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Renal and liver injury following the treatment of COVID-19 by remdesivir

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ABSTRACT

Remdesivir initially was intravenously administrated to treat the Ebola disease however right now it has been administered to treat COVID-19 in some countries. However it is necessary to find the exact effect of remdesivir in patients with COVID-19. Remdesivir solution is administered with a cyclodextrin carrier that filters solely by the glomeruli; thereby patients with abnormal renal function cannot eliminate it quickly; therefore, remdesivir can lead to renal failure or liver dysfunction during therapeutic process of COVID-19. Assessment of renal function in patients with COVID-19 who have acute kidney injury (AKI) or end-stage renal disease is fundamental.

Mini-Review

Implication for health policy/practice/research/medical education:
In the patients taking remdesivir, liver and kidney function tests should be monitored daily, and remdesivir should be held in patients with increased liver enzymes or kidney function impairment.

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Introduction

Remdesivir was first developed by the Gilead pharmaceutical company and has the ability to treat a wide range of viruses, such as severe acute respiratory syndrome (SARS), *Marburg marburgvirus* and the Middle East respiratory syndrome (MERS). It was used to treat the Ebola virus epidemic in West Africa from 2013 to 2016 (1, 2). Remdesivir is considered as a mono phosphoramidate medication of an adenosine analogue that has a broad antiviral spectrum (3). The Food and Drug Administration has authorized the emergency administration of remdesivir to treat hospitalized patients with COVID-19 in the United States because remdesivir can reduce recovery time by 31% (one-third). This declaration on remdesivir was happed after publishing of the results of the administration of this drug on 61 patients (22 patients from the United States, 22 patients from Europe or Canada, and 9 patients from Japan) who received at least one dose of remdesivir. Mortality was 18% in patients under mechanical ventilator who received remdesivir and 5% in patients who did not need a mechanical ventilator (4,5). There are some side effects of remdesivir including nausea, phlebitis, headache, constipation, pain in the extremities and ecchymosis (5,6).

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Methods

In this mini-review, international databases including PubMed, Web of Science and Scopus were considered for search of English articles from 31 December 2019 to 15 August 2020. All type of articles was included. Keywords were COVID-19, novel coronavirus, 2019-nCoV, coronavirus disease 2019, renal involvement, renal injury, renal failure, kidney injury, kidney failure, kidney involvement, remdesivir, veklury, GS-5734, liver injury, and liver involvement. After collection of articles of interest, references imported to Endnote software and removed duplicate titles. The selected studies were performed on humans and published in English.

COVID-19 and kidney at a glance

While, a clinical study revealed that about one-third of patients who developed COVID-19 experienced acute renal failure (ARF), however in the patients more than 60 years, two-thirds of patients had ARF since the antigen against novel coronavirus accumulates in renal tubules following COVID-19 (7). Recent clinical studies in patients with COVID-19 showed that 27% of patients have elevated plasma creatinine and urea nitrogen levels while proteinuria occurs in 63% of the studied individuals (7, 8).

COVID-19 and liver at a glance

Liver involvement accompanied by high alanine aminotransferase (AST), lactate dehydrogenase (LDH) and aspartate aminotransferase (ALT) has been firstly presented in Wuhan in which involved 43% of the patients developed COVID-19 (9). In the study carried out on 417 Chinese patients with COVID-19, the increased liver tests were presented in the majority of the patients (76.3%) and accordingly 21.5% of patients reported liver injury during hospitalization especially during the 14 days after admission. Additionally, patients who have increased level of liver tests, have higher chance for severe form of COVID-19 (4). In Wuhan, 15.4% of the patients with COVID-19 had acute liver injury (10).

Remdesivir and COVID-19-related renal failure

As mentioned, remdesivir was intravenously administrated to treat the Ebola disease, in which it was enough to tolerate by the patients with Ebola; however, this drug is less effective than several monoclonal antibodies. Remdesivir has been utilized to treat COVID-19 in some countries, while, there is further need to study the exact effect of remdesivir in patients with COVID-19 (11).

