Treatment Patterns of Tocilizumab Utilization for Progressive Respiratory Distress during the COVID-19 Pandemic

Kimberly R. Barber[1,*], Kristen Hartnett[2], Jennifer R. Hella[1], Roya Z. Caloia[2] and Virginia LaBond[2]

[1]*Department of Research, Ascension Genesys Hospital, Grand Blanc MI, 48439, USA*

[2]*Department of Emergency Medicine, Ascension Genesys Hospital, Grand Blanc MI, 48439, USA*

Abstract: *Purpose*: This study's objective was to describe treatment patterns of patients receiving then experimental drug tocilizumab for severe respiratory illness.

Methodology: It is a retrospective case series of patients receiving tocilizumab for COVID-19 at a 380-bed hospital between 03/01/202 and 05/31/2020. Treatment patterns for tocilizumab for this series of ICU patients was modeled using a Spearman rho correlation for ranked associations.

Results: There was significant variation in frequency and serial testing of inflammatory markers. There was no correlation between tocilizumab initiation and worsening respiratory status (r=0.19, p=.48) or between days since dosing and survival (R= -0.02, p= .95). No clear pattern emerged from tocilizumab administration during the pandemic.

Conclusion: Protocols for untested new treatments are needed to overcome the uncertainty physicians face during pandemics.

Keywords: Respiratory Distress, COVID 19 Treatment, Tocilizumab.

1. INTRODUCTION

The World Health Organization (WHO) declared COVID-19 a pandemic on March 11th, 2020 [1]. Infection had escalated in the United States with hospitalizations quickly overwhelming the healthcare system [2]. Clinical features of patients diagnosed with COVID-19 in early 2020 suggested that up to 29% of severe cases had a progression of respiratory injury developing into acute respiratory distress syndrome (ARDS) [3]. ARDS was largely attributed to a severe cytokine storm that many patients were experiencing [4]. Review of pathologic characteristics of patients dying of COVID-19 demonstrated interstitial pulmonary infiltrates, pulmonary edema and increased serum concentrations of highly pro-inflammatory cytokines including interleukin-6 which plays an important role in inflammatory reaction and immune response [5].

An early front runner in the treatment for severely ill Covid-19 patients was tocilizumab, a monoclonal antibody that inhibits interleukin-6 from binding to signaling receptors [6]. Tocilizumab was approved for treatment of rheumatoid arthritis in 2010 and at the time of the early pandemic, the product was not labeled for use regarding this discussion and was considered investigational during the midpoint of the pandemic when an emergency use authorization was granted in June 2021. Randomized trials from the first half of 2020 suggested slight but significantly less clinical deterioration among patients treated with tocilizumab but no mortality benefit [7]. Trials continued to be reported in the second and third quarter of 2020 that contradicted the early findings [8,9].

1.1. OBJECTIVE

We undertook a case series of severely ill Covid-19 patients to determine whether consistencies existed for those receiving tocilizumab while hospitalized during the initial pandemic.

2. MATERIALS AND METHODS

This case series was performed at a 380 -bed Midwestern suburban community hospital. It was approved by the Ascension Genesys Institutional Review Board on June 9, 2020 (ME 20 020). The study is a retrospective review and was approved as an expedited submission which included consent and HIPAA authorization waiver.

3. DATA SOURCE

Pharmacy records were reviewed to identify all patients receiving Tocilizumab (TCB) for the treatment of COVID-19 from 03/01/2020 - 05/31/2020. Following identification of these patients and retrospective review and analysis of their medical record, characteristics and treatment variations were identified.

*Address correspondence to this author at the Department of Research, Ascension Genesys Hospital, Ste 2452 One Genesys Parkway, Grand Blanc Mi, 48439, USA; Tel: 810.606.7722; E-mail: kimberly.barber@ascension.org

Retrospective chart review was performed for day 0 through day 30 of hospitalization. We recorded patient demographics, respiratory status pre and post tocilizumab administration, co-treatment with other medications, frequency of laboratory values and imaging being obtained as well as final outcome for patients. Respiratory status was quantified on an interval scale according to type of support (0= room air, 1= nasal cannula, 2= hi flow oxygen, 3=bipap, 4= ventilator). Respiratory decline was defined as a numerical increase on the scale in requirement for respiratory support from their initial status.

4. STATISTICAL MODELING

4.1. Univariate Analysis

Data was descriptively analyzed using means and standard deviations to report on continuous variables such as age and total dosage. Individual dosages, respiratory status and time (length of ICU stay in days) were analyzed by medians. Rates and percentages were calculated for dichotomous and frequency variables such as gender, presence of comorbid conditions and type of medication.

