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The Effect of Remdesivir In Hospitalized Patients with COVID-19: Descriptive Observational Study in Basra Governorate, Iraq

Haider Abd-Awn Alawi [1], Ali Rahim Hashim [2], Hassan Ala Farid[3]

1. Internal medicine resident , Candidate for Iraqi Board of medical specialization / Basra Teaching hospital
2. Professor of internal medicine , College of medicine – University of Basra / Basra Teaching hospital
3. Neurology Resident , College of medicine – University of Basra / Basra Teaching hospital

ABSTRACT

Background :"COVID-19,2019" orCoronavirus is an infections malady bring about by acuterespiratory disorder"coronavirus 2SARS-CoV-2". The first case was diagnosed in China, "Wuhan", in Dec. 2019.Then, the virus extends all over the world, causing continuous pandemic.The treatment of the virus basically depends on Repurposed antiviral medications. Remdesivir is the only approved antiviral agent for the treatment of "Covid-19"on Oct. 22, 2020. It is indicated for treatment of Children at the age of twelve and the hospitalized adults.

Method : This is a cross sectional observational study hold in single center in Basra governorate at the south of Iraq , the study includes 368 hospitalized patients with "COVID-19" , The variables used in the study includes : The characteristics of patients , As well as the degree of lung involvement from the chest CT , And oxygen saturation . Two groups of patients were included in this study "those who receive Remdisvir, and those who did not kept on Remdisvir during their hospitalization". The outcome of the patient and the duration of hospitalization wereassessed. The statistical analysis was done by using SPSS.

Results&Conclusions : The Remdesivir is effective in " 70.9 % " of patients , and the percentage of recovery among those with Remdisvir was higher than those who were not kept on it during their course of illness , and the higher recovery rate is achieved when this drug is administered early during illness. The use of Remdisvir is shorten the duration of hospitalization , especially if used early in disease . The early use of Remdisvir is associated with low incidence of cytokine storm in compare with late or non Remdesivir users.

Recommendation : We recommend the early use of Remdisvir during hospitalization , further analytical study is required .

Key words : Remdesivir , COVID-19 , Antivirus

INTRODUCTION

Coronavirus disease 2019 "COVID-19" is defined as contagious disease caused by a novel coronavirus which called severe acute respiratory syndrome "coronavirus 2 SARS-CoV-

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2"that was first diagnosedin an outbreak of respiratory illness cases inChina, Wuhan. [(1)]The CDC declaredon April 3, 2020, asuggestion that the people in public, even those without symptoms, should wear face masks in public places where social-distancing measures are hard to achievetodiminish the spread of thevirus. [(2)]

The Introductions of "COVID-19" extend from asymptomatic or mellow indications to extreme or serious symptoms and mortality. Symptoms start to develop from two days to two weeks after the attack of the virus. [(3)]Among "COVID-19"patients, 81% were mild "absent or mild pneumonia", 14% were severe "hypoxia, dyspnoea, >50% lung involvement within 24-48 hours", 5% were critical "shock, respiratory failure, multiorgan dysfunction", and 2.3% were fatal. [(4)]The most serious manifestation of this virus appears to be pneumonia. [(5)]

The individuals at high risk of infection involve people in areas with continuous local transmission, healthcare workers caring for patients with "COVID-19", close contacts of infected persons, and travellers returning from countries where local spread has been reported as well as those with immune compromise status as the patients with Diabetes mellitus , malignancies and those on immunotherapies .[(6)]The disease that causes infection extends basically when aninfected people came into contact with others.[(7)]

The infected man can spread small droplets and aerosols that contain the virus. Infected people transmit the virus by their nose and mouth when they cough, sneeze, sing, speak or breathe. Some people infected when the virus enters their eyes, nose and mouth. The contaminated surfaces also can cause the infection and participated in the spread of the virus.[8]

Most patients recoup from the severe stage of the malady. Yet, other people proceeds to encounter a range of impacts for a long time after recovery which is known as "long COVID or post COVID syndrome",it is noticed that there is a serious harm to the organ, Multi-year studies advised for further explanations the long-term symptoms of the disease. [(9)]

On the 8th of February 2021, confirmed "COVID-19" infections number over 105 million cases all over the world and has resulted in over 2.3 million deaths. Globally, nearly all countries have reported laboratory-confirmed cases of "COVID-19". [(10)]

