Single Versus Multiple Doses of Tocilizumab in Critically Ill Patients with Coronavirus Disease 2019 (COVID-19): A Two-center, Retrospective Cohort Study

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Keywords: COVID-19, SARS-Cov-2, Tocilizumab, Multiple-dose, Single-dose, Critically ill, Intensive Care Units (ICUs).

Posted Date: May 26th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-526150/v3

Version of Record: A version of this preprint was published at Journal of Critical Care on December 1st, 2021. See the published version at https://doi.org/10.1016/j.jcrc.2021.08.007.

Abstract

Background:

In COVID-19 patients, increased IL-6 levels have been associated with poor disease prognosis. The use of tocilizumab shown to be effective in treating COVID-19 with varying success. This study aims to evaluate the effectiveness and safety of using a single dose of tocilizumab compared with multiple doses in critically ill COVID-19 patients.

Methods:

This study is a two-center, retrospective cohort, in which patients who received tocilizumab and were admitted to the ICU at two tertiary hospitals from March 1st, 2020, until January 31st, 2021were included. Patients were divided into two groups based on the number of doses of tocilizumab they received. Furthermore, we gathered additional data from the patients, such as but not limited to demographic data, vital signs, and laboratory markers. Multivariable logistic and generalized linear regression were used. We considered a *P* value of < 0.05 statistically significant.

Results:

Two hundred sixty-one patients were included in this study; 72.4% received a single dose of tocilizumab, while the rest (27.6%) had received multiple doses. Most of the patients were male, with an average age of 59.2. After adjusting for possible confounders**,** the 30-day mortality (HR 0.92; 95% CI, 0.48-1.75 *p* = 0.79) and in-hospital mortality (HR 0.69; 95% CI, 0.36-1.31 p = 0.25) were not significantly different between the two groups. On the flip side, patients who received multiple doses of tocilizumab have higher odds of secondary infection compared with a single dose (OR 3.06; 95% CI, 1.18-7.89 p = 0.02).

Conclusion:

Multiple doses of tocilizumab were not associated with a statistically significant difference in ICU and hospital mortality in critically ill patients infected with COVID-19. In contrast, it was associated with higher odds of secondary infections compared to a single dose.

Background

Coronavirus disease 2019 (COVID-2019) is a global pandemic that rapidly spread worldwide[1]. Since the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) emergence, it has affected more than a hundred million individuals and caused more than three million deaths globally [2]. Patients affected with COVID-19 usually manifest with respiratory symptoms ranging from mild to severe pneumonia and acute respiratory distress syndrome (ARDS) [3], [4]. Around 10-15% of patients with moderate to severe symptoms require hospitalization, and up to 5% require intensive care unit (ICU) admission with a mortality rate ranging from 26% to 38% [5]–[9].

The clear pathophysiology of the SARS-CoV-2 remains undetermined [9]. However, several reports have shown an elevation in proinflammatory cytokines in response to SARS-COV-2 [3], [9]. In critically ill patients, patients experience a state called "cytokine release syndrome" (CRS). During this state, the body produces inflammatory cytokines and chemokines that have been associated with the occurrence of ARDS and secondary hemophagocytic lymphohistiocytosis[9], [10]. These reactions may contribute to multiple organ failure and increased mortality[9], [10]. In COVID-19 patients, increased interleukin-6 (IL-6) levels are linked with poor disease prognosis [11]. Thus, several studies have assessed the use of therapeutic agents targeting IL-6 in critically ill patients [6], [12]–[15].

