

To Assess the Role of to Cilizumab with or without Remdesivir in Covid-19 Diabetic Patients

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Abstract

Background: The clinical presentation of Covid-19 positive person can range from asymptomatic to severe pneumonia with acute respiratory diseases. The major impact of Covid-19 is identified on respiratory system of the human and leading to death. There are different types of treatment options available for managing the health of the people but first was remdesivir that approved by the FDA. The dexamethasone has been associated with decreased mortality in recovery of the medicine trail. Apart from this, the major benefits of interleukin 6 antagonists are still subject of debate as tocilizumab FDA approved the interleukin 6 for treatment considering the side effects too.

Aim: The study aims to assess the role of tocilizumab with or without remdesivir in COVID-19 diabetic patients

Method: The current study is retrospective, single centered, observational cohort and based on the patients who were diagnosed with Covid-19 considering the PCR test and hospitalized at ESI Chitrakoot Nagar, Udaipur under RNT Medical College, Udaipur from October-20 to December-21. The study has involved the patients who were 18 years and older and had the clinical association with diabetes mellitus. Moreover, the respiratory findings also defined as infiltrates, SPO₂ < 93% on room air and requirements of respiratory assistance. For the current study, the data was collected related to demographics, co-morbidities, symptom, oxygen support category, laboratory values and outcome of the therapies. The level of oxygen support was analyzed considering the ACTT-1.

Results: There were total of 127 patients considered for analyzing the role of tocilizumab with or without remdesivir in COVID-19 diabetic patients. The group 1 is involving the 54 patients and group 2 has 73 covid-19 patients. According to the outcome of the analysis, the mean age of both groups were 62 and 64 years for group 1 and 2. There was significant difference identified for respiratory support received by the patients and obesity, COPD and CVD. However, there was no significant difference found for diabetes patients as the P value was more than 0.05. As per the outcome of the study focusing on the Chi Square, most of the variables have shown significant difference but Remdesivir, and low vitamin D levels have shown the no significant difference

Conclusion: From the analysis, it has been concluded that the combinations of tocilizumab and remdesivir did not have any significant difference in mortality but the patients who recovered from the covid-19 has influenced with diabetic issues. The improvement in practice and advancement in laboratory trail has helped to improve the effectiveness of these treatment options.

Keywords: COVID-19, Mortality, Tocilizumab, Remdesivir, Intubation

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Introduction

Covid-19 was first reported in Wuhan, China during December 2019 and spread globally and affected the health of the people. According to the WHO report, there were more than 1.2 billion cases around the globe and 10 million deaths [1]. The clinical presentation of Covid-19 positive person can range from asymptomatic to severe pneumonia with acute respiratory diseases [2]. The major impact of Covid-19 is identified on respiratory system of the human and leading to death. The common laboratory findings of the Covid-19 include the Leukopenia, lymphopenia, elevated aminotransferase, C-reactive protein, D-dimer, ferritin, and lactate dehydrogenase [3]. As per the analysis of the WHO, the major symptoms of Covid-19 involve the diarrhea, dizziness, anosmia, sore throat, abdominal pain, anorexia and vomiting [4,5].

Moreover, the key factors that promote the severe impact of health of the individual involves the age, male sex, pre-existing chronic disease in lungs and heart as well as the diabetes mellitus [6]. However, there are different types of treatment options available for managing the health of the people but first was remdesivir that approved by the FDA. The dexamethasone has been associated with decreased mortality in recovery of the medicine trail [7]. Apart from this, the major benefits of interleukin 6 antagonists are still subject of debate as tocilizumab FDA approved the interleukin 6 for treatment considering the side effects too [8]. Additionally, the newer

effects of tocilizumab are still unclear for hospitalized patients of Covid-19 [9]. The medical experts have considered the tocilizumab and remdesivir combination therapy for offering the treatment to the patients of covid-19.

The trail of REMDCTA was not meeting the desired outcome for offering the treatment to the patients of covid-19 [10]. The combination of tocilizumab and remdesivir did not meet the secondary endpoints that include the death and clinical status. However, many clinical experts have recommended tocilizumab and remdesivir considering the standards process for offering the treatment of the patients [11]. The improvement in practice and advancement in laboratory trail has helped to improve the effectiveness of these treatment options [12].