"The World Health Organization" "WHO" startedon March 2020 to make researches about theimpacts of some medications: "anti-malarial drugs hydroxychloroquine";andchloroquine an experimental drug called "Remdesivir"; two "anti-HIV"medications, "lopinavir/ritonavir"; and "interferon-beta".[(11)] On April 2020 more than three hundreds original clinical trials were afoot [(12)]

The randomised trial in the U.K. proved on June 2020 that "dexamethasone" helps to reduce mortality by 1/3 for patients who are seriouslyill on "ventilators" and 1/5 for those taking"supplemental oxygen".[(13)]on Sep. 2020, the "WHO" produced a guidance on how to use"corticosteroids" for "COVID-19". The "WHO" says that"systemic corticosteroids" rather than no "systemic corticosteroids" for the treatment of patients with serious"COVID-19". [(14)]

On October 22, 2020, Remdesivir, an antiviral agent, is the only medication approved for treatment of "COVID-19". It is prescribed for treatment of "COVID-19" in hospitalized adults and children twelve years and older who weigh nearly 40 kg. [(15)]

Research on the antimalarial drugs hydroxychloroquine and chloroquine proved that they were ineffective, and that they might only reduce the antiviral activity of Remdesivir. [(16)]

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In Nov. 2020, the"WHO" issued s guideline on therapeutics for "COVID-19" that contains recommended conditions about the use of "Remdesivir", taken from the results from the "WHO Solidarity trial". [17]While the European treatments Agency declared that they will update information to help if a revision to the authorization of "Remdesivir" is wanted. [18]

In European, "Remdesivir" is prescribed for the treatment of "Coronavirus 2019" in adults and adolescents suffering from pneumonia and require oxygen. [19]"Remdesivir" is indicated In the United States for adults and adolescents for the treatment of "COVID-19" that need hospitalization.[20]the "FDA" declareddon Nov. 2020 an "emergency use authorization""EUA" for the combination of "baricitinib" with "Remdesivir", for the treatment of suspected or laboratory confirmed "COVID-19" in hospitalized patients two years of age or older that require "supplemental oxygen", "invasive mechanical ventilation", or "extracorporeal membrane oxygenation" "ECMO".[21]

"Remdesivir"is a spectrum antiviral medication that is used abroadthat is developed by the "biopharmaceutical company Gilead Sciences"[22]. It is madeby intravenousinfusion. [23]. In 2020 "COVID-19" pandemic, "Remdesivir" was authorized for emergency use to treat "COVID-19" in around fifty places all over the world.[24]"Remdesivir"is Adenosine nucleotide prodrug that distributes into cells, where it is metabolized to form the pharmacologically active nucleoside triphosphate metabolite. Inhibits SARS-CoV-2 RNA-dependent RNA polymerase, which is essential for viral replication. [25]

The raised blood levels is the most shared side effect in healthy people, andthe most shared side effects in people with "COVID-19"are nausea. [26]Other likely side effects of "Remdesivir" involve: "Infusion-related reactions". It has been seen during a "Remdesivir" infusion or around the time Remdesivir was given. Symptoms andsigns of infusion-related reactions mightinvolve, nausea,low blood pressure,sweating, vomiting, and shivering. [27]another common adverse effects in studies of "Remdesivir for "COVID-19" involve organ impairment, and respiratory failure involving low count of platelets that help with clotting, low potassium,low albumin, and yellow discoloration of the skin. [28]

"Remdesivir" was first created and developed by "Gilead Sciences" in 2009, to treat hepatitis C and respiratory syncytial virus "RSV".[29] It did not work against hepatitis C or RSV, but was then repurposed and studied as a potential treatment for " and "Marburg virus" infections.[30] A collaboration of researchers from the Centers for Disease Control and Prevention "CDC" and "Gilead Sciences" subsequently discovered that "Remdesivir" had antiviral activity *in vitro* against multiple "filoviruses", "pneumoviruses", "paramyxoviruses", and "coronaviruses".[31]

THE AIMS

The study aims to :

1. Assess the effect of Remdisvir on the outcome of hospitalize patients with covid-19 .
2. Determine the best time for Remdisvir initiation ,during illness .
3. Study the relationship between the effect of Remdisvir and the severity the disease .