Tocilizumab is a recombinant humanized anti-interleukin-6 receptor monoclonal antibody approved to treat rheumatoid arthritis and other rheumatologic diseases. Since the CRS may induce ARDS, many studies have investigated the off-label use of tocilizumab in patients with COVID-19 pneumonia [6], [12]–[15]. These studies' results about tocilizumab efficacy and safety in critically ill patients are conflicting [3], [6], [14]–[17]. Moreover, the dosing regimen of tocilizumab used varied among the previous studies [6], [12], [16]–[18]. Several randomized controlled (RCT) studies demonstrated the efficacy of single or more doses of tocilizumab in critically ill COVID-19 pneumonia patients [6], [16], [18]. On the other hand, two other randomized studies showed no mortality benefit for a single dose of tocilizumab in moderately ill patients with COVID-19 [12], [17]. However, most studies compared tocilizumab to standard care or placebo [6], [12], [17], [18]. Up to this point, there are no studies available compared various tocilizumab dosing regimens' effect on the improvement of patients' clinical outcomes or mortality. Therefore, this study aims to compare the effectiveness of a single dose tocilizumab to multiple doses tocilizumab regimen in critically ill patients with COVID-19.

Patients And Methods

Study design

This is a two-center retrospective cohort study that included critically ill patients with confirmed COVID-19 who were admitted to the ICU at two tertiary hospitals in Saudi Arabia between March 01, 2020, to January 31, 2021. COVID-19 diagnosis was confirmed according to reverse transcriptase-polymerase chain reaction (RT-PCR) obtained from nasopharyngeal or throat swabs. Patients were followed during ICU stay.

Participants

Patients who were 18 years of age or older and admitted to ICU with confirmed COVID-19 were eligible for inclusion. Patients were excluded if the ICU length of stay (LOS) was less than a day or labeled as "Do-Not-Resuscitate" code status within 24 hours of ICU admission. Eligible patients were classified into two groups based on the number of doses for tocilizumab during ICU stay. Multiple-dose of tocilizumab was defined as using two or more doses of tocilizumab during ICU stay.

Setting

This study was conducted in two tertiary governmental hospitals; King Abdulaziz Medical City, Riyadh, and King Abdulaziz University Hospital, Jeddah. The primary site for this study is King Abdulaziz Medical City (Riyadh). The study was approved by King Abdullah International Medical Research Center in February 2021 (Ref.# NRC21R/024/01).

Data collection

Data gathered from the patients' electronic medical records included demographic data, comorbidities, vital signs and laboratory tests, severity scores (i.e., Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) scores), Glasgow Coma Score (GCS). In addition, acute kidney injury (AKI), the need for mechanical ventilation (MV), and MV parameters (e.g., PaO2/FiO2 ratio, FiO2 requirement) within 24 hours of ICU admission were also collected (See additional file 1). Furthermore, renal profile, liver function tests (LFTs), coagulation profile (i.e., INR, aPTT, fibrinogen, D-dimer), and inflammatory markers (e.g., CRP, procalcitonin, serum iron) within 24 hours of ICU admission. Besides, the inflammatory markers as a follow-up during ICU stay were collected. Tocilizumab and systemic corticosteroid use were recorded for the eligible patients. Moreover, microbial isolates (i.e., bacteria and fungus) were identified in the blood, urine, wound, drainage, cerebrospinal fluid (CSF), and respiratory specimens. All patients were followed until they were discharged from the hospital or died during the in-hospital stay, whichever occurred first.

Study Outcomes

The study aims to compare the effectiveness and the safety of two tocilizumab dosing regimens. The primary outcomes was the in-hospital and 30-day ICU mortality compared between the single versus multiple tocilizumab doses administered to critically ill patients with COVID 19. The secondary outcomes were the hospital LOS, ICU LOS, MV duration, and ICU-related complication (s) during ICU stay (i.e., secondary infection, AKI, acute liver injury, respiratory failure requires MV, thrombosis/infarction).

Definition (s)

Secondary infection was identified through the blood, urine, wound, drainage, cerebrospinal fluid (CSF), and/or respiratory cultures. The bacterial or fungal growth considered significant if the growth is ≥ of 100,000 CFU/ml in sputum or endotracheal aspiration shows; bronchoalveolar lavage (BAL) shows growth ≥of 10,000 CFU of single organism/ml for protected specimen brushes (PSBs), and ≥100,000 CFU of single organism/ml for BAL fluid. Additionally, urinary cultures were considered significant if showing a growth of ≥100,000 CFU/ml of no more than two species of microorganisms [13]. Cultures were excluded if the laboratory reported them as a "contaminant sample". According to the Clinical Laboratory Standards Institute (CLSI) *Resistant organisms* were defined as the non-susceptibility to at least three or more antimicrobial agents. Susceptibility of microorganisms created using documents and breakpoints based on [19], [20]

