IMPACT OF REMEDSIVER ON OUTCOME OF HOSPITALIZED COVID-19 PATIENTS.

Dheyaa Khalf Al-Omer[1], Dr. Abbas F. Hlaihel[2], Dr. Majeed Mohan Thajeel Alhamami[3], Dr. Ali Abid Saadon[4]

[1]University of Thi-Qar- collage of medicine
[2]University of Thi-Qar collage of medicines
[3]F. I. B. M. S, Lecturer College of Medicine, University of Thi-Qar
[4]M.B.CH.B M.Sc, Ph.D community physician,
Community medicine department collage of medicine-university of Thi-Qar

I. INTRODUCTION

Corona virus disease 2019 (COVID-19) first pandemic caused by corona virus called SARS-Cov2 which appeared in late 2019 in china caused a cluster cases of pneumonia then spread to more than 200 countries causing great number of cases and significant number of death and shortage in heath care services [1]

Replication novel corona virus [SARS-Cov2] usually lead to many of the clinical manifestations of COVID-19, antiviral therapies are being considered for the treatment of COVID-19.

Mechanisms through which these drugs act including inhibit viral entry, viral membrane fusion and endocytosis, or the activity of the SARS-CoV-2 3-chymotrypsin-like protease (3CLpro) and the RNA-dependent RNA polymerase [2]

The viral replication usually active early in the course of COVID-19, so antiviral therapy may have the greatest role before the illness progresses into the hyperinflammatory state that can characterize the advance stages of disease, including critical illness [3]

Role of antiviral in hospitalized patient with severe or critical COVID-19 are studied and most of them prove that did not show significant benefit in reducing mortality in those patients [4]

Animal models showed that remdesivir has in vivo antiviral activity while lopinavir-ritonavir and hydroxychloroquin doesn't showed the activity [5]

Remdesivir (GS-5734) was discovered by Gilead Sciences is and it is one of therapeutic agents for treating RNA-based viruses that had global potential including EBOV and the Coronaviridae family viruses exemplified by Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS).

Most studies demonstrated that (remdesivir) had a broad activity against RNA viruses, multiple studies studied antiviral activity demonstrating its activity against coronaviruses.

Antiviral activity was confirmed against SARS, MERS zoonotic coronaviruses, as well as the circulating human coronaviruses, causative agents of the common cold

Also de Wit et al. demonstrated that remdesivir had both prophylactic and therapeutic activity against MERS in a nonhuman primate in vivo model. [6]

Remdesivir is an intravenous nucleotide prodrug of an adenosine analog. Remdesivir act through binding to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription. It has demonstrated in vitro activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [7]

Wang et al. studied 237 patients (158 assigned to remdesivir and 79 to placebo) in China early in the pandemic and showed a shorter time to improvement (a two-point improvement) with remdesivir: 21.0 days (95% CI, 13.0 to 28.0) in the remdesivir group and 23.0 days (95% CI, 15.0 to 28.0) in the placebo group (hazard ratio for clinical improvement, 1.23; 95% CI, 0.87 to 1.75). [8] John H. Beigel e tal trial data showed that remdesivir was superior

to placebo in shortening the time to recovery in e hospitalized patients with Covid-19 and had evidence of pneumonia [9]

II. PATIENTS AND METHODS

Retrospective analytic study involve 204 patients admitted to Al-Hussein teaching hospital [isolated centre in Al-Nassiryia city centre of thi-qar province diagnosed by CT-chest with or without PCR 102 of them received Remdisivr and 102 not receiving any antiviral therapy

Age, sex , co-morbid disease and severity for both group are record

Both group received corticosteroid , antibiotic and heparin and other medical all of them are recorded

The outcome of hospitalized patients are assessed by duration of hospitalization , need for RCU and discharge well or death

Those received remdisvire are taken then for five day

200 mg on day 1 then 100 for another 4 days

III. RESULTS

This study involve 204 hospitalize patients with COVID-19 prove by CT scan of the chest ans or PCR [102 patients received remdisvire in addition to other medication and 102 patients not received ant antiviral therapy]

Table 1: Distribution according to age and duration of disease

		N	Mean	Std. Deviation	ANOVA	F	Sig.
Age	Remedesvir	102	52.08	9.415	Between Groups	6.984	.009
	None	102	55.44	8.747			
	Total	204	53.76	9.220			
duration	Remedesvir	102	10.90	3.446	Between Groups	.976	.324
	None	102	11.36	3.211			
	Total	204	11.13	3.330			

