Comparative Therapeutic Efficacy and Safety of Remdesivir monotherapy and its Combination of Lopinavir/Ritonavir in COVID-19 Patients

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Abstract

Objectives: The treatment of COVID-19 infection remains a challenge because till now, there is no approved therapy for it. This study aimed to estimate the difference in the therapeutic efficacy and safety between remdesivir as monotherapy and its use in combination with lopinavir/ritonavir provided with standard supportive care. Methods: This is a prospective randomized cohort study included 1043 adult patients with confirmed moderate and severe COVID-19 infection. Treatment of all patients followed Egyptian Ministry of Health COVID-19 protocol as the first group received IV remdesivir 200 mg on day 1, followed by 100 mg once daily, for 5 days while the second group received lopinavir/ritonavir 400/100 mg twice daily, for 5 days with the same remdesivir regimen in the first group. All laboratory and clinical parameters were assessed before and after treatment duration. Results: There was no significant difference related to improvement parameters such as laboratory data and improvement time between the two groups. On the other hand, hepatotoxicity of the second group (combination) was significantly higher compared with that of the first one. The elevation on liver enzymes was affected by the severity of the disease, the severe cases showed a high enzyme elevation rate. Conclusion: Remdesivir as monotherapy and its use in combination with lopinavir/ritonavir is effective in the management of moderate COVID 19 subjects than severe cases. The combination of remdesivir with lopinavir/ritonavir is not recommended due to the increased hepatotoxicity effect.

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(combination) was significantly higher compared with that of the first one. The elevation on liver enzymes was affected by the severity of the disease, the severe cases showed a high enzyme elevation rate.

Conclusion: Remdesivir as monotherapy and its use in combination with lopinavir/ritonavir is effective in the management of moderate COVID 19 subjects than severe cases. The combination of remdesivir with lopinavir/ritonavir is not recommended due to the increased hepatotoxicity effect.

Key words: Remdesivir ; Lopinavir/Ritonavir; COVID 19; Hepatotoxicity

Introduction

The Coronavirus disease 2019 (COVID-19) is a type of viral pneumonia that is released from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There are very few options for the effective treatment for viral diseases as COVID 19 (1, 2). The presence of different protein targets in certain drugs, in addition to many viral illnesses, leads to overlapping in the molecular paths (3). Therefore, reusing variable drugs for achieving different objectives and determining their effective uses can be a very helpful method in decreasing the time that is required to find new therapy for emergency diseases (4). The widespread clinical and laboratory efficacy and the well-known knowledge about the antiviral mechanisms of remdesivir and lopinavir/ ritonavir combination in the treatment of certain diseases such as the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), was an important cause for using them in novel COVID 19 infection (5). Therefore, a lot of permissions have been given by the World Health Organization (WHO) for examining different drugs in clinical trials to estimate their efficacy and safety against COVID-19 infection (4, 6). The administration of drugs alone or in combinations have been tested as remdesivir alone; a combination of lopinavir (LPV) and ritonavir (RTV); a combination of lopinavir, ritonavir, interferon-beta (IFNb); and hydroxychloroquine (HCQ) (7).

Remdesivir is a broad-spectrum antiviral nucleotide agent. It was used for the treatment of Ebola virus (EBOV) infection in 2017 (8). It has a great antiviral efficacy against a lot of RNA viruses such as the Ebola virus, Hendra virus, MERS-CoV, SARS-CoV, and respiratory syncytial virus (RSV). It is considered a monophosphoramidate prodrug and an adenosine analog (9). In the human body, remdesivir is metabolized by conversion of its prodrug form into its active form, GS-441524, which disorganizes the viral RNA polymerase and evades proofreading by viral exonuclease, leading to a decrease in RNA production. So, the antiviral mechanism of remdesivir can be considered as a delayed chain stopping of nascent viral RNA (10).

Lopinavir (LPV) is a human immunodeficiency virus 1 (HIV-1) protease inhibitor which, in most cases, is used in combination with ritonavir (RTV) to increase the half-life of LPV by the inhibition of cytochrome P4507 (11, 12).