The International Classification of Diseases, Tenth Revision, Clinical Modification (ICD10-CM) codes were used to define Thrombosis/infarction during ICU stay (i.e., myocardial infarction (MI), ischemic stroke, pulmonary embolism, deep vein thrombosis) during ICU stay[21]. While the acute kidney injury (AKI) was defined based on the Acute Kidney Injury Network (AKIN) definition [22], and the acute liver injury was defined as alanine aminotransferase (ALT) exceeding three times the upper limit of normal or double in patients with elevated baseline ALT during the hospital stay. Moreover, respiratory failure was identified either as hypoxemic respiratory failure (PaO2 < 60 mm Hg with a normal or low arterial carbon dioxide tension (PaCO2) or hypercapnic respiratory failure (PaCO2 > 50 mm Hg) that requires mechanical ventilation.

Statistical analysis

Categorical variables are presented as number (percentage), numerical variables (continuous variables) as mean and standard deviation (SD), or median and lower quartile (Q1) and upper quartile (Q3), as appropriate. The normality assumptions were assessed for all numerical variables using a statistical test (i.e., Shapiro–Wilk test) and graphical representation (i.e., histograms and Q-Q plots).

Baseline characteristics, baseline severity, and outcome variables were compared between the two groups. We compared categorical variables using the Chi-square or Fisher exact test. We compared the normally distributed continuous variables using student t-test and other non-normally distributed continuous variables with the Mann-Whitney U test.

Multivariable logistic , negative regression regression were used to find out the relationship between the number of tocilizumab doses and the study outcomes other than mortality considered in this study. Multivariable Cox proportional hazards regression analyses were performed for 30-day and in-hospital mortality and also Kaplan-Meier (KM) plots were generated for these outcomes. All multivariable analyses were adjusted for the for patient's APACHE II score, systemic corticosteroids during ICU stay, CPK, lactic acid, and lymphocytes within 24 hours of ICU admission.

Model fit assessed using the Hosmer-Lemeshow goodness-of-fit test for logistic regression, assumption of equidispersion were violated so negative binomial regression was used to assess non normal outcomes. Proportionality assumption was assessed before using cox regression for analyzing time to event outcomes.. The odds ratios (OR), hazard ratio (HR) or estimates with the 95% confidence intervals (CI) were reported as appropriate. No imputation was made for missing data as the cohort of patients in our study was not derived from random selection. We considered a *P* value of < 0.05 statistically significant and used SAS version 9.4 for all statistical analyses.

Results

A total of 738 patients were screened, but only 261 patients were included in this study. Of those included, 189 (72.4%) received a single dose of tocilizumab with a median (Q1, Q3) dose of 400 mg (400.0, 670.0), and 72 (27.6%) patients received multiple doses of tocilizumab, with a median dose of 400 mg (400.0,

480.0). Among patients who received multiple doses of tocilizumab, 65 patients (90.3%) received two, and seven patients (9.7 %) received three doses, respectively. The median time interval between the doses is 12 hours (12.0, 72.0).

The baseline demographic and clinical characteristics were generally balanced between the two groups (table 1 and table 2). The majority of patients included were male (76%), with a mean age of 59.2 (SD±12.67) (Additional file 1 – Table 1). Among the 261 patients included, the predominant underlying comorbidities were diabetes mellitus (55%), followed by hypertension (54%), and dyslipidemia (21%). All of the comorbidities were similar between the two groups except for dyslipidemia. Patients who received a single dose of tocilizumab had significantly higher baseline dyslipidemia than patients who received multiple tocilizumab doses (24.2% vs. 12.7% respectively, *p*=0.0427) (Additional file 2 – Table 2).

