care hospitals in western Connecticut heavily impacted by the COVID-19 surge between March 1st, and May 31st, 2020. We included patients in the study if they were >18 years old, admitted as inpatients during this timeframe, and billed with the ICD-10 code for COVID-19 (U.07.1). We excluded patients if they had a bacterial or fungal infection present at the time of admission or were taking immunosuppressant medications.

We further refined our sample by identifying all patients prescribed tocilizumab during their inpatient stay. We matched patients using a 1:1 ratio to develop a corresponding control group among patients who did not receive tocilizumab.[24] We used individual matching by age group (10-year increments), gender, and admission to the intensive care unit and excluded patients from the study if they did not successfully match with a control. In total, there were 128 total patients in the study with 64 in each group who received and did not receive tocilizumab, respectively [Figure 1]. We did not follow patients beyond time to event being either infection, discharge or death.

Measures

We collected all variables using manual medical record abstraction. The primary outcome was any healthcare-associated bacterial or fungal infection, including bloodstream, urinary tract, skin, soft tissue, organ-space, and pneumonia. We used the National Healthcare Safety Network (NHSN) definitions to identify infections both associated with and independent of invasive devices (i.e., central line, Foley catheter, ventilator).[25] We documented patients as having the primary outcome if they met all site-specific or device-associated criteria. Patients who met some but not all criteria were not documented as positive for the primary outcome (i.e., positive urine culture with <100,000 cfu/ml). We also documented the infection event date for time-dependent analyses.

The primary exposure variable was any dosage of tocilizumab administered to a patient with COVID-19. We documented the date of first administration for time-dependent analyses.

We included age as a continuous variable in our analysis since matches were performed in increments of 10 years. We also included central line, Foley catheter, and ventilator days as confounders, defined as the number of days a patient had the invasive device from date of placement to date of discontinuation. We also included co-morbidities that may contribute to infection such as diabetes, active cancer, and body mass index (BMI) (continuous). Finally, we included whether the patient received hydroxychloroquine or had surgery during the relevant inpatient stay.

Statistical analyses

We used StataSE 16 for all statistical analyses.[26] We computed descriptive statistics to reflect the number and percentage of patients for each categorical variable and mean with standard deviation for continuous variables. We performed univariate analyses to assess exposure group differences with the Chi-square and independent student's t tests. There were no missing data in this dataset, and the alpha for all hypothesis testing was set *a priori* at 0.05.

We included tocilizumab as a time-varying variable in all analyses.[27] Entry into the cohort began at admission for all patients to account for immortal time bias. The event date in the analysis corresponded with the infection event date defined by NHSN.[25] We did not follow patients for infection postdischarge and censored patients at date of discharge or death (for those who expired without experiencing the event).

We performed a Kaplan–Meier analysis to assess the crude difference in cumulative probability of HAI across exposure groups and used the log-rank test to determine the difference in survival functions. We also performed Cox regression analysis to determine the hazard ratio, 95% confidence interval (CI), and *P* value for HAI by exposure group. We included age, central line, Foley catheter, and ventilator days, BMI, diabetes, cancer, administration of hydroxychloroquine, and inpatient surgery in the model to account for hypothesized confounding per the classical definition. Each covariate has an evidence-based association with the outcome and
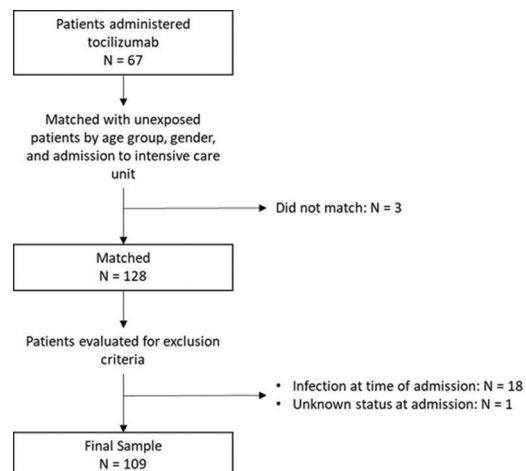

Figure 1: Study enrollment for matched retrospective cohort. N = number

is not in the causal pathway. Finally, we verified the assumption for proportional hazards by examining Schoenfeld residuals.

RESULTS

Sample characteristics

We identified 67 patients who met the inclusion criteria and received tocilizumab during their inpatient stays [Figure 1]. Three patients did not match with any controls and were eliminated from the sample. Of note, two of three patients were between 18 and 21 years old. Given the low prevalence of COVID-19 in this age group during the surge, it is not surprising they failed to match. The remaining 64 patients matched successfully, and we reviewed 128 patient records for exclusion criteria. We identified 18 patients with bacterial or fungal infections present on admission and removed them from the sample ($N_{unexposed} = 13$; $N_{exposed} = 5$). One patient transferred in from another facility and did not have information available regarding infections at time of admission. After that exclusion, the final sample size was 109.