Aim

The study aims to assess the role of tocilizumab with or without remdesivir in COVID-19 diabetic patients

Material and Methods

The current study is retrospective, single centered, observational cohort and based on the patients who were diagnosed with Covid-19 considering the PCR test and hospitalized at ESI Chitrakoot Nagar, Udaipur under RNT Medical College, Udaipur from October-20 to December-21. The study has involved the patients who were 18 years and older and had the clinical association with diabetes mellitus.

Moreover, the respiratory findings also defined as infiltrates, $SPO_2 < 93\%$ on room air and requirements of respiratory assistance. Moreover, the patients were evaluated for the study treated with standard of care plus tocilizumab (group 1) or standard plus care tocilizumab and remdesivir (group 2).

The study has excluded the patients who had tocilizumab and remdesivir more than 72 hours after time of admission or not meeting the inclusion criteria of the hospital as per the covid-19 protocol. For the study, the exclusion criteria were patients with no requirement of respiratory supplementation, hypersensitivity of tocilizumab or excipients, pregnant or breastfeeding and having issues related to the TB, fungal and other viral infection.

Study variables

For the current study, the data was collected related to demographics, co-morbidities, symptom, diabetes mellitus, oxygen support category, laboratory values and outcome of the therapies. The level of oxygen support was analyzed considering the ACTT-1. There were three categories defined for maintaining the standards process of analyzing the issues of the patients. Category 1 is nasal cannula or simple mask. Category 2 is non-invasive positive pressure ventilation, continuous positive airway pressure and high flow of oxygen as well as non-rebreather. Category 3 involves mechanical ventilation or

extracorporeal membrane oxygenation. These were considered most severe requirements within 24 hours of admission of the patients. Apart from this, the primary analysis was done on the basis of hospital length of stay and mortality. Secondary outcome of study includes the assessment of tocilizumab adverse impact on diabetic patients.

Statistical analysis

For the study, continuous variables were reported using median and interquartile range and categorical variables which were summarized as percentage. For the analysis of data, Chi Square was used for testing the categorical values and univariate. Moreover, Chi Square and ANOVA were also used to identify variable associated with outcome considering the multivariate analysis.

Results

For study, the patients were divided into two groups. Group 1 is having standards care plus tocilizumab and group 2 is having care plus tocilizumab and remdesivir. There were total of 127 patients considered for analyzing the role of tocilizumab with or without remdesivir in COVID-19 diabetic patients. The group 1 is involving the 54 patients and group 2 has 73 covid-19 patients. The total cases of covid-19 were involving 49 cases with mild (Category 1), 51 cases were moderate (category 2) and 27 severe (category 3).

Table 1: Characteristics of patients

Characteristic	Treatment		P value
	Group 1 Standard of care + tocilizumab (n = 54)	Group 2 Standard of care + tocilizumab + remdesivir (n = 73)	
Average Age - median (IQR)	62 (54.65)	64 (52.65)	0.0008
Sex -No. (%)			0.3
Male	30 (55.5)	48 (65.7)	
Female	24 (44.4)	25 (34.2)	
Respiratory support received - No. (%)			< 0.0001

Category 1	33 (61.1)	16 (21.9)	
Category 2	13 (24)	36 (49.3)	
Category 3	8 (14.8)	21 (28.7)	
Previous coexisting disease - No. (%)			
Obesity	23 (42.5)	42 (57.5)	0.2
COPD	5 (9.2)	8 (10.9)	0.5
CVD	29 (53.7)	55 (75)	0.01
Reduced kidney function	24 (44)	26 (36)	0.3
Current smoker - No. (%)	1 (2)	10 (14)	0.02
Avg. Glucose at Admission (mg/dl)	142	145	0.23
Avg. Glucose at Discharge (mg/dl)	157	166	0.03

The table 1 has provided the information related to characteristics of the patients and discussed the issues and other parameters. According to the outcome of the analysis, the mean age of both groups were 62 and 64 years for group 1 and 2. There was significant difference identified for respiratory support received by the patients and obesity, COPD and CVD.

However, there was no significant difference found for diabetes patients as the P value was more than 0.05. Further, increased glucose level was observed at the time of discharged from the time of admission in both the groups, however, it was not significantly different both the groups at both times.