In this study the mean age of those received remdesivir is 52.08 while the mean those not received remdesivir is 55.44 with significant difference p value 0.009

The mean duration of hospitalization for those taking remdesivir is 10.90 while duration of hospitalization for non remdesivir is 11.36 with non significant difference p value 0.324

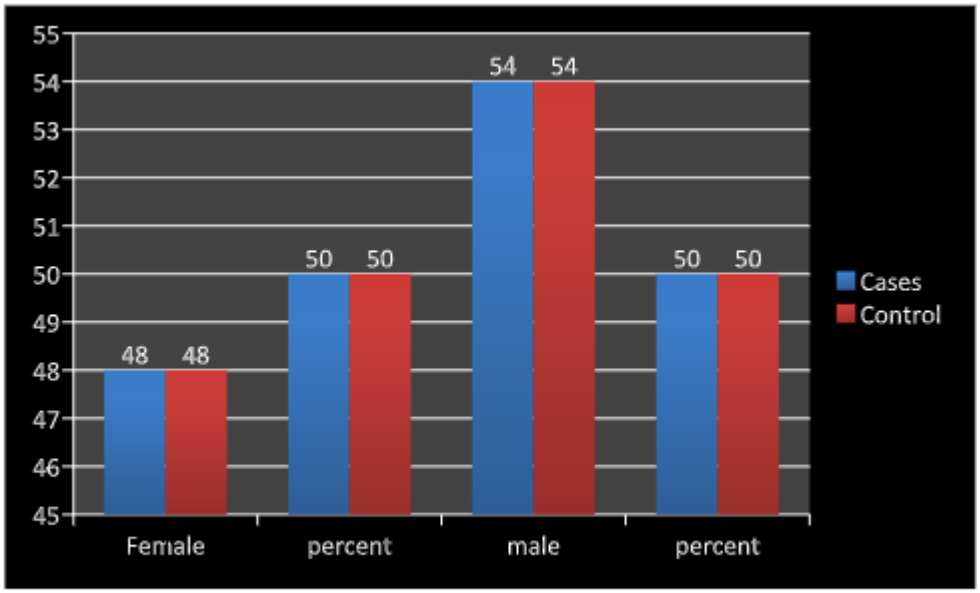


Figure 1: Distribution according to gender

In this study there is 104 male [54 received remdesivir and 54 not received remdesivir] 92 female [48 received remdesivir and 48 not receiving remdesivir] with slight male predominant and there is no difference in sex ratio between two groups

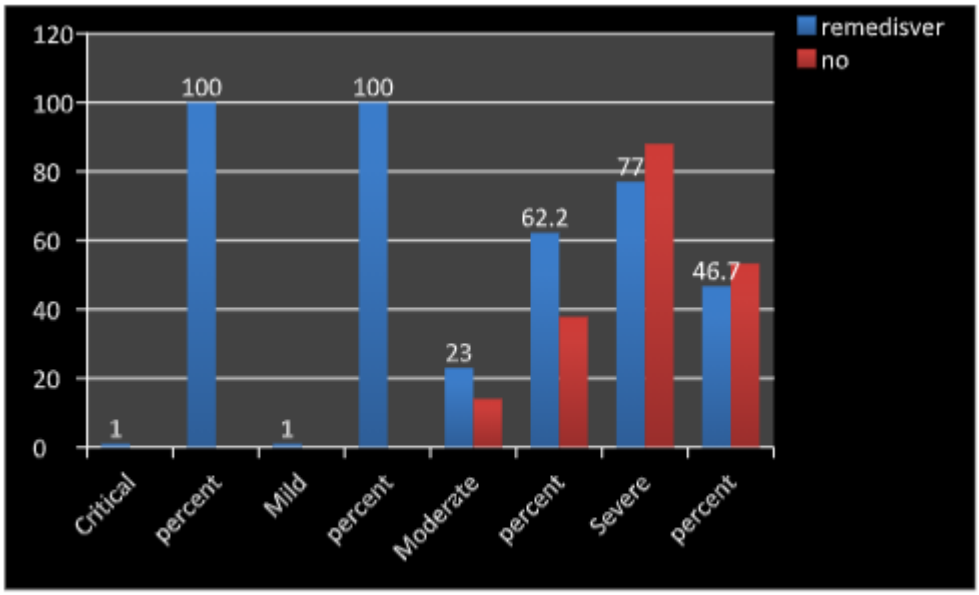


Figure 1: Distribution according to severity of the cases

Fischer exact test=4.764 P vale=0.085

There no significant difference regarding the severity of disease between two group p value 0.085