Remdesivir prescription should be traded off cautiously in pregnant or breast-feeding women, cirrhosis, ALT or AST more than five times the upper limit of normal range and severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2 or receipt of continuous renal replacement therapy). In a randomized clinical trial 158 patients divided into remdesivir group and 79 patients divided into placebo group. This study showed that the most common adverse events in the intervention group were anemia, constipation, hypoalbuminaemia, hypokalemia, increased total bilirubin, and thrombocytopenia. Additionally, in the placebo group, the most common adverse events were hypoalbuminaemia, constipation, anemia, hypokalemia, increased AST, hyperlipidemia, and increased total bilirubin. According to the serious adverse events, the two groups were different (12% in the intervention group versus 5% in the control group). In the remdesivir group, more patients discontinued the drug compared to the control group (12).

Remdesivir is administered intravenously and has limited water solubility; therefore it is given with a cyclodextrin carrier. This carrier is filtered solely by the glomeruli; thereby patients with normal renal function eliminate it quickly. Conversely, patients with acute kidney injury (AKI) are at risk of cyclodextrin accumulation. Each 100 mg of remdesivir powder contains 3 gr of cyclodextrin, and the solution contains 6 g. In addition, based on the experience with voriconazole, both dialysis and continuous renal replacement therapy should effectively remove cyclodextrin (13). Sulfobutylether-beta-cyclodextrin sodium (SBECD) is applied in the formulation process as a solubilizing agent because remdesivir has limited aqueous solubility feature. Since SBECD has a renal excretion root, patients with moderate or severe renal impairment have exposure to SBECD. Hence a close look on eGFR (estimated glomerular filtration rate) is needed in the time of administration of remdesivir, especially in patients with renal impairment. The discontinuation of remdesivir is required if eGFR levels drop to half level from baseline. Remdesivir has contraindication in patients with severe renal impairment (eGFR less than 30 mL/min) (14).

Remdesivir-induced liver injury in patients with COVID-19

According to the Gilead company declaration, laboratory abnormalities during the phase-1 trials were presented as the increased liver enzymes, coagulopathy and blood sugar in <5% of the patients. Additionally, serious adverse events were septic shock and AKI in 23% of cases, in such a way that 8% of the patients discontinued because of the side effects after the use of remdesivir (15). Wang et al carried out a study on 61 patients taking remdesivir consisting of a loading dose of 200 mg intravenously on the admission day and 100 mg daily for the other days for ten days. The increase of liver enzyme was observed in 12 patients. In addition, renal impairment was observed in seven patients

with invasive ventilation and AKI in two patients with invasive ventilation (12).

Currently, there is very low-evidence regarding the potential hepatotoxicity of remdesivir. Considering its effective results in patients developed COVID-19 infection and the high frequency of liver involvement following COVID-19, the attribution of liver dysfunction to the administration of remdesivir is challenging and further studies are needed in this regard (16).

Zampino et al to study the liver injury in treated COVID-19 patients revealed that remdesivir may cause hepatocellular toxicity. Although there were five patients (low-number) however, obvious increasing trend of bilirubin and ALT/AST was found following remdesivir administration. They suggested close monitoring of liver function tests in patients taking remdesivir for treating COVID-19 (17).

Conclusion

Nephropathy and liver involvement may occur due to direct inflammatory effect of cytokines following COVID-19. Both liver and renal dysfunctions are prognostic factors in the mortality rate of COVID-19 and usually happen in severely ill patients. Remdesivir can also lead to renal dysfunction or liver involvement during medical treatment of COVID-19. Therefore, prescribing drugs such as remdesivir should proceed with extreme caution. Patients who had liver disease or who undergo continuous or intermittent dialysis or those with transient AKI may not be the safe candidates to receive remdesivir. Therapy assessment in patients with COVID-19 who have AKI or end-stage renal disease is fundamental in which needs primary assessments of the pros and cons, while the patients with COVID-19 are at high risk for suffering from lots of morbidity and mortality. In the patients taking remdesivir, liver function tests must be monitored daily, and remdesivir should be held in patients with high ALT level more than five times the allowable limit.

Authors' contribution

MMR, EJ, BL, MF and SF prepared the manuscript. RV, MF and SF critically revised the manuscript.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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