4.2. Bivariate Analysis

The Spearman correlation coefficient for ranked variables was used to model the correlation between tocilizumab days since dosing and survival. For the sample, n raw days X_i Yi were converted to ranks R(Xi), R(Yi) and rs is computed as

$$R_s = pR(X), R(Y) = \frac{\text{cov}(R(X), R(Y)}{{}^{\sigma}R(X)\,{}^{\sigma}R(X)}$$

Where:

p denotes Pearson correlation coefficient applied to the rank variables.

$\text{cov}(R(X), R(Y)$ is the covariance of the rank variables.

${}^{\sigma}R(X)\,and\,{}^{\sigma}R(X)$ are the standard deviations of the rank variables.

The ranks are computed using the formula:

$$R_s = \frac{1 - 6\Sigma\, d^{2i}}{n(n^2 - 1)} \quad (1)$$

Where:

d is the difference between the two ranks of each observation and n is the number of observations.

The Pearson r correlation coefficient for normally distributed variables was used to model the correlation between total dosage and respiratory status. The above model was used except the independent and dependent variables retained their parametric characteristics for continuous and median values.

Table 1: Patient Characteristics

Demographics	
	N=15*
Age (Mean, SD)	60.1 (15.6) Range (21 - 90)
Gender (n,%)	
Male	9 (60)
Female	6 (40)
Race (n,%)	
Caucasian	7 (46.7)
African American	6 (40)
Asian	1 (6.7)
Missing	1 (6.7)
Comorbidities (n,%)	
Diabetes	10 (66.7)
Chronic Obstructive Pulmonary Disease	2 (13.3)
Obesity	6 (40)
Hypertension	11 (73.3)
Hyperlipidemia	7 (46.7)
Adjunct COVID-19 Pharmacotherapy (n,%)	
Tocilizumab	15 (100)
Azithromycin	14 (93.3)
Plaquenil	12 (80)
Methyl prednisone	15 (100)
Remdesivir	1 (6.7)
Convalescent Plasma	1 (6.7)
Inflammatory Laboratory Markers	
CRP (n, %)	
Day -1	2 (13.3)
Day 0	4 (26.6)
Day +1	3 (20)
Ferritin (n, %)	
Day -1	5 (33.3)
Day 0	8 (53.3)
Day +1	8 (53.3)
D-Dimer (n, %)	
Day -1	5 (33.3)
Day 0	9 (60)
Day +1	10 (66.7)

*All denominators are n=15.

5. RESULTS AND DISCUSSION

Of 17 patients having received tocilizumab, 15 patients (6 women and 9 men) were identified to have received the medication as part of the treatment regimen for COVID-19 illness. Demographic data for patients reviewed can be seen displayed in Table **1**.

All 15 patients received tocilizumab, either as a single dose (400 mg) or twice (total of 800 mg). Day of first tocilizumab dose given varied for each patient with no clear pattern in terms of ventilator initiation or when respiratory status worsened (Table **2**). Even though the first day of respiratory decline and first day of ventilator initiation were highly correlated (r=0.90, p≤.001), there was no correlation between the day of tocilizumab initiation and day of worsening respiratory status (r=0.19, R^2= .038, p=.48) or between the day of tocilizumab initiation and day of ventilator initiation (r= -0.02, R^2= .004, p=.31). Treatment with other medication modalities varied largely across the 15 patients (Table **1**).

Respiratory status on presentation to the hospital varied significantly across the patients: one on room air, seven on nasal cannula support, two on high flow oxygen support, one patient on Bipap support and four patients on mechanical ventilation. On the day of tocilizumab administration: one patient was on nasal cannula, two on high-flow, two on BiPAP and ten patients were on mechanical ventilation. Respiratory status was trended for seven days following tocilizumab administration (day 0), with irregular and diverse shifts in status demonstrated (Figure **1**). Figure **1** presents the correlation between the day of tocilizumab initiation and day of worsening respiratory status showing no pattern (nor significant correlation) between the two (r=0.19, R^2=.038, p=.48). There was no consistent pattern of tocilizumab associated with severity (worsening or improving respiratory status).

The frequency with which laboratory values, including D-Dimer, CRP and Ferritin (inflammatory) were obtained in the peri-tocilizumab administration period were recorded and demonstrated significant variation between and across patients in frequency and serial testing. The frequency with which inflammatory markers were evaluated in the day preceding, day of and day following tocilizumab administration are summarized in Table **1**.

Chest x-rays were the primary imaging obtained on patients with COVID illness having received tocilizumab and the frequency was near daily. Of the 30 days of hospitalization that data was obtained for each patient, the majority of patients had x-rays obtained daily (incidence density = 89%).

Six patients died during hospitalization, six were discharged to home and three were discharged to an extended-care or subacute-rehabilitation facilities. There was no correlation between days since tocilizumab dosing and survival (Table **2**: R= -0.02, p=.95).