The mean age of patients in the sample was 56.3 years, and the majority of the sample was male (73.4%) and predominantly non-Hispanic (52.3%) [Table 1]. The majority of patients who did not identify as a race were Hispanic (77.1%). There were no exposure group differences in any of the covariates, though the mean length of follow-up time in the cohort was longer in the exposed group than the unexposed group (10.7 days vs. 7.9 days, respectively). The median time from admission to tocilizumab administration was 3 days (range = 0–12).

Kaplan-Meier analysis

There were 19 HAIs identified in the sample [Table 2]. The Kaplan–Meier survival curve stratified by exposure group is shown in Figure 2. We found there was not a statistically significant difference in the time to event across exposure groups (log-rank test: $P = 0.81$).

Cox regression

We verified that the crude and full models met the assumption of proportional hazards. Neither the crude nor the adjusted Cox regression analysis demonstrated a statistically significant difference in the hazard rate of HAI between exposure groups. The crude hazard rate of HAI for patients given tocilizumab was 0.97 times that of patients not given tocilizumab (95% CI = 0.37, 2.52, $P = 0.943$). The adjusted hazard rate of HAI for patients given tocilizumab was 0.85 times that of patients not given tocilizumab (95% CI = 0.29, 2.52, $P = 0.780$) after controlling for age, device days, BMI, diabetes, cancer, hydroxychloroquine, and inpatient surgery.

DISCUSSION

Tocilizumab may be a viable treatment for the CRS seen in later stages of COVID-19 infections. Due to its mechanism of action

Table 1: Descriptive statistics for COVID-19 patients selected into the sample from two Western Connecticut healthcare facilities between March 1 and May 31, 2020

Variables	Total (*n*=109)	Unexposed* (*n*=50)	Exposed (*n*=59)	*P*
Age, mean (SD)	56.3 (13.7)	55.2 (13.3)	57.2 (14.0)	0.439
Body mass index, mean (SD)	31.0 (6.5)	29.7 (6.1)	32.0 (6.7)	0.069
Length of follow-up time‡, mean (SD)	9.4 (5.9)	7.9 (5.6)	10.7 (5.9)	0.010
Length of time in intensive care§, mean (SD)	8.7 (7.4)	7.8 (7.4)	9.4 (7.5)	0.467
Central line days‖, mean (SD)	10 (7.0)	9.9 (7.3)	10.0 (7.0)	0.965
Foley catheter days¶, mean (SD)	9.7 (7.7)	9.1 (8.5)	10.2 (7.1)	0.631
Ventilator days**	9.4 (7.5)	8.1 (7.4)	10.6 (7.6)	0.292
Gender (male), *n* (%)	80 (73.4)	37 (74.0)	43 (72.9)	0.895
Race, *n* (%)				
White	48 (44.0)	22 (44.0)	26 (44.1)	0.164
Black/African American	10 (9.2)	8 (16.0)	2 (3.4)	
Asian	1 (0.9)	0 (0.0)	1 (1.7)	
Indian	6 (5.5)	17 (34.0)	27 (45.8)	
Does not identify	44 (40.4)	3 (6.0)	3 (5.1)	
Ethnicity, *n* (%)				
Non-Hispanic	57 (52.3)	29 (58.0)	28 (47.5)	0.192
Hispanic	48 (44.0)	18 (36.0)	30 (50.8)	
Does not identify	4 (3.7)	3 (6.0)	1 (1.7)	
Diabetes (yes), *n* (%)	34 (31.2)	13 (26.0)	21 (35.6)	0.281
Cancer (yes), *n* (%)	5 (4.6)	2 (4.0)	3 (5.1)	0.787
Surgery (yes), *n* (%)	3 (2.8)	1 (2.0)	2 (3.4)	0.659
Hydroxychloroquine (yes), *n* (%)	75 (68.8)	37 (74.0)	38 (64.4)	0.281
Intensive care (yes), *n* (%)	52 (47.7)	24 (48.0)	28 (47.5)	0.955
Healthcare-associated infection (yes), *n* (%)	19 (17.4)	7 (14.0)	12 (20.3)	0.385

*Primary exposure is tocilizumab, ‡Time from admission to censor due to event or discharge, §Among patients in the intensive care unit (*n*=52), ‖Only among patients that had a central line (*n*=42), ¶Only among patients that had a Foley catheter (*n*=46), **Only among patients with a ventilator (*n*=44), ‡‡%: Percent; mean days. SD: Standard deviation, *n*: Number, BMI: Body mass index

Table 2: Description of healthcare-associated infections experienced by patients in the sample to determine the difference in secondary bacterial and fungal infections following the use of tocilizumab among COVID-19 patients

Infection type (NHSN code)	Exposure group[†]	Age	Microorganism
Central line-associated LCBI 1	Exposed	74	*Bacteroides* spp.[‡]
ENDO	Exposed	57	Methicillin-resistant *Staphylococcus aureus*
GIT	Exposed	63	Imaging only
LCBI 1	Exposed	54	*Serratia* spp.
PNU1	Exposed	72	N/A
VAC	Exposed	40	N/A
VAC	Exposed	30	N/A
VAC	Exposed	72	N/A
VAC	Exposed	54	N/A
VAP	Exposed	40	N/A
LCBI 1	Unexposed	56	*Candida albicans*
PNU1	Unexposed	51	N/A
PNU1	Unexposed	68	N/A
VAC	Unexposed	77	N/A
VAC	Unexposed	55	N/A
VAC	Unexposed	30	N/A

