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ANTIVIRAL AGENTS

# Renal and Hepatic Toxicity Analysis of Remdesivir Formulations: Does What Is on the Inside Really Count?

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**ABSTRACT** It has been postulated that the injectable solution formulation of remdesivir could be more nephrotoxic than the lyophilized powder since it contains twice as much sulfobutylether-$\beta$-cyclodextrin (SBECD). Therefore, we evaluated 1,000 hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) who received remdesivir lyophilized powder or solution. A logistic regression model accounting for baseline confounders identified that neither the use of the injectable solution (odds ratio [OR], 1.05; 95% confidence interval [CI], 0.49 to 2.29; $P = 0.901$) nor a creatinine clearance of $<30$ ml/min at the time of remdesivir initiation (OR, 1.39; 95% CI, 0.51 to 3.5; $P = 0.499$) was significantly associated with acute kidney injury. Regarding hepatotoxicity, there was no significant difference in early discontinuation of remdesivir due to abnormal liver function tests between patients who received the lyophilized powder versus those who received solution (0.9% versus 2.3%, $P = 0.09$).

**KEYWORDS** lyophilized, remdesivir, SARS-CoV-2, solution, renal failure

More than 3 million people have died from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the death toll continues to rise in the absence of effective treatment options (1). Although remdesivir has not been shown to decrease mortality in patients diagnosed with SARS-CoV-2, it has been shown to be superior to placebo in shortening the time to recovery in adults hospitalized with SARS-CoV-2 (2, 3). Although the World Health Organization (WHO) has issued a conditional recommendation against the use of remdesivir in hospitalized patients, remdesivir is, at present, the only drug that is FDA approved for the treatment of SARS-CoV-2, and clinical guidelines from the National Institutes of Health (NIH) recommend the use of remdesivir in hospitalized patients with SARS-CoV-2 who require supplemental oxygen (2, 4).

Remdesivir is available as a lyophilized powder or injectable solution. Specifically, the injectable solution contains 6 g of sulfobutylether-$\beta$-cyclodextrin (SBECD), whereas the lyophilized powder contains 3 g of SBECD per 100 mg of remdesivir (5). Due to the concern that SBECD may accumulate in patients with renal disease, the NIH guidelines also suggest preferential use of the lyophilized powder formulation of remdesivir in lieu of the injectable solution (2).

However, while accumulation of SBECD in animals has been associated with liver necrosis and nephrotoxicity, these adverse effects have not been observed in humans (6). Furthermore, an observational study has reported no significant difference in the risk of adverse effects when remdesivir injectable solution was administered in 20 patients with renal impairment compared to that in patients without renal impairment (7). These findings were consistent with our previous experience, which also failed to identify a significantly increased risk of acute kidney injury (AKI) or abnormal liver function tests among 40 patients with a creatinine clearance (CrCl) of less than 30 ml/min who received remdesivir injectable solution (8). However, in the absence of robust

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**TABLE 1** Full bivariate analysis