One of the more reliable indications of patients' illness severity and progression was their respiratory status. Figure **1** illustrates patients oxygen

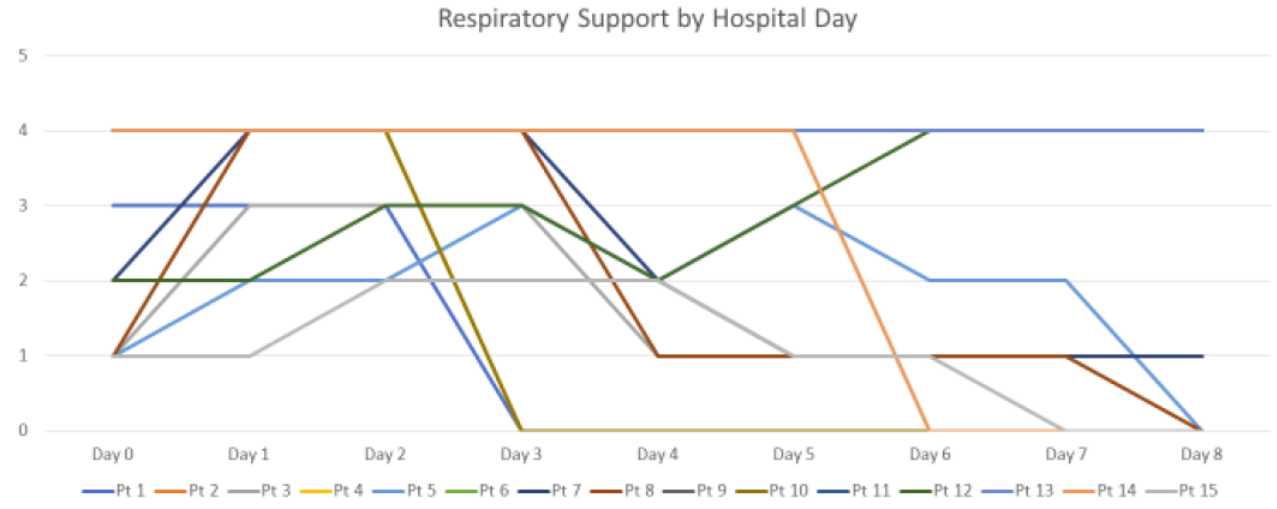

Figure 1: Individual patient respiratory support experience during the first 8 days of admission in which a majority (67%, 10/15) had received tocilizumab. Respiratory support changes were inconsistent, with escalations and declines within and between patients. (Y axis: 0=room air, 1=nasal cannula, 2=hi flow, 3=bi pap, 4=ventilator).

Table 2: Correlation of Day of Hospitalization that Respiratory Status Worsened with Day of Hospitalization that First Dose of Tocilizumab was Given and Survival

Patient#	1st Day of Respiratory Decline	Day of 1st TCB Dose	1st Day Vent Initiated	Days Since TCB	Comments (Disposition)
1	6	8	--	2	Not on ventilator during hospitalization (Died day 10)
2	1	10	1	20	
3	2	1	--	17	Not on ventilator during hospitalization
4	0	1	0	1	On ventilator day of admission (Died day 3)
5	2	4	--	20	Not on ventilator during hospitalization
6	0	1	0	13	On ventilator day of admission (Died day 14)
7	1	2	2	9	
8	3	3	3	6	
9	4	18	4	21	
10	0	21	0	1	On ventilator day of admission (Died day22)
11	1	2	1	28	
12	4	3	9	27	
13	1	11	2	10	(Died day 21)
14	5	16	12	6	(Died day 22)
15	3	2	--	6	Not on ventilator during hospitalization

[0] indicates pre-hospital admission day.

requirements prior to and after administration of tocilizumab. The graph does not demonstrate the improvement of respiratory status one would expect following the drug's administration and, in some cases, demonstrates the opposite: worsening respiratory status progressing to death. The Spearman correlation between treatment and respiratory severity as well as survival would be high if observations have a similar ranking within each dependent outcome (highest correlation of +1 or -1) thus demonstrating a perfect monotonic relationship between variables. Instead, this case series demonstrated total inconsistency with dissimilar ranking within each dependent variable. The coefficients of determination (R2= .038 and R2= .004) indicate a very low, nonsignificant association in which the two variables are dissimilar and/or fully opposed to a correlation. Less than 4% of the variation in tocilizumab treatment, respectively, is explained by the data. The lack of consistency in the pattern was demonstrated by the correlation modeling and visualized in the scattered pattern of Figure **1**.