Gastrointestinal side effects of remdesivir and lopinavir/ritonavir combination have been observed during their administration in the treatment of COVID 19 patients especially hepatotoxicity (13, 14). However, different heterogeneous cases of liver damage may be present under hepatotoxicity terms with rare symptoms or the appearance of jaundice after 1 to 8 weeks after the initiation of the treatment (15). Consequently, reduction of the treatment dose or discontinuation of these drugs should be done upon the appearance of hepatotoxic effect (16).

Till now, antiviral therapy such as hydroxychloroquine, remdesivir, lopinavir/ritonavir can be considered as drugs under trial and have not been formally approved in the treatment of COVID-19 (17). Therefore, a multifaceted viral target study was recommended to evaluate and compare the therapeutic efficacy and the safety of using Remdesivir monotherapy and the combination of lopinavir /ritonavir and Remdesivir and to determine the mortality rate, the length of stay in the hospital, and the medication effect on clinical and laboratory parameters in patients with moderate and severe COVID-19 infection.

The current study aimed at studying the efficacy and hepatotoxicity of using remdesivir alone and in combination with lopinavir/ritonavir for treatment of COVID-19 adult subjects of moderate to severe cases.

2. Patients and methods

2.1 Study design and participants

The study was prospective, randomized, cohort study that included 1043 adult patients aged [?] 18 years with confirmed COVID-19 infection between October 1, 2020, and January 30, 2021, from the Hospital of Health Insurance, Beni-Suef, Egypt. These patients were randomized into two groups. The first group of patients (n = 574) received IV remdesivir of 200 mg on day 1 followed by 100 mg once daily infused over 60 minutes for 7 days while the second group of patients (n = 469) received lopinavir/ritonavir 400/100 (Kaletra®), twice daily for 7 days with the same remdesivir regimen used in the first group in addition to the standard management.

2.2 Clinical classification and clinical follow-up

Egyptian Ministry of Health COVID-19 protocol was used as a guideline for therapeutic management of moderate and severe COVID-19 cases included in the study in addition to the studied antivirals. Both groups were received the same standard management, as well as steroids such as dexamethasone 6 mg/day, was added.

Inclusion criteria included the following: A) Patients with COVID-19 infection who were confirmed with polymerase chain reaction (PCR); B) pulmonary involvement which was detected by oxygen saturation (Sa02) of <92% when at ambient air or respiratory rate (RR) > 30, or PaO2/FiO2 ratio < 300; for severe cases or between 92: 95 % for moderate cases. C) Worsening of lung involvement defined as an increase in the number and /or extension of pulmonary areas of consolidation, need for increased FiO2 to maintain stable O2 saturation or worsening O2 saturation of >3% with stable FiO2.

Exclusion criteria included A) baseline evaluation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels > 3:5 fold the upper limit of the normal range and estimated creatinine clearance less than 30 ml/min; B) Pregnancy; C) Known hypersensitivity to drugs or any component of the formulation, D) Serious co-morbidities as hepatic patients Child-Pugh class C.

2.3 Study population

The following baseline features were analyzed: age, sex, duration of symptoms, comorbidities (smoking history, chronic kidney disease, arterial hypertension, cancer, type 2 diabetes mellitus, coronary artery disease, and chronic obstructive pulmonary disease), baseline clinical status (need for supplementary oxygen therapy, need for invasive or noninvasive ventilation, body temperature), chest computed tomographic (CT) scan and serum inflammatory markers (CRP, ferritin, LDH).

2.4 Clinical outcomes

2.4.1 Primary outcomes:

The proportion of clinically improved patients in the interventional group compared with the proportion of improved patients in the other group.

Patients' clinical improvement (recovery) was assessed based on improvement in oxygenation or patient discharge, and death.

Time to clinical improvement.

Mortality rate.

2.4.2 Secondary outcomes

Monitoring of adverse events: the occurrences of adverse events were recorded daily, with a focus on the elevation of AST or ALT level > 3x the upper limit of the normal range.

