ISSN: 2474-3658

Schneider et al. J Infect Dis Epidemiol 2021, 7:238
DOI: 10.23937/2474-3658/1510238
Volume 7 | Issue 11
Open Access

Journal of
Infectious Diseases and Epidemiology

ORIGINAL ARTICLE

Impact of Adding Remdesivir to Tocilizumab in Hospitalized Patients with Coronavirus Disease

Chelsea A Schneider, PharmD[1], Jenny Martinez, PharmD[1], Kathleen Jodoin, PharmD[1] and William R Wolowich, PharmD[2]*

[1]*Department of Pharmacy, Mount Sinai Medical Center, Miami Beach, Florida, USA*

[2]*Department of Pharmacy Practice, Nova Southeastern University, Fort Lauderdale, Florida, USA*

***Corresponding author:** *Chelsea Schneider, PharmD, Department of Pharmacy, Mount Sinai Medical Center, 4300 Alton Road, Suite 2020, Miami Beach, Florida 33140, USA, Tel: +1-305-674-2121*

Abstract

Background: Several treatments have been utilized in the management of COVID-19 and only remdesivir is FDA-approved at this time. Tocilizumab is an interleukin-6 antagonist that has controversial data regarding its benefits in hospitalized COVID-19 patients. Remdesivir in addition to tocilizumab has not shown any additive benefit to date; however, randomized controlled trials are in process.

The objective of this study was to assess the role of tocilizumab with or without remdesivir in reducing mortality and hospital length of stay in hospitalized patients with COVID-19.

Methods: This retrospective, single centered, observational cohort study, included hospitalized patients with confirmed COVID-19 and clinically associated respiratory findings (infiltrates AND SPO2 < 93% or required respiratory assistance). Patients were excluded if they had a known hypersensitivity to tocilizumab or excipients, were pregnant or breastfeeding, had a known active infection (bacterial, TB, fungal or viral other than COVID-19), an AST/ALT greater than 5 times the upper limit of normal, an absolute neutrophil count of less than 500/mm3, a platelet count of less than 50,000 mm3, a documented history of bowel diverticulitis, perforation, or malignancy. Patients were evaluated based on clinical characteristics, pertinent laboratory data, and clinical outcomes. The primary endpoint was mortality at discharge and hospital length of stay. The secondary endpoint includes safety outcomes. The treatment groups compared standard of care plus tocilizumab versus standard of care plus tocilizumab and remdesivir. Standard of care included vitamin C, corticosteroids, and antibiotics.

Results: 127 patients had data for analysis including 54 patients (group 1) that received standard of care plus tocilizumab and 73 patients (group 2) that received standard of care plus tocilizumab and remdesivir. Survival in group 1 was 83% compared to 81%in group 2, p = 0.7. Length of survival was not different by group when adjusted for those who recovered (24.3 vs. 30.4 days, p = 0.33). Length of stay for those who recovered was significantly different by group when adjusted for mortality (10.6 vs. 16.6 days, p = 0.01). Logistic regression revealed a higher mortality in patients age > 65 (RR 11, p = 0.003) and kidney insufficiency (RR 7.2, p = 0.004). Multivariate regression found an increased length of stay for patients with respiratory categories 2 or 3, p = 0.001.

Conclusions: This study found no reduction in mortality and an increased length of stay in survivors attributed to standard of care plus tocilizumab and remdesivir when compared with standard of care plus tocilizumab.

Keywords

COVID-19, Mortality, Tocilizumab, Remdesivir, Intubation

Introduction

COVID-19 was first reported in Wuhan, China during December 2019. At the time of this study in October 2020, more than 41 million cases had been reported globally with more than 1 million deaths. Cases have been reported in all 50 of the United States, with about 700,000 cases per week in Florida [1,2].

The clinical presentation of COVID-19 positive persons can range from asymptomatic to severe pneumonia with acute respiratory distress syndrome (ARDS) and death. Respiratory failure is one of the leading causes of death in patients with COVID-19 [3].