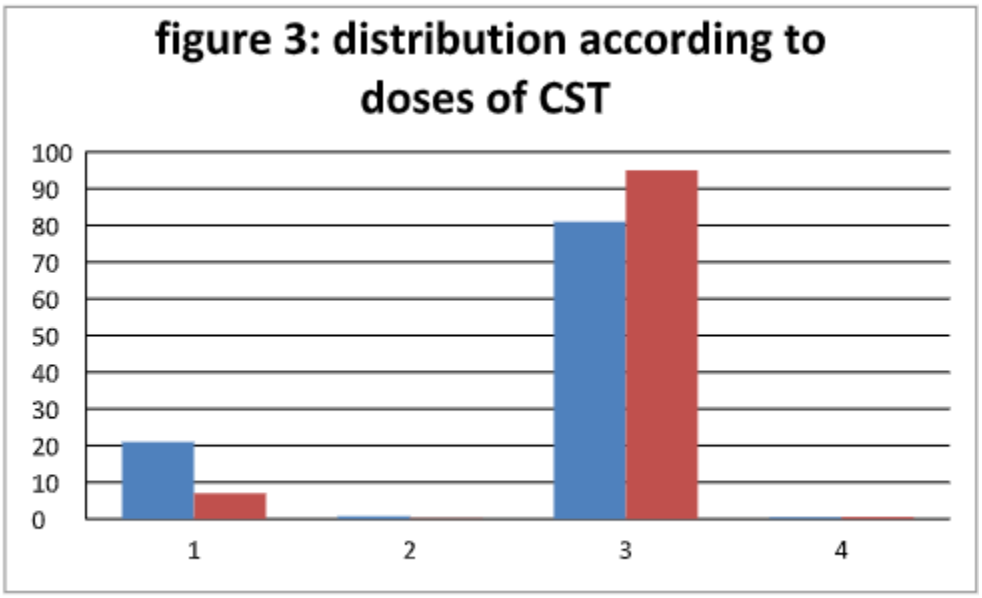
Table 1: Distribution according to chronic medical illness of disease, number of other drugs used and ICU admission

		COVID-19		Total	
		Remedesver	No		
CMD	0	72	84	156	5.190
		46.2%	53.8%	100.0%	0.126
	1	18	14	32	
		56.3%	43.8%	100.0%	
	2	7	3	10	
		70.0%	30.0%	100.0%	
	3	5	1	6	
		83.3%	16.7%	100.0%	
Other drugs	.00	66	80	146	7.489
		45.2%	54.8%	100.0%	0.197
	1.00	14	13	27	
		51.9%	48.1%	100.0%	
	2.00	7	4	11	
		63.6%	36.4%	100.0%	
	3.00	9	3	12	
		75.0%	25.0%	100.0%	
	4.00	5	2	7	
		71.4%	28.6%	100.0%	
	5.00	1	0	1	
		100.0%	0.0%	100.0%	
ICU	No	79	78	157	0.028
		50.3%	49.7%	100.0%	0.868
	Yes	23	24	47	
		48.9%	51.1%	100.0%	
Total		102	102		204
		50.0%	50.0%		100.0%