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)	30	10	0.003	0.7 (0.2-3)
Age (≥ 65 vs. < 65)	32	5	0.001	11.0 (2-62)
Reduced Kidney function†	37	5	< 0.0001	7.2 (1.6-33)
Respiratory category	28	4	0.0008	6.5 (1-42)
Cardiovascular disease‡	23	7	0.03	0.6 (0.09-3.7)
Remdesivir	20	17	0.7	0.7 (0.2-2.7)
Diabetes mellitus	26	13	0.06	0.8 (0.2-2.9)
Methylprednisolone	36	15	0.03	5.5 (0.8-36)
Dexamethasone	18	33	0.3	4.6 (0.3-72)
Low Vitamin D Levels	31	21	0.5	1.0 (0.2-6)

Table 2 has provided the information related to the factor that influence the mortality and considered the different variables such as Respiratory category,

Reduced Kidney function, Remdesivir, Cardiovascular disease and Diabetes mellitus. As per Chi Square, most of the variables have shown significant difference but Remdesivir, and low vitamin D levels have shown the no

significant difference. Apart from this, Multivariate logistic regression analysis has provided the information related to the risk ratio. As per the outcome of the analysis, the Dexamethasone and Methylprednisolone have shown no significant difference as P value was > 0.05 . Rest of the variables has shown significant difference as P value was < 0.05 .

Table 3: Factors Influencing Length of Stay

	Univariate ANOVA Analysis (n=127)		P value	Multivariate Regression Analysis (n = 127)		P value
	Length of Stay			Length of Stay		
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

Table 3 has provided the information and analysis related to factors influencing the length of hospital stay. According to analysis, there are various factors that have direct influence on the health of the covid-19 patients. As per the outcome of the study, the length of stay was affected due to mortality, age, kidney function and cardiovascular disease as well as respiratory category. These have shown no significant differences as P value is less than 0.05 for all variables based on the ANOVA analysis.

Discussion

According to analysis of the study, the major benefits of interleukin 6 antagonists are still subject of debate as tocilizumab FDA approved the interleukin 6 for treatment considering the side effects too. Additionally, the newer effects of tocilizumab are still unclear for hospitalized patients of Covid-19. The

medical experts have considered the tocilizumab and remdesivir combination therapy for offering the treatment to the patients of covid-19.

The combination of tocilizumab and remdesivir did not meet the secondary endpoints that include the death and clinical status. However, many clinical experts have recommended tocilizumab and remdesivir considering the standards process for offering the treatment of the patients. The improvement in practice and advancement in laboratory trail has helped to improve the effectiveness of these treatment options. According to the outcome of the analysis, the mean age of both groups were 62 and 64 years for group 1 and 2. There was significant difference identified for respiratory support received by the patients and obesity, COPD and CVD. However, there was no significant difference found for diabetes patients as the P value was more than 0.05.

Moreover, as per the Chi Square, most of the variables have shown significant difference but Remdesivir, and low vitamin D levels have shown the no significant difference. Apart from this, Multivariate logistic regression analysis has provided the information related to the risk ratio. As per the outcome of the analysis, the Dexamethasone and Methylprednisolone have shown no significant difference as P value was > 0.05 . Reset of the variables has shown significant difference as P value was < 0.05 .

As per the study of Judge Kolaski and Qadeer, (2022) [13] a systematic analysis concluded both diabetes and cardiovascular disease were associated with severe COVID-19. 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 [14,15]. The length of stay was affected due to mortality, age, kidney function and cardiovascular disease as well as respiratory category. Additionally, the combinations of tocilizumab and remdesivir have affected the health of the diabetic patients. [16]

Conclusion

From the analysis, it has been concluded that glucose level increases at the time of discharged from the time of admission in both the groups, however, it was not significantly different both the groups at both times. Further, the combinations of tocilizumab and remdesivir did not have any significant difference in mortality but the patients who recovered from the covid-19 has influenced with diabetic issues. The recovery of the patients using the combination was good but the level of severity of sugar was increased that has negative impact on the health of the patients. The improvement in practice and advancement in laboratory trail has helped

to improve the effectiveness of these treatment options.