Citation: Schneider CA, Martinez J, Jodoin K, Wolowich WR (2021) Impact of Adding Remdesivir to Tocilizumab in Hospitalized Patients with Coronavirus Disease. J Infect Dis Epidemiol 7:238. doi.org/10.23937/2474-3658/1510238

Accepted: November 23, 2021: **Published:** November 25, 2021

Common laboratory findings include: Leukopenia, lymphopenia, elevated aminotransferase, C-reactive protein, D-dimer, ferritin, and lactate dehydrogenase. Symptoms can include but are not limited to: Diarrhea, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting [4]. Factors that have shown to promote a more severe disease course include: Advanced age, male sex, pre-existing chronic lung and heart disease, obesity, and diabetes mellitus [5].

To date, remdesivir is the first and only FDA approved medication for COVID-19, although dexamethasone has been associated with decreased mortality in the RECOVERY Trial [6]. The benefits of interleukin-6 antagonists remain controversial. Tocilizumab is an interleukin-6 antagonist that is FDA approved for the treatment of multiple inflammatory diseases including cytokine release syndrome [7]. Newer evidence is still unclear regarding the benefits of tocilizumab in hospitalized COVID-19 patients [8,9]. COVID-19 is associated with a dysregulated immune response and increased inflammatory markers, which is hypothesized to cause or exacerbate acute respiratory distress syndrome and multiorgan failure [10]. Increased levels of interleukin-6 have been linked to severe cases of cytokine release syndrome in COVID-19 patients opposed to lower levels reported in non-critical cases [11]. Tocilizumab and remdesivir combination therapy has been studied in phase III trials. The REMDACTA trial studied tocilizumab and remdesivir combination therapy versus remdesivir and placebo in patients requiring more than 6 L/min supplemental oxygen to maintain SpO_2 > 93%. The REMDACTA trial did not meet its primary endpoint of improvement in hospital discharge by day 28. Moreover, tocilizumab plus remdesivir did not meet key secondary endpoints, which included likelihood of death, progression to mechanical ventilation or death, and clinical status [12]. While certain practice guidelines [4] recommend tocilizumab use with standard of care, standard of care varies in practice and has evolved throughout the pandemic. Therefore, studies addressing the benefits of using tocilizumab particularly in combination with remdesivir are still needed to determine the recommendations for use in practice.

The aim of this study was to assess the role of tocilizumab and remdesivir vs. tocilizumab alone, in combination with standard of care, in hospitalized patients with COVID-19. Primary outcome metrics included mortality and hospital length of stay.

Methods

Study design and patients

This retrospective, single centered, observational cohort study reviewed patients who were diagnosed with COVID-19 by polymerase-chain-reaction (PCR) nasopharyngeal swab and hospitalized at Mount Sinai Medical Center (MSMC), Miami Beach, FL from March 10th, 2020 through September 19th, 2020. Eligible patients were 18 years or older and had clinically associated respiratory findings defined as infiltrates, SPO_2 < 93% on room air, and requirements for respiratory assistance. Patients evaluated in this study were treated with either standard of care plus tocilizumab (group 1) or standard of care plus tocilizumab and remdesivir (group 2).

Patients were excluded if they had received tocilizumab and remdesivir more than 72 hours after time of admission or did not meet hospital inclusion criteria for use per protocol. Hospital protocol excluded patients with no requirement of respiratory supplementation, known hypersensitivity to tocilizumab or excipients, pregnant or breastfeeding, known active infections at time of admission (bacterial, TB, fungal or viral other than COVID-19), AST/ALT greater than 5 times the upper limit of normal, absolute neutrophil count of less than 500/mm^3, platelet count of less than 50,000 mm^3, documented history of bowel diverticulitis, perforation, or malignancy. The study was approved by the MSMC institutional review board.

Treatment for COVID-19

On admission, all COVID-19 patients were started on standard of care (SOC) defined as vitamin C, corticosteroids, and antibiotics. Vitamin C was administered intravenously (IV) or orally in dosages of 500 mg, 1,000 mg, or 1,500 mg. Corticosteroids administered included dexamethasone 2-12 mg IV or oral and methylprednisolone 4 or 8 mg oral or 20-250 mg IV. Patients received antibiotics (regimen and frequency at the provider's discretion) for superimposed nosocomial bacterial infections. Patients received doxycycline 100 mg by mouth twice a day for 5 days.

Tocilizumab was administered as a one-time dose of 400 mg IV. Remdesivir was administered IV as a 200 mg dose on day 1 followed by 100 mg for 4 days or until hospital discharge, whichever came first. If the patient was mechanically ventilated and did not demonstrate clinical improvement, treatment with remdesivir was extended to a maximum of 10 days.