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METHODS

This is a cross sectional observational study hold in single center in Basra governorate at the south of Iraq (Basra teaching hospital who specialized in dealing with COVID 19 patients) and the data collected from 15th of July / 2020 to 15h of December / 2020 . the study includes 368 hospitalized patients with clinical , radiological and laboratory diagnosis of COVID 19 . The consent was obtained from the training and human development centre in Basra health directorate.The data were collected from the medical records in the wards , and intensive care units .

The variables used in the study includes :

- The characteristics of patients in relation to age (which further categorized into 4 groups : < 25 , 25 – 50 , 51 – 75 and above 76 years) , Sex (male and female) , Comorbidities (diabetes mellitus , hypertension , cerebrovascular disease , ischemic heart diseases , heart failure , atrial fibrillation , chronic kidney disease , bronchial asthma or COPD , hemoglobinopathies , malignancy , and immunocompromised patients) and plotted as absent if the patient has no comorbidities or present if the patient has any,
- As well as the degree of lung involvement from the chest CT (below 50 % and higher than 50 %) ,
- And oxygen saturation which categorized into (below 70 % , from 70% - 90% and above 90 %)

Two groups of patients were included in this study :

- those who receive Remdisvir during their course of illness , which further subclassified into early Remdisvir users who receive the drug within the 1st ten days of presentation.
- and those who receive it lately , after the 10 days . The other groups are those who did not kept on Remdisvir during their hospitalization .

The outcome of the patient was assessed in this study and categorized as :

- Died : due to respiratory failure or other COVID-19 related complication .
- Recovered : and this was assessed clinically through the improvement of the O2 saturation , respiratory rate , general condition and by inflammatory biomarkers as C-reactive protein , ESR , Ferritin and LDH) .

The other variables included in this study were :

- The duration of hospitalization (short which means less than 7 days , and long hospital staying that means more than 7 days)
- and the presence cytokine storm or release syndrome which plotted as present or absent (through clinical and biochemical assessment) .

The statistical analysis was done by using SPSS (Statistical package for the social sciences) version 20 , the categorized variables were expressed by count and percentage , the results was expressed in form of tables , the association between the variables was assessed by using Qi square test and the significant threshold was set at a P value less than 0.05 .

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THE RESULTS

The total number of patients involve in this study is (368) , their characteristics in relation to age , sex , comorbidities , degree of lung involvement and oxygen saturation are summarized in the table (1) below .

Table (1) : The characteristics of patients who involve in the study

The Age		The sex		Comorbidities		Lung involvement		O2 saturation		
Mean	SD	Male	Female	Present	Absent	< 50 %	> 50 %	< 70 %	70-90 %	>90 %
45	19.6	180	188	151	217	236	132	65	131	172

From the total number of patients , (179) receives (Remdisvir) , the table (2) below shows the relationshipbetween the outcome of patients (Recovery and discharge home Vs. Death) and the use of (Remdisvir) during the course of illness .

Table (2) : The Cross tab between the outcome and the use of Remdisvir

The severity of illness		Out come		Total
		Recovery	Death	
Remdisvir	Yes	127 (70.9%)	52 (29.1 %)	179
	No	103 (54.5 %)	66 (45.5 %)	189
Total		230	138	368
Statistical numbers		P value : 0.001		

From the total number of patients who receive Remdisvir (179) , (129) patients start the drug early in the course of disease , while (50) commenced the drug lately , the table (3) below shows the relationship between the outcome of patients (Recovery and discharge home Vs. Death and the times of initiating (Remdisvir) during the course of illness (early Vs.
late) .

Table (3) : The Cross tab between the outcome and the time of initiating Remdisvir

The severity of illness		Out come		Total
		Recovery	Death	
Time	Early	119 (92.2 %)	10 (7.8 %)	129
	Late	8 (16 %)	42 (84 %)	50

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Total	127	52	179
Statistical numbers	**P value : 0.001**		

In order to assess the effect of the Remdisvir with the severity of respiratorydisease , the table (4) below , demonstratethe relationship between the degree of lung involvement and the level of oxygen saturation with the outcome in patient who are on Remdisvir .