References

1. Schneider CA, Martinez J, Jodoin K, Wolowich WR. Impact of Adding Remdesivir to Tocilizumab in Hospitalized Patients with Coronavirus Disease. *J Infect Dis Epidemiol*. 2021; 7:238.
2. Ali S, Khalid S, Afridi M, Akhtar S, Khader YS, Akhtar H. Notes From the Field: The Combined Effects of Tocilizumab and Remdesivir in a Patient With Severe COVID-19 and Cytokine Release Syndrome. *JMIR public health and surveillance*. 2021 May 19;7(5):e27609.
3. Castle RD, Williams MA, Bushell WC, Rindfleisch JA, Peterson CT, Marzolf J, Brouwer K, Mills PJ. Implications for Systemic Approaches to COVID-19: Effect Sizes of Remdesivir, Tocilizumab, Melatonin, Vitamin D3, and Meditation. *Journal of Inflammation Research*. 2021; 14:4859.
4. Rosas IO, Diaz G, Gottlieb RL, Lobo SM, Robinson P, Hunter BD, Cavalcante AW, Overcash JS, Hanania NA, Skarbnik A, Garcia-Diaz J. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. *Intensive care medicine*. 2021 Nov;47(11):1258-70.
5. Sarhan RM, Harb HS, Abou Warda AE, Salem-Bekhit MM, Shakeel F, Alzahrani SA, Madney YM, Boshra MS. Efficacy of the early treatment with tocilizumab-hydroxychloroquine and tocilizumab-remdesivir in severe COVID-19 Patients. *Journal of infection and public health*. 2022 Jan 1;15(1):116-22.
6. Kelleni MT. Tocilizumab, remdesivir, favipiravir, and dexamethasone repurposed for covid-19: A comprehensive clinical and pharmacovigilant reassessment. *SN comprehensive clinical medicine*. 2021

- Apr;3(4):919-23.
7. Naqvi M, Zakowski P, Glucksman L, Smithson S, Burwick RM. Tocilizumab and remdesivir in a pregnant patient with coronavirus disease 2019 (COVID-19). *Obstetrics & Gynecology*. 2020 Nov 1;136(5):1025-9.
 8. Mohanty B, Sunder A, Satyanarayan B, Kumar M, Shukla R, Ahmed A. Success rate of Remdesivir, Convalescent Plasma, and Tocilizumab in moderate to severe Covid-19 pneumonia: our experience in a tertiary care center. *Journal of Family Medicine and Primary Care*. 2021 Nov 1;10(11):4236-41.
 9. Nhean S, Varela ME, Nguyen YN, Juarez A, Huynh T, Udeh D, Tseng AL. COVID-19: a review of potential treatments (corticosteroids, Remdesivir, tocilizumab, bamlanivimab/etesevimab, and casirivimab/imdevimab) and pharmacological considerations. *Journal of pharmacy practice*. 2021 Oct 1:089719002 11048 139.
 10. Soin AS, Kumar K, Choudhary NS, Sharma P, Mehta Y, Kataria S, Govil D, Deswal V, Chaudhry D, Singh PK, Gupta A. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. *The Lancet Respiratory Medicine*. 2021 May 1;9(5):511-21.
 11. Strohbehn GW, Heiss BL, Rouhani SJ, Trujillo JA, Yu J, Kacew AJ, Higgs EF, Bloodworth JC, Cabanov A, Wright RC, Koziol AK. COVIDOSE: Low-dose tocilizumab in the treatment of Covid-19. *medRxiv*. 2020 Jan 1.
 12. Zhou Y, Li J, Wang L, Zhu X, Zhang M, Zheng J. Acute Kidney Injury and Drugs Prescribed for COVID-19 in Diabetes Patients: A Real-World Disproportionality Analysis. *Frontiers in Pharmacology*. 2022;13.
 13. Judge R, Kolaski S, Qadeer F. Use of tocilizumab, remdesivir, and high-dose methylprednisolone prevents intubation in an ESRD patient with COVID-19 pneumonia. *SAGE Open Medical Case Reports*. 2022 Jan; 10:20 50313X211069023.
 14. Mohammed, ebtehaq mustafa. (2020). Explanatory Factor analysis to determining the risk factors of cardiovascular disease: A hospital-based case-control study. *Journal of Medical Research and Health Sciences*, 3(8).
 15. Vitiello A, Ferrara F, Zovi A, Trama U, Boccellino M. Pregnancy and COVID-19, focus on vaccine and pharmacological treatment. *Journal of Reproductive Immunology*. 2022 Apr 21:103630.
 16. Langer-Gould A, Smith JB, Gonzales EG, Castillo RD, Figueroa JG, Ramanathan A, Li BH, Gould MK. Early identification of COVID-19 cytokine storm and treatment with anakinra or tocilizumab. *International Journal of Infectious Diseases*. 2020 Oct 1;99:291-7.