Study variables and assessments

Data was retrospectively collected on patients' demographics, comorbidities, symptoms, oxygen-support category, laboratory values, therapies, and outcomes. Oxygen-support categories were defined according to the ACTT-1 [13] Study as category 1 (nasal cannula or simple oxygen mask), category 2 (non-invasive positive pressure ventilation, continuous positive airway pressure, biphasic positive airway pressure, automatic positive airway pressure, high flow oxygen or non-rebreather), and category 3 (mechanical ventilation or extracorporeal membrane oxygenation). The oxygen status recorded for documentation was

according to the most severe requirement within 24 hours of admission. Main outcomes evaluated were hospital length of stay and mortality. Secondary outcomes included the assessment of tocilizumab adverse events.

Statistical analysis

Continuous variables were reported using median and interquartile range (IQR), and categorical variables were summarized as percentages. Chi Square was used for univariate tests of categorical values, such as the primary endpoint of overall mortality. Chi-Square or ANOVA was also used to identify variables associated with outcomes for use in multivariate analysis. Kaplan-Meier survival plots were used to describe time to event data regarding mortality (with discharge due to recovery censored) and length of stay (with discharge due to death censored). It is important to recognize that the Kaplan Meir estimates of mortality computes the restricted mean "survival" time (RMST) of people who expired (all-cause mortality) by treatment group. Length of stay and RMST are used interchangeably in this report. The Kaplan Meir estimate of length of stay is the restricted mean survival time in patients who recovered [13]. Cox proportional hazard analyses were then completed following the survival analysis. Logistic or multivariate regressions were used to test differences between the treatment groups to analyze predictors of mortality and length of stay. NCSS was used for all statistical analyses [14].

Results

Baseline characteristics of the patients

Patients evaluated in this study were treated with either standard of care plus tocilizumab (group 1) or standard of care plus tocilizumab and remdesivir (group 2). A total of127 patients, group 1 (n = 54) and group 2 (n = 73), presenting with COVID-19 were included in this study. Of the included cases, 49 (39%) were mild (respiratory category 1), 51 (40%) were moderate, and 27 (21%) severe (respiratory category categories 2 and 3). Both treatment groups had

Table 1: Characteristics of the Patients at Baseline

Characteristic	Treatment		
	Group 1 Standard of care + tocilizumab (n = 54)	Group 2 Standard of care + tocilizumab + remdesivir (n = 73)	P value
Average Age - median (IQR)	63 (54.65)	65 (52.65)	0.0008
Ethnicity - No. (%)			0.2
White or Caucasian	3 (5)	10 (14)	
Hispanic or Latino	46 (85)	51 (70)	
African American	4 (7)	7 (10)	
Other	1 (2)	5 (7)	
Sex -No. (%)			0.3
Male	29 (54)	46 (63)	
Female	25 (46)	27 (37)	
Respiratory support received - No. (%)			< 0.0001
Category 1†	35 (65)	14 (19)	
Category 2†	12 (22)	39 (53)	
Category 3†	7 (13)	20 (27)	
Previous coexisting disease - No. (%)			
Obesity‡	25 (46)	44 (61)	0.2
Diabetes	16 (30)	29 (40)	0.24
COPD	3 (6)	7 (10)	0.5
CVD§	29 (54)	55 (75)	0.01
Reduced kidney function¶	24 (44)	26 (36)	0.3
Current smoker - No. (%)	1 (2)	10 (14)	0.02

†Category 1: Nasal cannula, humidified nasal oxygen, simple face mask; Category 2: High flow, non-rebreather, BIPAP, CPAP; Category 3: ECMO, mechanical ventilation, PRVC/AC, APRV, assistance/control. When tested via Chi-square, group 2 has significantly more patients receiving higher levels of respiratory support ($p < 0.0001$); ‡Obesity was defined as a body mass index of 30 or greater; §Cardiovascular disease included heart failure, stroke, myocardial Infarction, peripheral artery disease, coronary artery disease, hyperlipidemia or hypertension; ¶Reduced kidney function was defined as an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2.

similar characteristics at baseline (Table 1). Median age and number of comorbidities were 65 years (IQR: 53-65) and 2 (IQR: 1-3), respectively. The median respiratory category in group 1 and 2 was category 1 and 2, respectively. Group 2 included more cases of cardiovascular disease (CVD), and smokers. In group 1, 7 (13%) versus 20 (27%) in group 2 required mechanical ventilation, $p < 0.001$.