The patients in both groups had similar baseline severity scores (i.e., APACHE II and SOFA scores), MV needs, acute kidney injury within 24 hours of ICU admission, and systemic corticosteroids use during ICU stay. Furthermore, the baseline C-reactive protein (CRP) was also similar in both groups 164.5 mg/L (112.0, 267.0) vs. 169.0 mg/L (117.0, 217.0), *p*=0.45 (Additional file 1 – Table 1).

Primary outcomes

The 30-day mortality was 34.9% vs 37.5%, P=0.69 and in-hospital mortality was 43.6% vs 47.2%, *p*=0.60 respectively. At multivariable cox proportional hazards regression analyses after adjusting for the possible confounders, the 30-day mortality (HR 0.92; 95% CI, 0.48-1.75 *p*= 0.79) and in-hospital mortality (HR 0.69; 95% CI, 0.36-1.31 *p*= 0.25) were not significantly different between the patients who received single-dose and multiple doses of tocilizumab (Table 1). Moreover, the overall survival probabilities were similar during hospital stay between the two groups (Figure 1).

Secondary outcomes

In crude analysis, it was observed that the ICU complications during ICU stay, including respiratory failure requiring MV, acute kidney injury, liver injury, and thrombosis, were all similar in both groups. However, patients who received multiple doses of tocilizumab had significantly more secondary infections (62.5% vs. 46.8%, *p*= 0.02). Additionally, based on the multivariable logistic regression, there was a three-fold higher odds of secondary infections in patients who received multiple doses than a single dose of tocilizumab (OR 3.06; 95% CI, 1.18-7.89 *p*= 0.02) (Table 2). Among patients who received multiple doses and have a secondary infection, the most common type of infection observed was pneumonia (82.2 %), followed by bacteremia (48.8%). Moreover, the most common microorganisms were yeast (44.4%), followed by *Acinetobacter spp*. (33.3%), *Staphylococcus spp*. (24.4%) and *Pseudomonas spp*. (20 %).

This study showed no difference in MV duration during ICU stay (5.0 days vs. 8.0 days, *p*=0.30), ICU LOS (9.0 days vs. 9.0 days, *p*=0.89), and hospital length of stay (16.0 days vs. 22.0 days, *p*=0.08) (Table 2). Moreover, as shown in Table 3, no differences in inflammatory markers such as serum iron level,

fibrinogen level, CRP level, and procalcitonin level when patients were given single or multiple doses of tocilizumab. However, D-dimer level was significantly higher in patients given multiple doses of tocilizumab 7.14 (2.31, 31.05) vs. 3.70 (1.49, 12.57), p=0.01.

Discussion

In this retrospective study, including critically ill patients with COVID-19, the multiple tocilizumab doses group had significantly higher odds of secondary infection than the single-dose group. However, there was no statistical difference between the two groups regarding the in-hospital mortality, ICU mortality rate, AKI, liver injury, and thrombosis during ICU stay. Several RCTs and observational studies have evaluated either single or multiple doses of tocilizumab in patients with COVID-19. Yet, tocilizumab's safety and efficacy results compared to standard care or placebo are contradicting [12], [13], [15], [17], [18], [23], [24].

A randomized clinical trial evaluated single-dose tocilizumab versus usual care in ICU patients with COVID-19 found no significant difference in 15-day, in-hospital, and 28-days mortality between the two groups [17]. Other RCTs also reported no mortality benefits in patients who received multiple doses of tocilizumab than standard therapy [6], [14]Contrary to that, two large RCTs using one or more tocilizumab doses in critically ill patients with COVID-19 reported improved survival [13], [16], [18], and an increase in the duration of organ support-free days[16]. Moreover, A systemic review and meta-analysis found that tocilizumab use in critically ill patients with COVID-19 reduces mortality and improves patients' outcomes [3]. However, the exact number of patients who received single versus multiple doses was not clearly stated in any previous studies mentioned. Also, none of these studies compared the mortality benefits between various tocilizumab regimens [3], [16].