Table (4) : The Cross tab between the outcome and the severity of lung disease in patients on Remdisvir

The severity of illness		**Out come**		**Total**
		Recovery	Death	
Saturation	< 70 %	6 (21 %)	22 (78.6 %)	28
	70 - 90 %	36 (59 %)	23 (41 %)	61
	> 90 %	85 (94.4 %)	5 (5.6 %)	90
Total		127	52	179
Statistical numbers		**P value : 0.001**		
The severity of illness		**Out come**		**Total**
		Recovery	Death	
Lung involvement	< 50 %	86 (81.9 %)	19 (18.1 %)	105
	> or = 50 %	41 (55.4 %)	33 (44.6 %)	74
Total		127	52	179
Statistical numbers		**P value : 0.001**		

The relationship between the effect of Remdisvir in the present of comorbidities is shown in table (5) below as well as the table show the sex and age difference in relation to the outcome among patients who were receiving Remdisvir .

Table (5) : The Cross tab between the outcome and pre-existing medical illness , Sex and age in patients on Remdisvir

The severity of illness		**Out come**		**Total**
		Recovery	Death	
Co-morbidities	Present	58 (65.9 %)	30 (34.1 %)	88
	Absent	69 (75.8 %)	22 (24.2 %)	91
Total		127	52	179
Statistical numbers		**P value : 0.144**		
Sex	Male	88 (71.5%)	35 (28.5)	123
	Female	39 (69.6)	17 (30.4)	56
Total		127	52	179
Statistical numbers		**P value : 0.795**		
Age / years	< 25	3 (75 %)	1 (25 %)	4

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	25 - 50	65 (89 %)	8 (11 %)	73
	51 - 75	54 (62.1 %)	33 (37.9 %)	78
	> 75	5 (33.3 %)	10 (66.7 %)	15
Total		127	52	179
Statistical numbers		**P value : 0.001**		

Finally , the Table (6) below will show , the duration of hospitalization in relation to the use of Remdisvir weather early or late , in compare with the length of hospital staying among Remdisvir non-user patients in addition to the need of ICU admission . as well as this table demonstrate the evidence of cytokine release syndrome among early or late Remdisvir users and Remdisvir non-users .

Table (6) : The Cross tab between the use or non-use of Remdisvir and the duration of hospitalization , ICU admission , and the cytokine storm syndrome

The severity of illness	**Hospitalization**		**ICU Admission**		**Cytokine storm**		**Total**
	Short	Long	No	Yes	Absent	Present	
No Remdisvir	74 (39.2 %)	115 (60.8 %)	117 (62%)	72 (38 %)	10 (5.3 %)	179 (94.7 %)	189
Early Remdisvir	92 (71.3 %)	37 (28.7 %)	120(93 %)	9 (7 %)	110 (85.3 %)	19 (14.7 %)	129
Late Remdisvir	22 (44 %)	56 (56 %)	39 (78 %)	11 (22 %)	13 (26 %)	37 (74 %)	50
Total	188	208	276	92	133	235	368
Statistical numbers	**P value : 0.001**		**P value : 0.002**		**P value : 0.001**		

DISCUSSION

The European Medicines Agency "EMA" providedon April 2020, recommendations on the use of "Remdesivir" for "COVID-19" inEurope.[32]On 11 May 2020, "The Committee for Medicinal Products for Human Use" "CHMP" of the "EMA" provided recommendations to expand the compassionate use of "Remdesivir" to patients that are not on mechanical ventilation. [33]

The "US Food" and "Drug Administration" gave"Gilead Company" the emergency use authorization "EUA"for Remdesivir to be used and distributed by licensed health care providers to cure children and adults hospitalized with serious"COVID-19". Severe "COVID-19" is defined as patients with oxygen saturation "SpO2"<= 94% on room air or in need ofsupplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation "ECMO", a heart–lung bypass machine.[27]

In Iraq, on June / 2020, theministry of health published an updated protocol for treatment of COVID-19 19 and authorized the use of Remdesivir in severe cases who met the following criteria (respiratory rate more than 30 cycleper minutes or Saturation below 93 % or PaO2/FiO2 less than 300 or lung infiltrate above 50 % of the lung field (according to the ministry order A 30267, dated at 28th of June 2020)[34]