Primary outcomes

No significant difference was found when evaluating the primary outcome of mortality, but a significant difference was found in length of stay of those who recovered. Chi-square analysis revealed17% all-cause mortality at discharge in group 1 and 19 % in group 2, $p = 0.7$. The restricted mean survival time (RMST) in those who died was not significantly different, 30.4 days in

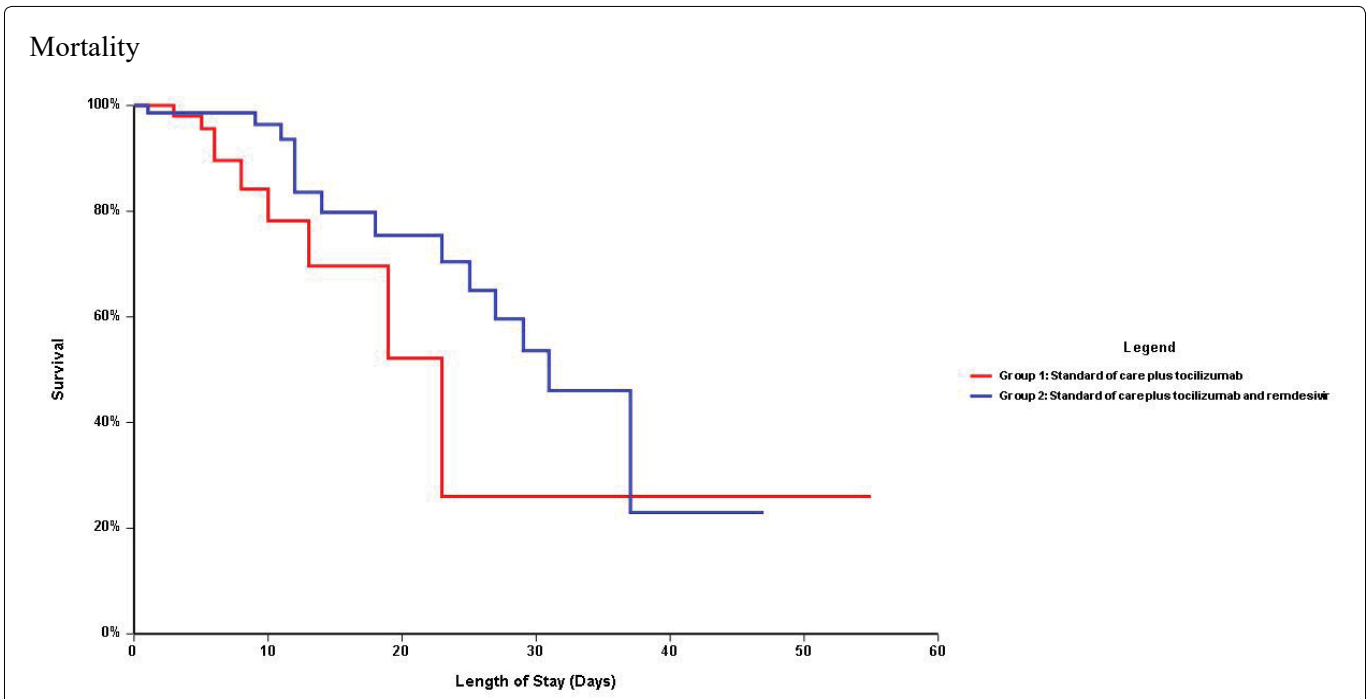

Figure 1: Survival plot illustrating the probability that an individual survives beyond time "length of stay". Discharge due to recovery is censored. The restricted mean survival time (RMST) in those who expired was not significantly different, 30.4 days in group 2 vs. 24.3 days in group 1, $p = 0.3$.