Based on the available evidence on tocilizumab efficacy, the National Institutes of Health (NIH) COVID-19 treatment guidelines recommend using a single dose of IV tocilizumab combined with steroid in hospitalized patients experiencing COVID-19 induced rapid respiratory decompensation [25]. The Saudi Ministry of Health (MOH) protocol for patients with COVID-19 (version 2.8) also recommends the same dosing regimen as the NIH within 24 hours of ICU admission for patients exhibiting hyperinflammatory symptoms on invasive or non-invasive MV, high flow nasal cannula. [26]Yet, many practitioners tend to prescribe more than one dose of tocilizumab if the patients did not improve clinically, according to the published data.

Tocilizumab use was linked with higher secondary infections, which could be explained due to its immunosuppression properties. A single-center retrospective study by Quartuccio L et al., found that almost 42% of the patients who received tocilizumab experienced bacterial infection [24]. In this study, the secondary infection odds was significantly higher in patients who received multiple doses of tocilizumab [24]. This is inconsistent with a study by Kimmig et al. where a single dose of tocilizumab was also associated with the presence of secondary bacterial infections (p = 0.033) in critically ill COVID-19 [27]. However, this study did not compare the occurrence to multiple doses as in our study [22].

Another observational study by Somers et al., including COVID-19 patients on MV, found that patients who received tocilizumab had more superinfections than those who did not (54% vs. 26%; p <0.001) [28]. Contrarily, a recent meta-analysis of 8 RCTs of hospitalized COVID-19 patients found a lower risk of secondary infections in patients who received tocilizumab [29]. The infection follow-up period was 28 days for six RCTs and longer in the remaining two RCTs [29]. However, the confidence interval was wide despite the large sample size, and the statistical difference did not persist when limiting the analysis to double-blind RCTs (a total of three, with a sample size of 1058 patients)[29]. The lower risk of secondary infections found in this meta-analysis is surprising as immunomodulators are associated with a higher risk of infections [29]. It is also worth mentioning that the number of tocilizumab doses was not discussed in this meta-analysis or any of the included RCTs [12], [13], [29].

In our study, we observed no difference in ICU and hospital length of stay of patients who received single-dose compared with patients given multiple doses of tocilizumab (0.20 [-0.18,0.59] p=0.30), (0.17 [-0.17,0.52] p=0.32), respectively. However, when tocilizumab was compared to placebo in the COVACTA trial, a lower median time to discharge from the hospital or ready to discharge in the tocilizumab group compared with placebo (20 days vs. 28 days), and the median duration of ICU stay was lower in the tocilizumab group [15]. Also, the RECOVERY trial showed using tocilizumab was associated with a shorter hospital LOS [18]. A recent systemic review and meta-analysis including 1583 patients with severe and critical COVID-19 showed no difference in hospital LOS [3]. In addition, fifteen comparative studies of 2383 patients reported that the hospital discharge before day 14 was also not statistically significant between the two groups. Even though these meta-analysis findings are comparable to our results, such comparison is still limited because there is no evaluation of the number of tocilizumab doses and its relation with ICU or hospital LOS differences [3].

Our study is the first to compare two different tocilizumab dosing regimens (Single vs. multiple) due to the scarcity of published data regarding its clinical efficacy and safety. However, it has some limitations that need to be noted. The retrospective and observational nature of the study puts the study at risk for residual confounding, despite adjustment for possible confounders. Also, interleukin-6 levels, which can predict the severity of the disease and guide the tocilizumab, have limited availability at our institution (s). Furthermore, the decision to prescribe tocilizumab to COVID-19 patients was driven by the institutional and the MOH treatment protocols, which continued to change with the emergence of new data [26]. Moreover, the decision of single vs. multiple doses of tocilizumab was based on clinical judgment. The timing between repetitive dosing could affect some of the clinical outcomes, which warrant further studies.

Conclusion

Our study suggests no differences in the efficacy between single and repetitive doses of tocilizumab in critically ill COVID-19 patients. However, multiple doses might be linked with a higher odds of secondary infection, giving the long half-life of tocilizumab and its known risk of increasing infections.

These findings raise concerns about the potential adverse effects and the lack of efficacy of receiving multiple tocilizumab dosing in COVID-19 critically ill patients. Further randomized clinical and interventional studies are required to confirm our findings.

Declarations

Acknowledgments

Not applicable.