[†]Primary exposure is tocilizumab, [‡]Species pluralis. NHSN: National Healthcare Safety Network, LCBI: Laboratory-Confirmed Bloodstream Infection, ENDO: Endocarditis, GIT: Gastrointestinal infection, VAC: Ventilator-associated condition, VAP: Ventilator-associated pneumonia, PNU1: Pneumonia, N/A: Does not require isolation of microorganism to meet infection criteria
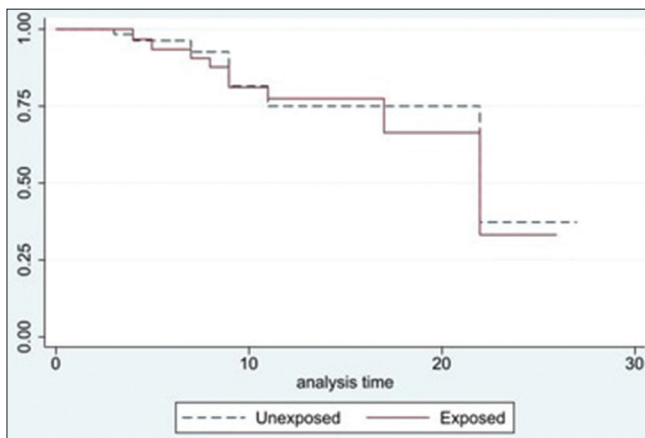

Figure 2: Kaplan–Meier survival estimates for patients exposed and not exposed to tocilizumab

and previous data from the rheumatoid arthritis population, there is a concern regarding the potential increased risk of HAIs with tocilizumab administration.[19] Several clinical trials are underway that test tocilizumab for the treatment of COVID-19 and our study can help for developing treatment protocols. Our study was notable for the lack of statistically different rates of HAIs and bacteremia, but a statistically significant difference in length of stay when comparing COVID-19 patients who did and did not receive tocilizumab.

We hypothesized that patients who received the IL-6 inhibitor would experience a higher incidence of HAI after controlling for confounders such as age, device days, and other risk factors. Our finding of no increased secondary infection rates in COVID-19 patients treated with tocilizumab is reassuring to clinicians who have used or are using this therapy for the treatment of CRS. The CI of the adjusted hazard ratio was between 0.29 and 2.52, however, making the point estimate difficult to interpret.

Other studies had similar findings with no significant differences in rates of bacteremia among those exposed to tocilizumab, although these were calculated as a secondary analysis.[28,29] The largest observational study of tocilizumab use in COVID-19 completed at Yale University reported a bacteremia rate of 4% in patients administered tocilizumab, lower than rates reported from China and New York City of 8% and 6%, respectively.[29-31] Our reported bacteremia rate was 5.1% in the patients who were exposed to tocilizumab versus 2.0% ($P = 0.623$). Although slightly higher than that reported at Yale, the difference is still not statistically meaningful.

In our study, the only statistically significant difference between groups was length of follow-up time. The patients exposed to tocilizumab had a longer time to event of infection, death, and/or discharge. There was one observed outlier in the tocilizumab group that received tocilizumab on day 12 of hospitalization, which likely skewed the results. However, the standard deviations were similar between both groups. Tocilizumab administration has been associated with longer hospital stays, thought to be due to both timing of drug administration and monitoring of potential complications. In our study, although matched for confounders, the patients who received tocilizumab may have had an observed higher clinical burden, which may also require longer hospital stays. A longer hospital stay could also be explained by multiple factors such as lack of clinical improvement, discomfort among providers and limited supply of medication.

This study was limited by the study design as this was not a randomized control trial and is at risk of selection and indication bias. This was also a small sample size with a wide CI which may be leading to a Type II error. A true difference in secondary infection rates may yet exist, and a larger study better powered

to detect such a difference would provide further information. One of the significant limitations of this study was the challenge of defining a secondary infection. The NHSN definition for secondary infections has strict diagnostic criteria that may differ from clinical practice. Differentiating co-infection with a bacterial or viral pneumonia on presentation, as well as identifying secondary pneumonias, was difficult. Although a poor potential marker of secondary pneumonias, ventilator-associated events were included and sensitivity analyses that removed these from the analysis did not change the results observed. Finally, we did not follow patients beyond discharge, so the long-term consequences of tocilizumab remain unknown.

Conclusions

Based on this study, it appears that receiving tocilizumab for the treatment of COVID-19 does not increase the incidence of secondary infections. Currently, there are several randomized clinical trials that are underway that test the safety and efficacy of tocilizumab for CRS in COVID-19, our trial can provide some reassurance regarding secondary infection rates.

Research quality and ethics statement

This study was approved by the Institutional Review Board / Ethics Committee approval number 20-12-108-337(c20). The authors followed applicable EQUATOR Network (http://www.equator-network.org/) guidelines during the conduct of this research project.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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