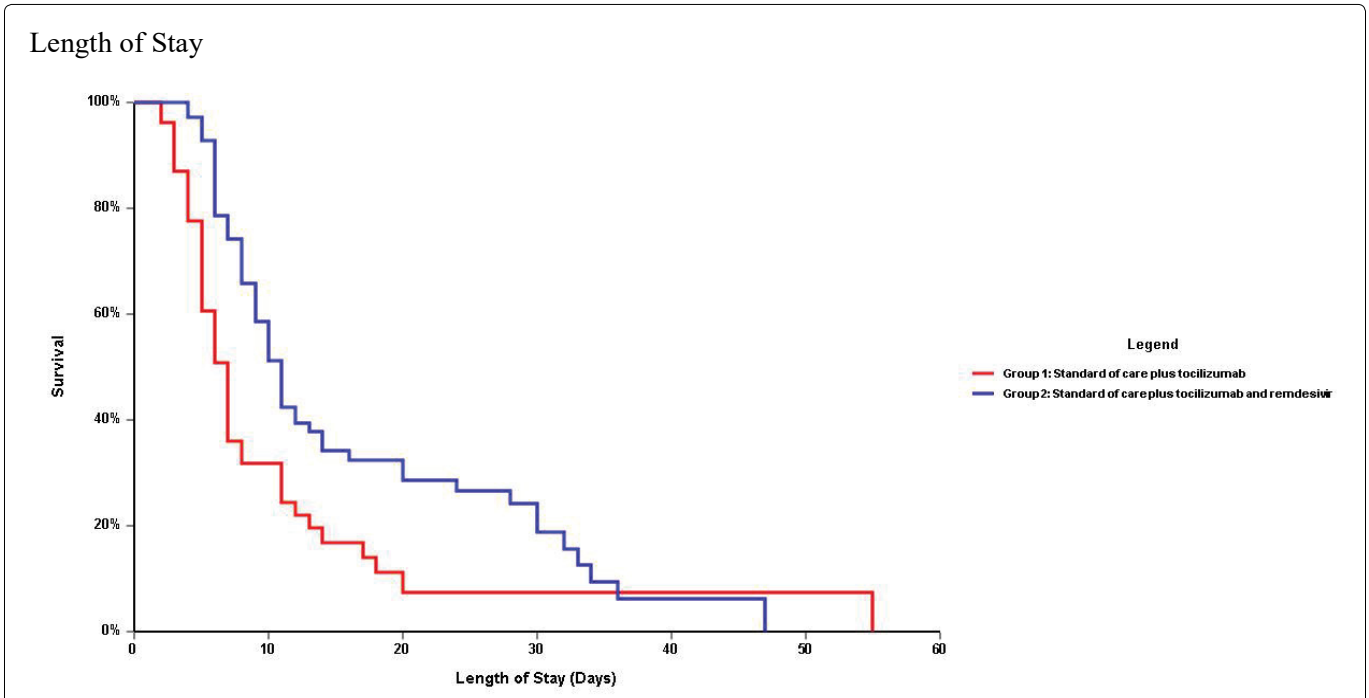

Figure 2: Survival plot illustrating the probability that an individual survives beyond time "length of stay". Discharge due to death is censored. For those who recovered, the restricted mean survival time (RMST) differed by group. Group 2 had significantly longer RMST (16.6 days, 13.5-19.7) compared to group 1 (10.6 days, 7.1-14), $p = 0.01$.

group 2 vs. 24.3 days in group 1, p = 0.3. For those who recovered, the restricted mean survival time (RMST) differed by group. Group 2 had significantly longer RMST (16.6 days, 13.5-19.7) compared to group 1 (10.6 days, 7.1-14), p = 0.01 (Figure 1 and Figure 2).

Secondary outcomes

No infusion related reactions or neutropenia occurred with the use of tocilizumab in either group. Two patients in group 2 developed an infection with documented positive culture within 13 days after the administration of tocilizumab, while no infection occurred in group 1. Fourteen patients experienced an increase of AST/ALT more than 5 times the upper limit of normal within 13 days after receiving tocilizumab, 5 patients (9%) in group 1 and 9 patients (12%) in group 2, p = 0.6. Additionally, seven patients experienced thrombocytopenia, 2 patients (4%) in group 1 and 5 patients (7%) in group 2, p = 0.4. Of these 7 patients with noted thrombocytopenia, one patient had a documented hemorrhage, while the others had negative HIT panels and no documentation of bleeding.

Univariate and multivariate analysis

Univariate categorical analysis revealed several effects on mortality (Table 2). Length of stay > 10 days (p = 0.003), age > 65 (p = 0.001), respiratory category (2, 3 vs. 1) (p = < 0.001), kidney insufficiency (p = < 0.001), cardiovascular disease (p = 0.03), and methylprednisolone use (p = 0.03) were found to have a statistically significant increased effect on mortality.