Author contributions

All authors contributed to data collections, analysis, drafted, revised, and approved the final version of the manuscript.

Funding

None.

Availability of data and material

The datasets used and/or analyzed during the current study are available from corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved in February, 2021 by King Abdullah International Medical Research Center Institutional Review Board, Riyadh, Saudi Arabia (Ref.#NRC21/024/01). All methods were performed in accordance with relevant guidelines and regulations.

Participants' confidentiality was strictly observed throughout the study by using anonymous unique serial number for each subject and restricting data only to the investigators. KAIMRC-IRB committee waived the informed consent due to its retrospective nature.

Consent for publication

Not applicable.

Competing interests

No author has a conflict of interest in this study.

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Tables

Table 1 Regression analysis for the primary outcomes

Outcomes	Crude analysis			Hazard Ratio (OR) (95%CI)	P-value $**
	Single-dose	Multiple-dose	P-value		
30-day mortality, n (%)Δ	66/189 (34.9)	27/72 (37.5)	0.69^^	0.92 (0.48 ,1.75)	0.79
In hospital mortality, n (%)Δ	82/188 (43.6)	34/72 (47.2)	0.60^^	0.69 (0.36 ,1.31)	0.25

ΔDenominator of the percentage is the total number of patients.
^^ Chi-square test is used to calculate the P-value.
$** Multivariate cox regression is used after adjusting for patient's APACHE II score, CPK baseline, lactic acid baseline, lymphocytes baseline and systemic corticosteroids during ICU stay to calculate hazard ratio and p-value.

Table 2 Regression analysis for secondary outcomes

Outcomes	Crude analysis			Odds Ratio (OR) (95%CI)	P-value $**
	Single-dose	Multiple-dose	P-value		
Respiratory Failure Required MV, n (%) $*$	29/61 (47.5)	5/20 (25)	0.08 **	0.23 (0.02 ,3.46)	0.29
AKI during ICU stay, n (%)	86/189 (45.5)	34/72 (47.2)	0.80 ^^	0.42 (0.15 ,1.20)	0.10
Liver Injury during ICU stay, n (%)	21/189 (11.1)	7/72 (9.7)	0.75 **	0.42 (0.07 ,2.48)	0.34
Thrombosis during ICU stay, n (%)	20/189 (10.5)	8/72 (11.1)	0.90**	1.26 (0.36 ,4.39)	0.72
Secondary infection, n (%)	88/188 (46.8)	45/72 (62.5)	0.02 ^^	3.06 (1.19 ,7.89)	0.02
Resistance organism, n (%)	36/53 (67.9)	18/31 (58.0)	0.31^^	1.00 (0.24 ,4.19)	>0.99
				beta coefficient (Estimates) (95%CI)	P-value $*
MV duration during ICU stay Days, Median (Q1,Q3) &	5.0 (1.0, 13.0)	8.0 (2.0, 14.0)	0.30^	0.53 (-0.25 ,1.31)	0.18
ICU Length of Stay Days, Median (Q1,Q3) &	9.0 (6.0, 16,0)	9.0 (6.0, 15.0)	0.89^	0.20 (-0.18 ,0.59)	0.30
Hospital Length of Stay Days, Median (Q1,Q3) &	16.0 (12.0, 27.0)	22.0 (14.0, 32.0)	0.08^	0.17 (-0.17 ,0.52)	0.32

Δ Denominator of the percentage is the total number of patients.

$*$ Denominator of the percentage is non-mechanically ventilated patients with 24 hours of ICU admission.

& Denominator is patients who survived.

^ Wilcoxon rank sum test is used to calculate the P-value.

^^ Chi-square test is used to calculate the P-value.

** Fisher Exact test is used to calculate the P-value.

$** Multivariate logistic regression is used after adjusting for patient's APACHE II score, CPK baseline, lactic acid baseline, lymphocytes baseline and systemic corticosteroids during ICU stay to calculate Odds ratio and p-value.