Over the three-month period in which we reviewed patients treated with tocilizumab for COVID-19, there was significant variation in patient evaluation and treatment regimens. Tocilizumab was proposed to be effective by decreasing cytokine storm and inflammatory response [6,10] yet when reviewing the

frequency of evaluation of inflammatory markers (D-dimer, CRP, Ferritin) a startlingly low number of patients had these markers checked on the day of tocilizumab administration. Additionally, few were re-evaluated in the day after administration of tocilizumab to follow progression (improvement vs worsening) of illness severity via inflammatory markers. This could indicate a lack of confidence in the treatment, lack of confidence in the evidence, or even an intensifying reliance on clinical judgement during the height of the pandemic. Confidence in a treatment or in the evidence when new treatments are introduced should have resulted in consistent associations between utilization and outcome. For example, in this series of cases, chest x-rays were routinely obtained and most likely was the main modality used to monitor pulmonary progression of illness.

Over the three-month study period we can see the variation of medications prescribed to patients as new studies were published and new treatment regimens proposed. This may highlight the lack of strong, peer-reviewed evidence during a time when superior treatment options are expeditiously needed. It starkly illustrates some of the pitfalls and challenges of medical treatment and protocol formation during a pandemic spread of a newly emerging pathogen.

6. CONCLUSIOINS AND RECOMMENDATIONS

Hindsight of one year after the start of the pandemic provides a stark contrast in the evidence for several COVID potential treatments including convalescent plasma, remdesivir, and most recently tocilizumab [8,9,11,12]. However, physicians do not have the luxury of time when a newly introduced pathogen is uncontrolled. While tocilizumab may have had the potential to blunt the cytokine storm in COVID positive patients, ultimately, it did not improve survival [8,10,13]. A similar study by Moreno-Perez, *et al.* in 2020 also found wide variation in use with optimal timing of tocilizumab remaining undefined [14]. They propose a severity grading system as an objective tool to assess appropriate timing to initiate treatment. We suggest a similar need for further consideration of issues that arise in practice. How to evaluate the patient who might benefit from administration of a potential but untested new treatment, what clinical status should determine its use and how frequently markers should be monitored post-administration are some of the questions that need to be addressed with future protocols that facilitate evolving information during a pandemic.

DECLARATIONS

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The Authors declare that there is no conflict of interest.

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REFERENCES

[1] European Center for Disease Prevention and Control. Cluster of pneumonia cases caused by a novel coronavirus, Wuhan, China. ECDPC Jan. 2020. (Cited May 5, 2020) Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Risk assessment-pneumonia Wuhan China 17 Jan 2020.pdf

[2] World Health Organization. Archived Timeline - COVID-19. WHO April 27,2020. (Cited May 5, 2020). Available at: https://www.who.int/news/item/27-04-2020-who-timeline---covid-19.

[3] Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. Lancet Infect Dis 2020; 20(7): 773. https://doi.org/10.1016/S1473-3099(20)30195-X

[4] Higny J, Feye F, Forêt F. COVID-19 pandemic: overview of protective-ventilation strategy in ARDS patients. Acta Clin Belg 2020; 76(6): 509-511. https://doi.org/10.1080/17843286.2020.1761162

[5] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395(10223): 507-513. https://doi.org/10.1016/S0140-6736(20)30211-7

[6] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, *et al.* Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020; 8(4): 420-422. https://doi.org/10.1016/S2213-2600(20)30076-X

[7] Xu X, Han M, Li T, Sun W, Wang D, Fu B, *et al.* Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci USA 2020; 117(20): 10970-10975. https://doi.org/10.1073/pnas.2005615117

[8] Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, *et al.* Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med 2020; 384: 20-30. https://doi.org/10.1056/NEJMoa2030340

[9] Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, *et al.* for the PlasmAr Study Group. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. N Engl J Med 2021; 384: 619-629. https://doi.org/10.1056/NEJMoa2031304

[10] Rosa IO, Brau N, Waters M, Go RC, Hunter BD, *et al.* Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med 2021; 1-13.

[11] Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019

(COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmun 2020; 111(102452). https://doi.org/10.1016/j.jaut.2020.102452

[12] Wang Y, Zhang D, Du G, *et al*. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020; 395(10236): 1569-1578. https://doi.org/10.1016/S0140-6736(20)31022-9

[13] Veiga V, Prats J, Farias D, *et al*. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomized controlled trial. BMJ 2021; 372: 84. https://doi.org/10.1136/bmj.n84

[14] Moreno-Perez O, Andres M, Leon-Ramirez JM, *et al*. Experience with tocilizumab in severe COVID-19 pneumonia after 80 days of follow-up: A retrospective cohort study. J Autoimmunity 2020; 114(102523): 1-8. https://doi.org/10.1016/j.jaut.2020.102523

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