Univariate analysis of factors impacting length of stay included mortality, age greater than 65, respiratory category, cardiovascular disease, and kidney insufficiency. All factors were associated with longer length of stay ranging from 3 to 5 days (Table 3).

Most of the univariate relationships with mortality or length of stay were eliminated when tested simultaneously in the multivariate regression models. The strongest predictor of mortality from logistic regression analysis was age > 65 [RR = 11 (2-62), p = 0.003], followed by kidney insufficiency [RR = 7.2 (1.6-33), p = 0.004] and respiratory category [RR = 6.5 (1-

Table 2: Factors influencing mortality

	Univariate Chi-square Analysis (n = 127)			Multivariate Logistic Regression Analysis (n = 127)	
	% Mortality		P value	Risk Ratio (C.I.)	P value
Variable (+ vs. -)	+	-			
LOS (≤ 10 vs. > 10 days)	31	10	0.003	0.7 (0.2-3)	0.7
Age (≥ 65 vs. < 65)	31	5	0.001	11.0 (2-62)	0.003
Reduced Kidney function†	38	5	< 0.0001	7.2 (1.6-33)	0.004
Respiratory category	27	4	0.0008	6.5 (1-42)	0.05
Cardiovascular disease‡	24	7	0.03	0.6 (0.09-3.7)	0.6
Remdesivir	19	17	0.7	0.7 (0.2-2.7)	0.6
Diabetes mellitus	27	13	0.06	0.8 (0.2-2.9)	0.7
Methylprednisolone	35	15	0.03	5.5 (0.8-36)	0.08
Dexamethasone	17	33	0.3	4.6 (0.3-72)	0.3
Low Vitamin D Levels	32	21	0.5	1.0 (0.2-6)	1.0

†Reduced kidney function was defined as an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2; ‡Cardiovascular disease included heart failure, stroke, myocardial Infarction, peripheral artery disease, coronary artery disease, hyperlipidemia or hypertension.

Table 3: Factors Influencing Length of Stay

	Univariate ANOVA Analysis (n=127)			Multivariate Regression Analysis (n = 127)		
	Length of Stay		P value	Length of Stay		P value
Variable (+ vs. -)	+	-		+	-	
Mortality	12	7.5	0.008	10.2	10.8	0.8
Age (≥ 65 vs. < 65)	10	7	0.02	12.7	13.7	0.8
Reduced Kidney function†	10.5	7	0.045	11.4	9.7	0.4
Cardiovascular disease‡	10	7	0.02	11.2	9.8	0.5
Respiratory category (Group 2 and 3 vs. 1)	11	6	0.001	15	6	0.001

†Reduced kidney function was defined as an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2; ‡Cardiovascular disease included heart failure, stroke, myocardial Infarction, peripheral artery disease, coronary artery disease, hyperlipidemia or hypertension.

42), p = 0.05]. The only significant predictor of increased length of stay in a multiple regression model was the respiratory category (p = 0.001).

Post hoc subgroup analysis

Patients with diabetes mellitus revealed 27% mortality compared to 13% mortality in patients without diabetes, p = 0.06. Dexamethasone use was associated with 17% mortality in patients who received dexamethasone vs. 33% in patients who did not receive it, p = 0.3.

In the first subgroup analysis, patients were reviewed to assess if corticosteroids were started early (within 48 hours of admission) or later. Majority of patients were initiated on corticosteroids within 48 hours of admission. However, 2 patients received corticosteroids outside of this time period and were in group 1, category 3 (mechanically ventilated), and survived at discharge.

In the second subgroup analysis, baseline vitamin D levels at admission were evaluated for 11 patients in group 1 and 33 patients in group 2. Of these patients, 7 (64%) in group 1 and 18 (55%) in group 2 had low vitamin D levels (< 30 ng/mL). Out of 44 patients that had vitamin D levels at admission, 12 expired (27%) while 32 were alive at discharge. In addition to the subgroup analysis of low vitamin D levels, the univariate analysis revealed that of the 12 patients that expired, 8 (66%) had low levels compared to 4 (33%) who had normal levels, p = 0.5.