Figures

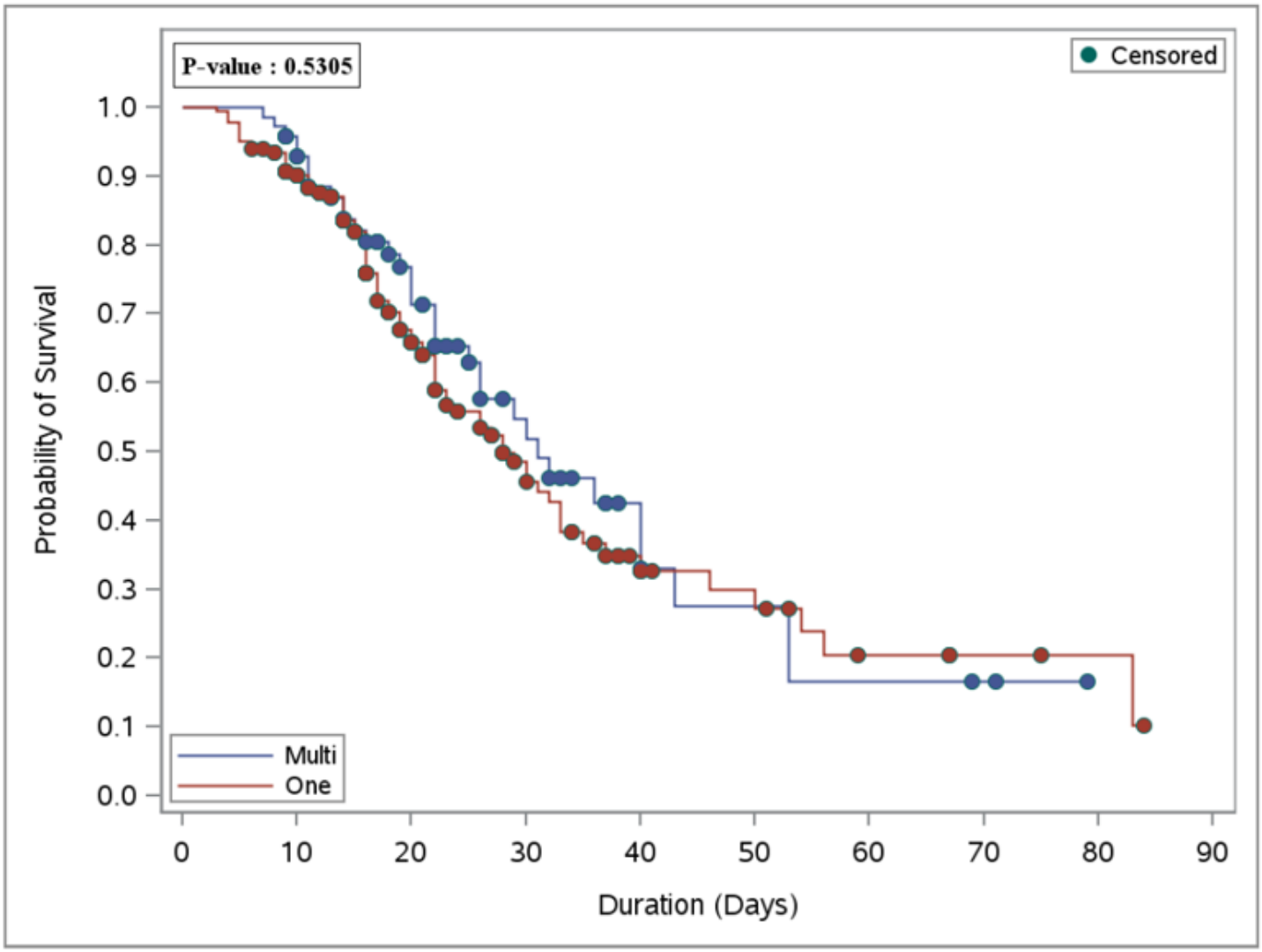

Figure 1

Overall survival plot comparing the single and multiple doses tocilizumab

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1DemographyandBaselinecharacteristics.docx
- Additionalfile2Comorbiditiesillness.docx
- AdditionalFile3.docx