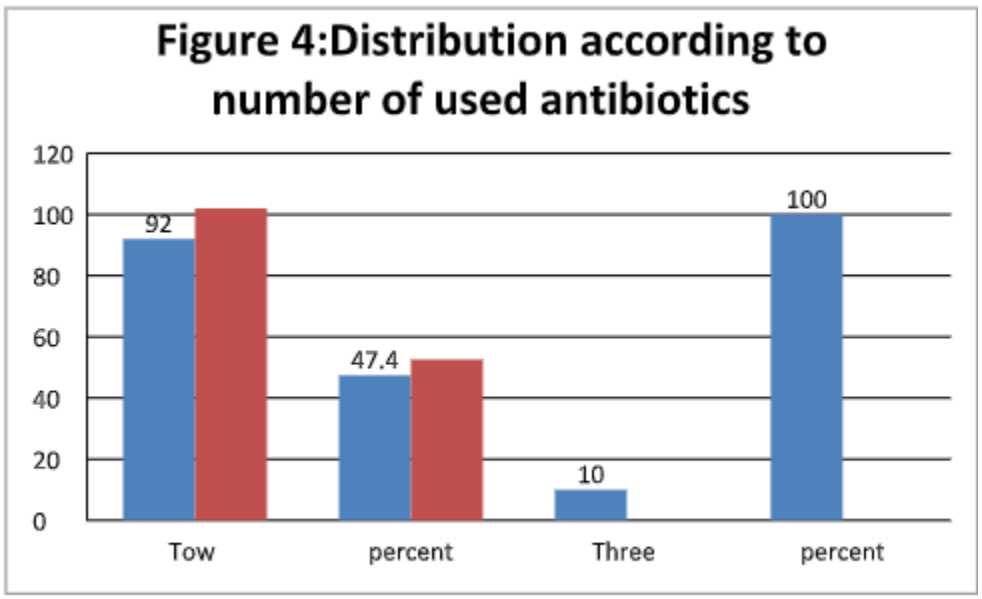
In this study there no significant difference between remdesivir and non remdeisivir regarding the presence of co-morbid disease with p value 0.126

There is no significant difference between remdesivir and non-remdesivir groups regarding the number of medication other than that specific for COVID-19 e.g anti diabetic , anti emetics and others with P value 0.197

There is non significance difference regarding the need for ICU admission between remdesivir and non- remdesivir groups p value 0.868



Chisquare =8.011, p =0.004



X^2=10.515 P value=0.001

Most of patient hospitalized with COVID-19 received two antibiotic but 10 patients of remedisivire three antibiotics with significant difference p value 0

Table 3: Final outcome of the comparative groups

					Total	
			Remedesivr	No		X2, P value
Well		No	9	8	17	0.64
			52.9%	47.1%	100.0%	0.800
		Yes	93	94	187	
			49.7%	50.3%	100.0%	
Death		No	93	94	187	
			49.7%	50.3%	100.0%	0.64
		Yes	9	8	17	0.800
			52.9%	47.1%	100.0%	
Total		Count	102	102	204	
		% within Well	50.0%	50.0%	100.0%	

In this study 93 paitents received remedsivir discharge well and 94 patients with remedsivir discharge well with no significant difference p value 0.800

In this study there is 9 patients dead received renedsivir and 8 patients not received remedsivir are dead with no significant difference p value 0.800

There in non significant difference between two groups regarding discharge well or not from hospital with p value 0.800

In this study death rate is the nearly [9:8] with no significant difference p value 0.800

IV. DISCUSSION

In this study the mean age of those received remdesivir is 52.08 while the mean those not received remdesivir is 55.44 with significant difference p value 0.009 this can be explained that most of physicians working in COVID-19 afraid of side effects of remdesivir in elderly and used it with caution .

In our study we found that intravenous remdesivir did not significantly improve the time to clinical improvement and duration of hospitalization

The mean duration of hospitalization for those taking remdesivir is 10.90 while duration of hospitalization for non remdesivir is 11.36 with non significant difference p value 0.324. Although this difference not statistically significant, patients receiving remdesivir had a less time to clinical improvement than those not receiving the drug

[10.9 to 11]. this go with Yaming etal study that showed no significant difference time in clinical improvement but those received remdesivir are faster time to recover [21 to 23] [10]

John H.Beigel trial showed that patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median, 10 days, as compared with 15 days; rate ratio for recovery, 1.29; 95% confidence interval [CI], 1.12 to 1.49; P<0.001), although in his trial duration of treatment with remdesivir extend 10 days [11]

In this study the ratio of male to female is the same in patient received remdesivir and those not received remdesivir with non significant difference but in each group male more in than female [54 :48 respectively] last global report shows no gender difference in patients although previous report showed slight male predominate[12]

In this study There is no significant difference in severity of disease in patients with remdesivir and those not receiving remdesivir

In this study there no significant difference between remdesivir and non remdesivir regarding the number of co-morbid diseases with p value 0.126

In this study there is no significant difference between remdesivir and non-remdesivir groups regarding the number of medication other than that specific for COVID-19 e.g. anti diabetic , anti emetics and others with P value 0.197

In this study there is non significance difference regarding the need for ICU admission between remdesivir and non- remdesivir groups p value 0.868