| Baseline demographics and treatment information | Value | | *P* value |
|---|---|---|---|
| | Lyophilized powder (*n* = 443) | Solution (*n* = 557) | |
| Age (yrs) (median [IQR])[a] | 68 (57–78) | 65 (55–77) | 0.033[b] |
| Female gender (*n* [%]) | 208 (47) | 255 (45.8) | 0.712[c] |
| Body mass index > 30 kg/m$^2$ (*n* [%]) | 229 (51.7) | 274 (49.2) | 0.432[b] |
| Cirrhosis (*n* [%]) | 13 (2.9) | 9 (1.6) | 0.158[c] |
| Diabetes mellitus (*n* [%]) | 149 (33.6) | 195 (35) | 0.65[c] |
| Heart failure (*n* [%]) | 59 (13.3) | 66 (11.8) | 0.485[c] |
| Hypertension (*n* [%]) | 302 (68.2) | 330 (59.2) | 0.004[c] |
| Renal transplant (*n* [%]) | 3 (0.7) | 4 (0.7) | >0.999[d] |
| Baseline Scr[e] (median [IQR]) | 0.8 (0.6–1) | 0.9 (0.7–1) | 0.002[b] |
| Days of symptom onset to remdesivir administration (median [IQR]) | 6 (3–9) (of 429) | 7 (4–10) (of 530) | <0.001[b] |
| Scr on the day of remdesivir administration (median [IQR]) | 0.9 (0.7–1.3) | 0.92 (0.7–1.2) | 0.823[b] |
| CrCl > 30 ml/min on the day of remdesivir administration by C-G[f] (median [IQR]) | 390 (88) | 491 (88.2) | 0.956[c] |
| eGFR on the day of remdesivir administration by MDRD[g] (median [IQR]) | 79.6 (54–106.5) | 81.3 (57.3–107.3) | 0.709[b] |
| ALT > 5× ULN on the first day of remdesivir administration (*n* [%]) | 10 (2.3) (of 438) | 15 (2.7) (of 553) | 0.669[c] |
| In AKI on the day of remdesivir initiation (*n* [%]) | 38 (8.6) | 36 (6.5) | 0.204[c] |
| Baseline oxygen requirement on the day of remdesivir administration (*n* [%]) | | | <0.001[c] |
| Room air | 29 (6.5) | 13 (2.3) | |
| Low-flow nasal cannula | 341 (77) | 327 (73.8) | |
| High-flow nasal cannula | 41 (9.3) | 100 (22.5) | |
| Nonrebreather face mask | 14 (3.2) | 48 (10.8) | |
| BiPAP/CPAP[h] | 11 (2.5) | 25 (5.6) | |
| Mechanical ventilation | 7 (1.6) | 44 (9.9) | |
| Vasopressor or inotrope use during remdesivir course (*n* [%]) | 17 (3.8) | 61 (11) | <0.001[c] |
| Mechanical ventilation during remdesivir course (*n* [%]) | 24 (5.4) | 72 (12.9) | <0.001[c] |
| Concomitant nephrotoxic drug (*n* [%]) | | | |
| Vancomycin | 46 (10.4) | 77 (13.8) | 0.1[c] |
| Aminoglycoside | 2 (0.5) | 1 (0.2) | 0.587[c] |
| Intravenous acyclovir | 1 (0.2) | 1 (0.2) | >0.999[d] |
| TMP-SMX[i] | 4 (0.9) | 5 (0.9) | >0.999[d] |
| Amphotericin B | 0 (0) | 1 (0.2) | >0.999[d] |
| ACE/ARB[j] | 91 (20.5) | 97 (17.4) | 0.209[c] |
| Loop/thiazide diuretics | 148 (33.4) | 190 (34.1) | 0.816[c] |
| Tacrolimus/cyclosporine | 5 (1.1) | 4 (0.7) | 0.52[d] |
| Intravenous contrast | 45 (10.2) | 69 (12.4) | 0.27[c] |
| NSAIDS[k] | 10 (2.3) | 11 (2) | 0.757[c] |
| Days of remdesivir treatment (median [IQR]) | 5 (5–5) | 5 (5–5) | 0.242[b] |

[a]IQR, interquartile range.
[b]Mann-Whitney U test.
[c]Chi-square test.
[d]Fishers exact test.
[e]Scr, serum creatinine.
[f]Cockgroft-Gault test.
[g]eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease.
[h]BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure.
[i]TMX-SMX, trimethoprim-sulfamethoxazole.
[j]ACE/ARB, angiotensin converting enzyme/angiotensin receptor blocker.
[k]NSAIDs, nonsteroidal anti-inflammatory drugs.

data and with continued concern for SBECD accumulation, the lyophilized formulation remains reserved for patients at risk for renal injury at some institutions (9). Thus, the purpose of this study was to identify if there was an increased risk of adverse effects between patients who received remdesivir lyophilized powder and injectable solution in the general population and those with renal disease.

