Letter to the Editor

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Remdesivir in Patients with Advanced Renal Failure and COVID-19

Fatemeh Yassari [1], Maryam Sadat Mirenayat [1], Atefeh Fakharian [1], Farin Rashid Farokhi [2], Parisa Honarpisheh [3]

[1] Chronic Respiratory Disease Research Center (CRDRC), National Research Institute of Tuberculosis and Lung Disease (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [2] Telemedicine Research Center of Masih Daneshvari Hospital, Chronic Kidney Disease Research Center, Shahid Beheshti university of Medical Sciences, Tehran, Iran, [3] Pediatric Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Disease (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Correspondence to: Honarpisheh P

Address: Pediatric Respiratory Disease Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Email address: parisa30m@yahoo.com

Dear Editor

The COVID-19 outbreak brings up increased concern for patients with kidney dysfunction and end-stage renal disease (ESRD). These patients are intrinsically immunocompromised and have associated comorbidities; thus, they are at increased risk for COVID-19 infection while their symptoms could be subtle.

On the other hand, COVID-19 itself leads to renal insufficiency. Therefore, these patients are considered a high-risk subgroup in the COVID-19 pandemic. The global COVID-19 pandemic has had a significant influence on the management of these patients and we confront specific challenges in these vulnerable populations. Given that remdesivir is one of the drugs considered to be effective in severe cases of coronavirus disease 2019 (COVID-19), it is important to assess the safety of this drug and particular attention to the dose adjustment and dialysis clearance in patients with renal impairment.

Remdesivir is a nucleoside analog that has been approved by the US Food and Drug Administration (FDA) for the treatment of hospitalized patients. In a study by Humeniuk et al on the pharmacokinetics of remdesivir in healthy people, renal excretion of remdesivir was determined about 10% as an unchanged drug (1) and about 50% as remdesivir nucleoside core (GS-441524) (2). This core is subsequently converted to a metabolite which after slow re-phosphorylation acts as an active drug (3).

Due to concerns about the accumulation of the drug's metabolites, patients with GFR < 30 cc/min have been excluded from most remdesivir studies; accordingly, there are only limited studies of treatment with remdesivir in critically ill patients. In a study of a 70-year-old man with ESRD on intermittent hemodialysis (IHD) without residual renal function who was receiving remdesivir for the treatment of lung failure due to COVID-19, it was found that the level of GS-441524 was high but stable between dialysis sessions. Its accumulation was prevented by IHD, while the level of remdesivir was always below the lower limit of the reference range and did not accumulate significantly. Also, there were no signs of drug-related toxicity (4).

In another study, remdesivir was used in two patients with COVID-19, one with renal impairment and the other without renal impairment. Plasma level of remdesivir measured 3-9 days after drug initiation. No significant difference was observed in the mean drug level between the two patients (5).

Because remdesivir has low water solubility, it contains a carrier named Sulfobutylether-beta-cyclodextrin sodium (SBECD) which is predominantly eliminate through kidney. However, because nephrotoxicity occurs only after prolonged exposure to high doses, renal toxicity would be rare during a short period of low dose treatment. In general, remdesivir is not recommended in adults and pediatric patients with eGFR < 30 mL/min unless the potential benefit outweighs the potential risks (6).

A study conducted by Kiser et al in patients with kidney failure treated with voriconazole which uses the same carrier found that continuous veno-venous hemofiltration (CVVH) effectively removes SBECD and thus, remdesivir can be safely administered in these patients (7). In addition, in patients with GFR <30cc/min, the lyophilized powder formulation of remdesivir which contains less amount of this carrier is preferable to liquid formulation (1).

In a multicenter case series from 4 hospital in USA, 18 patients (including 5 patients on renal replacement therapy (RRT)) received remdesivir despite that their GFR was <30 cc/min. Eight of the 13 patients who did not require renal replacement therapy experienced improved creatinine levels during remdesivir treatment. Of the remaining five patients, only one experienced a worsening in creatinine that was attributed to remdesivir by study investigators (8).

In a cohort study conducted by the Department of Pharmacy at the University of Chicago, twenty of 135 patients with COVID-19 had severe renal impairment (15 patients with GFR <30 cc/min and 5 patients on dialysis). One patient experienced an increase in serum creatinine following remdesivir, and in three others, there was continued creatinine elevation that started before remdesivir initiation (9).

In another multicenter retrospective study of hospitalized patients with SARS-CoV-2, safety outcomes were compared between patients with GFR <30 ml/min and GFR >30ml/min who received remdesivir. This study did not identify a significantly increased risk of acute kidney injury (AKI) between the two groups (10).

Generally, because COVID-19 itself is associated with renal impairment, it is difficult to differentiate if the observed creatinine elevation is related to COVID-19 or remdesivir. In addition, COVID-19 patients with renal insufficiency have worse outcomes due to comorbidities and their proper treatment can be potentially life-saving.

According to the abovementioned, we suggest that remdesivir prescription can be considered in cases with severe SARS-COV-2 infection and advanced renal failure (GFR<30) if the potential benefit outweighed the risk of renal toxicity.

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