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The European Unionon 3 July 2020 gave the medicine "Remdesivir" a conditional marketing authorization, for the treatment of coronavirus 2019 in adolescents andadults and children "aged twelve years and older with body weight at least 40 kilograms" with pneumonia that need supplemental oxygen.**(35)**

"Remdesivir" was admitted for medical use in the U. S. on Oct.2020.The U.S. "Food and Drug Administration" "FDA" admitted"Remdesivir" based on the agency's analysis of information from three controlled randomized, clinical trials that involved patients hospitalized with mild-to-acute"COVID-19".The "FDA" gave consent and reissued the revised "EUA" to "Gilead Sciences" Inc. The "FDA" admitted"Remdesivir" based mainly on evidence from three clinical trials "NCT04280705, NCT04292899, and NCT04292730" of 2043 hospitalized patients with "COVID-19".[79] The trials were directed at 226 sites in seventeen countries involving the U.S. **(36)**

In regards to our results , The Remdisvir is effective in approximately more than 2/3 of cases involve in this study (70.9 %) , and the percentage of recovery among those with Remdisvir was higher than those who were not kept on it during their course of illness , and the higher recovery rate is achieved when this drug is administered early during the course of illness , hence the recovery rate is 6 times higher among those who start Remdisvir early in compare with those who received it lately and these results were statistically significant . these results were of similarity to a double-blind, randomized, placebo-controlled trial of intravenous Remdesivir in adults who were hospitalized with Covid-19 in UK that involved 1062 patients which shows that the patients who received "Remdesivir" were found to be more likely than those who received placebo to have clinical improvement at day 15 (odds ratio = 1.5) and mortality were 6.7% with Remdesivir and 11.9% with placebo by day 15 and 11.4% with Remdesivir and 15.2% with placebo by day 29.**(37)**

The use of "Remdisvir" is shorten the duration of hospitalization, especially if used early in disease and decrease the rate of intensive care units'admissions, this again of staticallysignificant. as was published the average time for healing from "COVID-19" was ten days for the "Remdesivir" group in comparison to fifteen days for the "placebo" group, a statistically essential difference , and recovery was defined as either being discharged from the hospital or being hospitalized but not requiring oxygen supplement and does not need an ongoing medical care . **(37)**

Our results also show that the early use of "Remdisvir" is associated with low incidence of cytokine storm in compare with late or non"Remdisvir"using. According to some studies, the severity of "COVID-19" may depend on the magnitude of the "cytokine storm" and, at this stage; drugs that only decrease viremia may not be effective. Thus, antiviral drugs with anti-inflammatory activity could be important in treatment, due to their capacity to minimize the cellular damage caused by the hyperinflammatory process, mitigating the severity of the "COVID-19"crisis;"Remdesivir" is one of the anti-viral that has additional anti-inflammatory activities. **(38)**

The effect of Remdisvir on recovery , show that higher percentage among those who has no any comorbidities , among male but these were statically not significant , and regarding the age group , the best result of recovery is noticed among who is from 25 – 50 years with high death rate among who's their age higher than 75 years , and this result is of statical significant . the higher severity of diseases the lower recovery rate on Remdisvir and this was also

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statically significant , as the recovery rate is (55.4 %) for those with lung involvement (> 50 %) in compare with (81.9 %) for those with (< 50 %) lung involvement .

"Remdesivir", an antiviral agent, is currently the only drug that is approved by the "FDA" for the treatment of "COVID-19".It is recommended for use in hospitalized patients who require supplemental oxygen.[39] However, it is not routinely recommended for patients who require mechanical ventilation due to the lack of data showing benefit at this advanced stage of the disease.[40]

CONCLUSIONS

The Remdisvir is effective in approximately more than 2/3 of cases involve in this study ,the higher recovery rate is achieved when this drug is administered early during the course of illness , the higher severity of diseases the lower recovery rate on Remdisvir , The use of Remdisvir is shorten the duration of hospitalization , and decrease the need for ICU admission ,Our results also show that the early use of Remdisvir is associated with low incidence of cytokine storm

RECOMMENDATIONS

We recommend the early use of Remdisvir while hospitalization , if in case of limited financial resources , give Remdisvir for those of moderate to severe disease , middle age group , and those with no comorbidities to achieve the best outcome .Further analytical study is required .

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