This was a retrospective study of adult patients with SARS-CoV-2 admitted to one of five hospitals within the Yale New Haven Health System who received remdesivir lyophilized powder or injectable solution between 11 May 2020 and 26 November 2020. Remdesivir injectable solution was exclusively used up until 5 November 2020, while remdesivir lyophilized powder was predominantly used between 5 November 2020

**TABLE 2** Safety outcomes

| Category | Value | | *P* value |
|---|---|---|---|
| | Lyophilized powder | Solution | |
| Full cohort (*n* [%]) | 443 | 557 | |
| AKI using peak SCr[a] | 14 (3.2) | 25 (4.5) | 0.218[b] |
| AKI using end-of-therapy SCr | 8 (1.8) (of 433) | 17 (3.1) (of 548) | 0.216[b] |
| ALT $>$ 5$\times$ ULN on last day of remdesivir | 22 (5.1) (of 428) | 42 (7.7) (of 548) | 0.114[b] |
| Remdesivir discontinued early due to abnormal LFTs[c] | 4 (0.9) | 13 (2.3) | 0.09[d] |
| 30-day mortality | 59 (13.3) | 97 (17.4) | 0.074[b] |
| Subset of patients with renal disease[e] (*n* [%]) | 53 | 66 | |
| AKI using peak SCr | 2 (3.8) | 6 (9.1) | 0.297[d] |
| AKI using end of therapy SCr | 1 (2) (of 50) | 6 (9.2) (of 65) | 0.136[d] |
| ALT $>$ 5$\times$ ULN on last day of remdesivir | 1 (2) (of 49) | 6 (9.4) (of 64) | 0.137[d] |
| Remdesivir discontinued early due to abnormal LFTs | 0 | 0 | $>$0.999[d] |
| 30-day mortality | 16 (30.2) | 28 (42.4) | 0.189[d] |

[a]Scr, serum creatinine.
[b]Chi-squared test.
[c]Liver function tests.
[d]Fishers exact test.
[e]CrCl of $<$30 ml/min on the day of remdesivir initiation by Cockgroft-Gault test.

and 26 November 2020. Patients were excluded if they were on renal replacement therapy prior to remdesivir administration. Patients from our previous analysis were eligible for inclusion (8). Baseline serum creatinine (SCr) was defined using the most recent SCr available prior to hospitalization for SARS-CoV-2. Patients with a SCr on the day of remdesivir initiation which was 1.5 times the baseline SCr were deemed to be in AKI (10). The primary endpoint was peak SCr AKI, defined as the highest SCr during remdesivir therapy greater than 1.5 times the SCr used on the first day of remdesivir. Remdesivir was dosed in concordance with current prescribing recommendations (5). This study was deemed exempt by the institutional review board given that criteria were met as a quality improvement study. All statistical analyses were performed with the software R with the installed Commander package (11).

Of 1,030 patients who received remdesivir, 1,000 met inclusion criteria. There were 30 patients who were excluded because they required renal replacement therapy prior to remdesivir initiation. Of the patients who met inclusion criteria, 443 received the lyophilized powder and 557 received the solution. Those who received the lyophilized powder were older than those who received the solution (68 [57 to 78] years versus 65 [55 to 77] years, respectively, $P = 0.033$), more likely to have a history of hypertension (68.2% versus 59.2%, respectively, $P = 0.004$), were less likely to require vasopressors or inotropes during remdesivir therapy (3.8% versus 11%, respectively, $P < 0.001$), and were less likely to require mechanical ventilation during remdesivir therapy (5.2% versus 11.5%, respectively, $P < 0.001$) (Table 1).

Despite these baseline differences, there were no statistically significant differences, but there were trends toward a lower incidence of AKI using peak serum creatinine (3.2% versus 4.5%, $P = 0.218$) and early discontinuation due to abnormal liver function tests (LFTs) (0.9% versus 2.3%, $P = 0.09$) in patients who received remdesivir lyophilized

**TABLE 3** Multivariate logistic regression model of factors associated with AKI using peak Scr

| Factor | OR | 95% CI | *P* value |
|---|---|---|---|
| Remdesivir solution formulation | 1.05 | 0.49–2.29 | 0.901 |
| Medical history of hypertension | 1.09 | 0.49–2.53 | 0.843 |
| Mechanical ventilation during remdesivir | 4.33 | 1.35–13.05 | 0.012 |
| Vasopressor or inotrope use during remdesivir | 4.65 | 1.51–14.8 | 0.009 |
| Older age | 1.02 | 0.99–1.05 | 0.199 |
| CrCl $<$ 30 ml/min on the day of remdesivir initiation | 1.39 | 0.51–3.5 | 0.499 |
| Days of symptom onset to remdesivir administration | 1.01 | 0.94–1.06 | 0.819 |