Discussion

In this single-center, observational study, mortality and length of stay (RMST) were evaluated for the combination of remdesivir and tocilizumab vs. tocilizumab alone, in combination with standard of care. The primary outcome, mortality did not differ between study groups. The primary outcome restricted mean survival time was greater in group 2. Patients in group 2 were more critically ill, had increased complications during their stay, had more cardiovascular disease and kidney insufficiency in addition to more patients who were mechanically ventilated at admission. Length of stay for COVID-19 has been examined in a recent publication. The authors report a median length of stay of 5 days (IQR 3-9) for countries other than China. In addition, they report there “was a visible difference by discharge status, with patients who were discharged alive having longer length of stay than those who expired during their admission” [15]. We noted a similar finding in this cohort.

The efficacy of tocilizumab monotherapy in patients with COVID-19 has been studied in randomized controlled trials. COVACTA, did not meet its primary endpoint of improved clinical status in patients with COVID-19 associated pneumonia or the key secondary endpoint of reduced patient mortality [16]. Conversely, EMPACTA showed patients with COVID-19 associated pneumonia who received tocilizumab plus standard of care, were 44% less likely to progress to mechanical ventilation or death compared to patients who received placebo plus standard of care [17]. A more recent study, the REMAP-CAP Trial has also shown evidence to support the use of tocilizumab. This trial randomized adults to receive tocilizumab or sarilumab and found that IL-6 inhibitors improved in-hospital mortality and days free of organ support. Of note, 33% of the patients in this trial received remdesivir [18].

Several randomized controlled trials are pending results for tocilizumab in combination with remdesivir. As mentioned previously, the REMDACTA Trial did not show any additional benefits to combination therapy versus remdesivir and placebo [12]. Two well-matched cases were reported of SARS-CoV-2 (+) patients, developing respiratory failure, both receiving tocilizumab following severe inflammatory response, with or without remdesivir. The authors theorize that remdesivir administration is pivotal early in the course of the disease, since tocilizumab use alone cannot ensure inflammation control [19]. Remdesivir efficacy has also been called into question by one of us in a recently published pharmacokinetic simulation which placed most of the remdesivir in lung lysosomes and not where the virus is expected to be replicating [20].

A literature review of predictors on severe COVID-19 suggests an increased disease severity and/or mortality in patients aged > 55 [21]. A pooled analysis of several studies revealed a significant association of kidney insufficiency with severe COVID-19; however, at time of manuscript submission, no individual study had found a significant association of kidney insufficiency as a clinical predictor for severe COVID-19 [22]. Additionally, a systematic analysis concluded both diabetes and cardiovascular disease were associated with severe COVID-19 [23]. However, diabetes was not found to be a significant disease marker of progression in the published systematic analysis. Moreover, there have been few trials evaluating vitamin D levels on COVID-19 severity. One study discovered obese and diabetic patients were found to have low vitamin D levels more frequently [24] and another trial [25] reported vitamin D-deficient COVID-19 patients had a greater prevalence of hypertension and cardiovascular diseases, raised serum ferritin and troponin levels, as well as a longer length of hospital stay. This study also found low vitamin D levels are associated with an increase in inflammatory cytokines, upper respiratory tract infections, and thrombotic episodes [24]. In our study, an increased mortality was associated with age > 65, kidney insufficiency, and respiratory function on admission.

Our study has several limitations. Patients in group 2 were more clinically severe with regard to respiratory

status at admission. In addition, dosage regimens were non-standardized and there was no follow up to determine long-term survival rates. Mortality, length of stay and recovery are somewhat confounded in this study similar to ACTT-1 [26]. Confounding is addressed by censoring discharge due to death when examining length of stay with Kaplan Meier. Likewise, discharge due to recovery is censored when examining mortality.

Conclusion

In hospitalized patients with COVID-19, the combination of remdesivir and tocilizumab versus tocilizumab alone did not result in significant differences in mortality. The patients who recovered in the tocilizumab and remdesivir group had a longer length of stay compared to those who recovered in the tocilizumab and standard of care group. The overall longer length of stay in the tocilizumab and remdesivir group may be attributed to the severity of the cases in this group. Although this study did not show a benefit of tocilizumab and remdesivir combination, current evidence supports the addition of tocilizumab to remdesivir and dexamethasone for patients requiring high flow nasal cannula or noninvasive ventilation [4].

Acknowledgments

This study was not funded by any source.

Conflicts of Interest

The authors of this study report no conflicts of interest.