2.5 Chest computed tomography

Chest computed tomographic (CT) scans were carried out for all patients with COVID 19 infection and analyzed. The patients with severe COVID 19 infection had chest radiology showing more than 50% lesion or progressive lesion.

2.6 Statistical analysis

Data has been analyzed using SPSS version 25.0 (SPSS, Chicago, IL-USA). Continuous variables were reported as mean ± SD. Categorical variables were reported as numbers and percentages. T-test tests were applied to continuous variables and Chi-square and Mcnemar tests were used for categorical variables. P-values <0.05 were considered statistically significant. Response surface plots were produced by introducing input variables and output responses that were encoded numerically using design expert v 7.

2.7 Ethics statement

The study was carried out after approval from the Research Ethical Committee of Faculty of Pharmacy, Beni-Suef University with a serial number (REC-H-PhBSU-21001). Informed written consent was taken from each study subject and they were informed that their participation is voluntary, and they can withdraw from the study at any time. The study was performed according to the good clinical practices recommended by the Declaration of Helsinki and its amendments.

Results

About 1043 adult COVID-19 subjects were recruited in the study; they were divided into 2 groups their ages, expressed as mean ± SD, were 64.45 ± 12.01 and 60.18 ± 12.09 respectively for the first and second group. The first group included 574 (238 females) patients, while the second group included 469 (154 females). The two groups included 336 and 343 severe cases respectively and the rest of the cases were moderate (Table 1). Laboratory data were expressed in Table 2.

Regarding the effect of both interventions on the efficacy of treatment, the significance of each intervention was as follows; the mortality rate for remdesivir group was 21.95% which is not significantly different from that 22.39% of the remdesivir plus Kaletra® group.

Days till recovery of subjects were variable (5-15 days) between subjects of the same group but the mode was 7 days for both groups which reflected a non-significant effect of both treatments on the recovery days. Regarding the effect of other factors on the recovery days, the severity of the disease for remdesivir group showed a significant ($P<0.001$) effect on the number of days required for patient clinical improvement. Also, a significant ($P<0.01$) difference was observed regarding the second group and this difference was reflected by fewer recovery days for those with moderate severity compared with more days required for the severe cases. On the other hand, the relation between severity of the case and mortality rate was not the same for both groups. The second group has a significant ($P<0.01$) effect of case severity on the rate of mortality while the first group showed no significant difference.

The difference between the number of patients with abnormal laboratory values at baseline and after treatment was significant for most of the items but few items were not significant for both groups. D. Dimer test showed a non-significant difference for both groups. Also, the ALT test had a non-significant increase for remdesivir group only while it was significant ($P<0.001$) for the second group. For the second liver-related test, AST was significantly ($P=0.016$ for the first group and $P<0.001$ for the second group) higher after initiation of treatment for both groups. The magnitude of ALT and AST enzymes elevation expressed as folds showed that 203 (43.28%) of the recruited subjects showed more than 3 folds increase in ALT enzyme among subjects of the second group, while only 14 (2.44%) of the first group only had ALT levels elevated more than 3 folds. The same observation was related to AST levels, as 112 (23.88%) of the second group, subjects showed more than three folds increase in enzyme level, while the first group had no case with this elevation magnitude. Regarding LDH, ferritin, ALC, and CRP, all were improved after the initiation of treatment for both groups (Fig 1).

As shown in fig 2 and fig 3, response surface plots reflected the effect of treatment options and other variables

(age, gender, severity, and comorbidities) on mortality rate, and the response surface plots reflected the effect of different variables on mortality rate was shown in fig 2.