**TABLE 4** Descriptive report of pregnant patients

| Patient | Age of mother (yrs) | Days of remdesivir | EGA[a] (wks) | | Delivery procedure |
|---|---|---|---|---|---|
| | | | At remdesivir initiation | At delivery | |
| 1 | 27 | 3 | 39 | 39 | Vaginal (elective) |
| 2 | 27 | 5 | 39 | 39 | Vaginal (elective) |
| 3 | 35 | 4 | 36 | 36 (twins) | Cesarean (elective) |
| 4 | 18 | 4 | 39 | 39 | Cesarean (emergency) |

[a]EGA, estimated gestational age.

powder compared to those who received solution, respectively (Table 2). Additionally, in a subset of patients with a CrCl of <30 ml/min, a trend toward a lower incidence of AKI using peak serum creatinine that was not statistically significant was found in patients who received remdesivir lyophilized powder compared to that in patients who received the solution (3.8% versus 9.1%, respectively, $P = 0.297$). However, after accounting for baseline confounders using a multivariate logistic regression model, only mechanical ventilation (odds ratio [OR], 4.33; 95% confidence interval [CI], 1.35 to 13.05; $P = 0.012$) and vasopressor or inotrope use (OR, 4.65; 95% CI, 1.51 to 14.8; $P = 0.009$) were associated with peak Scr AKI (Table 3). However, use of the injectable solution formulation of remdesivir, older age, baseline hypertension, days of symptom onset to remdesivir administration, and a CrCl of <30 ml/min on the day of remdesivir administration were not significantly associated with peak Scr AKI.

Of the 7 renal transplant patients included, 3 (42.8%) had a CrCl of <30 ml/min, and 3 (42.8%) received the lyophilized formulation of remdesivir. There was 1 (14.2%) renal transplant patient who developed AKI according to the peak Scr. This patient had a baseline CrCl of <30 ml/min and received the solution formulation. There were no renal transplant patients who required early discontinuation of remdesivir due to abnormal LFTs or developed an alanine aminotransferase (ALT) level >5 times the upper limit of normal (ULN).

There were 4 patients who were pregnant at the time of remdesivir administration (Table 4). Patients 1 and 2 received remdesivir solution, while patients 3 and 4 received remdesivir lyophilized powder. All 4 pregnant patients had normal renal function and required a low-flow nasal cannula at the time of remdesivir initiation. No pregnant patients developed AKI while on remdesivir. Remdesivir was discontinued early in patient 4 due to an ALT level that was >5 times the ULN. Patients 1 and 3 were discharged from the hospital early and therefore did not complete the full remdesivir course. In terms of pregnancy outcomes, no mention of abnormalities in fetal growth, anatomic structures, physical functioning, or postnatal development were identified in the progress notes of the mothers at 5 months of follow-up.

This study is novel in that it is the first to evaluate the risk of adverse effects between patients receiving remdesivir lyophilized powder and injectable solution. In both the full cohort and among a subset of patients with renal disease, patients who received the injectable solution formulation of remdesivir did not have a significantly increased risk of AKI or early discontinuation of remdesivir due to abnormal LFTs compared to patients who received the lyophilized powder.

Nevertheless, limitations in this study are recognized. First, the retrospective quasiexperimental design resulted in several confounders in the bivariate analysis. However, after controlling for baseline confounders in a multivariate logistic regression model, neither the use of the injectable solution nor a CrCl of <30 ml/min at the time of remdesivir initiation was associated with peak Scr AKI. Second, given the small sample size of pregnant patients, renal transplant patients, and patients with a CrCl of <30 ml/min, further investigation is required in these patient populations to draw definitive conclusions. However, to our knowledge, this is the largest study to date to evaluate the risk of AKI in patients with a CrCl of <30 ml/min who received remdesivir. Observational studies, albeit with limited sample sizes, have also reported consistent safety outcomes in pregnant and renal transplant patients (12, 13).

Although further investigation is warranted, particularly in underrepresented patient populations, these data further support the safety of remdesivir in renal disease. Moreover, based on this large sample size, we conclude that the lyophilized powder formulation of remdesivir has no renal or hepatic safety advantages compared to the injectable solution.

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We declare no conflict of interest.

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