References

1. World Health Organization (2020) Coronavirus disease (COVID-2019) situation reports.
2. Centers for Disease Control and Prevention (2020) Coronavirus disease 2019 (COVID-19): Cases in U.S. 2020.
3. Ruan Q, Yang K, Wang W, Jiang L, Song J (2020) Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 46: 846-848.
4. National Institutes of Health (2020) Coronavirus Disease 2019 (COVID-19) treatment guidelines: Overview of COVID-19: Epidemiology, clinical presentation, and transmission 2020.
5. Kommoss FKF, Schwab C, Tavernar L, Schreck J, Wagner WL, et al. (2020) The Pathology of severe COVID-19-related lung damage. Dtsch Arztebl Int 117: 500-506.
6. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, et al. (2021) Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 384: 693-704.
7. Le R, Li L, Yuan W, Shord S, Nie L, et al. (2018) FDA approval summary: Tocilizumab for treatment of chimeric antigen receptor t cell-induced severe or life-threatening cytokine release syndrome. Oncologist 23: 943-947.
8. (2020) Tocilizumab to prevent clinical decompensation in hospitalized, non-critically ill patients with covid-19 pneumonitis (COVIDOSE). Clinical Trials.gov.
9. Gupta S, Wang W, Hayek SS, Chan L, Mathews KS, et al. (2021) Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. JAMA Intern Med 181: 41-51.
10. Mehta P, Mc Auley DF, Brown M, Sanchez E, Tattersall RS, et al. (2020) COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 395: 1033-1034.
11. Aziz M, Fatima R, Assaly R (2020) Elevated interleukin-6 and severe COVID-19: A meta-analysis. J Med Virol 92: 2283-2285.
12. REMDACTA Trial Press Release: Roche initiates phase III clinical trial of Actemra/RoActemra plus remdesivir in hospitalized patients with severe COVID-19 pneumonia.
13. Royston P, Parmar MKB (2013) Restricted mean survival time: An alternative to the hazard ratio for the design and analysis of randomized trials with a time to event outcome. BMC Med Res Methodol 13: 152.
14. NCSS Statistical Software (2021) NCSS 2021. NCSS, LLC, Kaysville, Utah, USA.
15. Rees EM, Nightingale ES, Jafari Y, Waterlow NR, Clifford S, et al. (2020) COVID-19 length of hospital stay: A systematic review and data synthesis. BMC Med 18: 270.
16. https://www.roche.com/media/releases/med-cor-2020-07-29.htm
17. https://www.globenewswire.com/news-release/2020/09/18/2095621/0/en/Roche-s-phase-III-EMPACTA-study-showed-Actemra-RoActemra-reduced-the-likelihood-of-needing-mechanical-ventilation-in-hospitalised-patients-with-COVID-19-associated-pneumonia.html
18. The REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, et al. (2021) Interleukin-6 receptor antagonists in critically ill patients with Covid-19 - Preliminary report. medRxix.
19. Akinosoglou K, Velissaris D, Ziazias D, Davoulos C, Tousis A, et al. (2021) Remdesivir and tocilizumab: Mix or match. J Med Virol 93: 56-58.
20. Wolowich WR, Kwon Y (2021) Simulation of drug in the lung can be misleading. Clinical Infectious Disease 72: 1677-1678.
21. Gallo Marin B, Aghagoli G, Lavine K, Yang L, Siff EJ, et al. (2021) Predictors of COVID-19 severity: A literature review. Rev Med Virol 31: 1-10.
22. Henry BM, Lippi G (2020) Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection. Int Urol Nephrol 52: 1193-1194.
23. Matsushita K, Ding N, Kou M, Hu X, Chen M, et al. (2020) The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: A systematic review and meta-analysis. Glob Heart 15: 64.
24. Weir EK, Thenappan T, Bhargava M, Chen Y (2020) Does vitamin D deficiency increase the severity of COVID-19. Clin Med (Lond) 20: e107-e108.
25. Hernández JL, Nan D, Fernandez-Ayala M, García-Unzueta M, Hernández-Hernández MA, et al. (2021) Vitamin D status in hospitalized patients with SARS-CoV-2 infection. J Clin Endocrinol Metab 106: e1343-e1353.
26. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, et al. (2020) Remdesivir for the treatment of Covid-19 - final report. N Engl J Med 383: 1813-1826.