Fig 2 A showed the effect of comorbidity numbers on mortality, it was clear that the higher the number of comorbidities for the subject, the higher the mortality rate. Subjects suffering from cardiovascular, diabetes, and respiratory diseases were among the severe subjects (encoded numerically = 2). Fig 2 B indicated the negative effect of increasing the subject's age on mortality rate, the older the patient the higher the mortality rate. Fig 2 C reflected the effect of disease severity on mortality for both groups, the severe cases had a higher mortality rate compared to moderate cases, and this was consistent with the effect of the comorbidities. Fig 2 D presented the effect of gender on mortality, for remdesivir group there was no difference between males and females, while for the second group it was noted that females have a higher mortality rate compared with males. Effect of treatment option, gender, and severity of the disease on liver enzymes was expressed in response surface plot (Fig 3); adding lopinavir/ritonavir to remdesivir resulted in a significant increase in liver enzymes in a short time. This increase was higher in females compared to males (Fig 3 A and B) and in severe cases compared with moderate (Fig 3 C and D).

For the second group, ALT and AST levels increased above 3 folds from the baseline for 203 (43.2%) and 112 (23.88%) respectively, with about 4.48% of subjects with increased levels above 8 folds. This effect was higher for females compared to males (Fig 3) for both ALT and AST; also the mortality rate was higher for females. Regarding the effect of age on mortality rate, subjects less than 40 years old had a lower mortality rate compared with older patients (Fig 2 B).

Discussion

COVID-19 treatment protocols differ from one country to another and many clinical trials are initiated around the world trying to indicate the beneficial effect of different antiviral therapies. Findings of clinical trials were controversial regarding the beneficial or non-beneficial role of certain antiviral mediations such as remdesivir and a combination of lopinavir/ritonavir drugs (18-21). Remdesivir has been reported to be clinically effective compared with placebo regarding the time needed for COVID-19 patient recovery. However, adverse effects of remdesivir were also reported in the same study for about 24.6% of recruited subjects (22). Studies carried on lopinavir/ritonavir showed a little benefit for improving the clinical outcome of subjects hospitalized with mild and moderate COVID-19 (23). Hence the current study aimed to evaluate the effect and hepatotoxicity of combining remdesivir with lopinavir/ritonavir.

Using lopinavir/ritonavir alone was reported to be less effective for the management of COVID-19 (24) while combining these antiviral drugs with interferon beta 1b has been reported to be safe and more effective compared with lopinavir/ritonavir alone in reducing the duration of coronavirus shedding, improving symptoms, and reducing hospital stay in subjects with mild to moderate cases (25). Also, Verdugo-Paiva et al, indicated that using lopinavir/ritonavir might play a role in improving outcomes of critical and severe cases of COVID-19 (26). Evidence of low certainty suggests that lopinavir/ritonavir may reduce mortality, but as the extent of the reduction differs among various risk groups, there should also be differences in any treatment decision. The evidence also shows that lopinavir/ritonavir can reduce the risk of developing or needing intrusive mechanical ventilation, but the certainty of developing respiratory failure, acute respiratory distress syndrome were reported with these studies (26-28). Hence, combining these antiviral drugs with remdesivir was proposed to enhance the later efficacy and improve COVID-19 patients' outcomes.

The finding of Beigel et al was consistent with findings related to remdesivir efficacy expressed by the percentage (76.83%) of the clinically improved subjects. Previous clinical trials studied the effect of duration therapy and showed that 5 days remdesivir treatment is more beneficial compared with 10 days of therapy (29). One of the most critically reported adverse events was acute hepatotoxicity which has been presented as a dramatic increase in liver enzymes 5 days after initiation of remdesivir therapy (30). However, the use of remdesivir in the current study did not result in a dramatic increase in liver enzymes which was confirmed by the absence of subjects that have elevated AST level 3 folds or more. These findings are consistent with the conclusion of a meta-analysis carried by Yiting et al. (31). There was no significant difference between the two

groups regarding the improvement of laboratory data reflecting the non-beneficial role for lopinavir/ritonavir. While the significant effect of combination groups was related to hepatotoxicity. Hence, combining lopinavir/ ritonavir with remdesivir is not recommended due to dual causes related to lack of efficacy and increased hepatotoxicity.