There is significant number of patient taking remdesivir [10 patients]received triple antibiotics with significant difference p value 0.001 this may be used due to presence of severe secondary bacterial infection

There is significant number of patients with remdesivir received high dose corticosteroid [20 to 7] with p value 0.004

there was no evidence suggesting that a higher dose of corticosteroids was associated with greater benefit than a lower dose of corticosteroids.[13]

In this study There in non significant difference between two groups regarding discharge well or not from hospital with p value 0.800

In this study there is 9 patients dead received remdesivir and 8 patients not received remdesivir are dead with no significant difference p value 0.800

There was no statistically significant difference in mortality by Day 29 between the remdesivir (11.4%) and placebo (15.2%) arms (HR 0.73; 95% CI, 0.52-1.03; P = 0.07). in The Adaptive COVID-19 Treatment Trial (ACTT-1)[14]

John H. Beigel etal study The 28-day mortality was similar for the two study arms (14% of participants in the remdesivir arm vs. 13% in the placebo arm).[11]

In the WHO Solidarity Trial death occurred in 301 of 2743 patients receiving remdesivir and in 303 of 2708 receiving its control (rate ratio, 0.95; 95% confidence interval [CI], 0.81 to 1.11; P=0.50)[15] while Pasquini et al. Retrospective, observational study showed significantly lower mortality in patients treated with remdesivir (56% vs 92%, P<0.001[16]

Goldman JD, Lye DCB, Hui DS, et a study showed hospitalized patients with severe COVID-19 who were not on mechanical ventilation or ECMO, remdesivir treatment for 5 or 10 days had similar clinical benefit.[17]

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
2. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA. 2020;323(18):1824-1836.
3. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplant. 2020;39(5):405-407.
4. Siemieniuk RA Bartoszko JJ Ge L et al. Drug treatments for covid-19: living systematic review and network meta-analysis.BMJ. 2020; 370m2980
5. Williamson BN Feldmann F Schwarz B et al.Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2.Nature. 2020; 585: 273-276
6. Richard T. Eastman, Jacob S. Roth Kyle R. Brimacombe Anton Simeono Min Shen Samarjit Patnaik, and Matthew Hall* Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19 Published 2020 by the American Chemical Society
7. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269-271.
8. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569-1578.
9. John H. Beigel, M.D., Kay M. Tomashek, M.D., M.P.H., Lori E. Dodd, Ph.D., Aneesh K. Mehta, M.D., S. Zingman, M.D., Andre C. Kalil, M.D., M.P.H., Elizabeth Hohmann, M.D., Helen Y. Chu, M.D., M.P.H., Annie Luetkemeyer, M.D., Susan Kline, M.D., M.P.H., Diego Lopez de Castilla, M.D., M.P.H., Robert W. Finberg, M.D., et al., for the ACTT-1 Study Group Members* Remdesivir for the Treatment of Covid-19 — Final Report N

Engl J Med 2020; 383:1813-1826
DOI: 10.1056/NEJMoa2007764

10. Yaming Wang etal :remdesivir in adult with severe COVID-19:a randomized ,double .multicentre trail , LANCET volume 385,issue 10236 , P1578,May 16 ,2020Tria10l
11. John H. Beigel, M.D., Kay M. Tomashek, M.D., M.P.H., Lori E. Dodd, Ph.D., Anees K. Mehta, M.D., Barry S. Zingman, M.D., Andre C. Kalil, M.D., M.P.H., Elizabeth Hohmann, M.D., Helen Y. Chu, M.D., M.P.H., Annie Luetkemeyer, M.D., Susan Kline, M.D., M.P.H., Diego Lopez de Castilla, M.D., M.P.H., Robert W. Finberg, M.D., Remdesivir for the Treatment of Covid-19 — Final Report N Engl J Med2020;383:1813-1826 DOI: 10.1056/NEJMoa2007764
12. sex ,gender and COVID-19 project :global health 5050:African population and health research centre
13. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19A Meta-analysis The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group JAMA. 2020;324(13):1330-1341. doi:10.1001/jama.2020.17023
14. Remdesivir (VEKLURY) [package insert]. Food and Drug Administration. 2020
15. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results -WHO Solidarity Trial Consortium December 2, 2020DOI: 10.1056/NEJMoa2023184
16. Pasquini Z, et. al. :J Antimicrobial Chemotherapy. Doi:10.1093/jac/dkaa321
17. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. N Engl J Med. 2020