5. Conclusion

Our findings indicated that remdesivir as monotherapy and its use in combination with lopinavir/ritonavir has a significant difference which was reflected by fewer recovery days for moderate COVID 19 subjects than severe ones. Treatment with remdesivir as a single drug seems to be more safe and effective in reducing mortality rate than its use in combination with lopinavir/ ritonavir. Also, the combination has a high hepatotoxic effect as elevated AST level 3 folds or more.

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Author contributions

Marian S. Boshra : Conceptualization, Methodology, Writing- Original draft preparation, Investigation,Writing- Reviewing and Editing; **Haitham Saeed** : Data curation, Software, Writing- Original draft preparation; **Ahmed E. Abou Warda** : Visualization, Supervision; **Rania M Sarhan:** Conceptualization, Methodology, Writing- Original draft preparation, Investigation,Writing- Reviewing and Editing

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Table 1 . Demographic data and medical characteristics at baseline.

	Group 1 (Remdesivir)	**Group 2 (Remdesivir + Kaletra)**
Age (mean ± SD)	64.45 ± 12.01	60.18 ± 12.09
Gender (n)	336 males, 238 females	315 males, 154 females
Severity (n)	336 severe, 238 moderate	343 severe, 126 moderate
Oxygen saturation (mean ± SD)	86.43 ± 11.79	84 ± 11
Max Temperature	38.14 ± 0.88	38.09 ± 0.69
Recovered cases (n)	448 (78.05%)	364 (77.61%)
Dead cases (n)	126 (21.95%)	105 (22.39%)
Comorbidities	**Comorbidities**	**Comorbidities**
Hypertension n (%)	287 (50%)	252(53.3%)
Diabetes n (%)	245(42.68%)	182 (38.81%)
Chronic kidney disease n (%)	28 (4.88%)	-
Chronic liver disease n (%)	21 (3.66%)	35 (7.46%)
Ischemic heart disease n (%)	140 (24.39%)	14 (2.98%)
Atrial fibrillation n (%)	63 (10.98%)	-
COPD n (%)	35 (6.1%)	-
Asthma n (%)	14 (2.44%)	14 (2.98%)
Obesity n (%)	14 (2.44%)	-
Ventilation	**Ventilation**	**Ventilation**
low supplementary oxygen n (%)	308 (53.66%)	175 (37.31%)
Non-invasive ventilation n (%)	231 (40.24%)	287 (61.19%)
Invasive ventilation n (%)	35 (6.1%)	21 (20.1%)
ICU admission n (%)	329 (57.32%)	343 (73.13%)

Table 2. Number (%) of subjects with abnormal Laboratory data for both groups at baseline and after end of therapy.

		D-Dimer	**LDH**	**Ferritin**	**CRP**	**ALC**	**ALT**	**AST**
Group 1	**Remdisivir (basline)**	224 (39.02%)	378 (65.85%)	406 (70.73%)	553 (96.34%)	511 (89.02%)	147 (25.61%)	280 (48.78%
	Remdisivir (after)	217 (37.8%)	364 (63.41%)	315 (54.88%)	441 (76.83%)	448 (78.05%)	224 (39.02%)	364 (63.41%
Group 2	**Remdisivir + Kaletra (basline)**	280 (59.7%)	378 (80.6%)	350 (74.63%)	455 (97.01%)	406 (86.57%)	133 (28.36%)	210 (44.78%

	D-Dimer	LDH	Ferritin	CRP	ALC	ALT	AST
Remdisivir + Kaletra (after)	231 (49.25%)	308 (65.67%)	378 (80.6%)	378 (80.6%)	287 (61.19%)	427 (91.04%)	378 (80.6%)

Figure legend

Figure 1. The number of subjects with abnormal laboratory data values at baseline and after treatment.

Figure 2. Response surface plot reflect the effect of different variables, A) comorbidities, B) age, C) disease severity, and D) subject gender on the mortality rate of both groups.

Figure 3. Response surface plot reflects the effect of different variables, A and B) Gender, and C and D) disease severity on liver enzyme elevations for both groups.

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