Cyclodextrin and Renal Function

The remdesivir drug label states that remdesivir is not recommended in adults with an eGFR < 30 mL/min, whereas the EUA had the additional comment, "unless the potential benefit outweighs the potential risk." Therefore, it is important to fully understand the rationale behind cautioning drug administration in this patient population. This recommendation is based on two factors: limited PK data in these patients and the presence of the inactive agent, sulfobutylether-β-cyclodextrin (SBECD) sodium salt, which can accumulate in patients with impaired renal function. SBECD is a substance known to improve the aqueous solubility and dissolution rates of therapeutic agents. It is renally excreted and its clearance is linearly correlated with creatinine clearance.[1,2]

In vivo animal studies have raised concerns about SBECD related nephrotoxicity. For example, mild toxicity in the kidney and liver as a consequence of vacuolation occurred in rats at the maximum dose of 3 g/kg, which is approximately 50-fold greater than the SBECD dose typically administered in humans.[3] Another example includes doses up to 1.5 g/kg, which produced no histopathological evidence of toxicity in dog kidneys.[3] Much of the available human data on SBECD in patients with compromised renal function comes from studies in patients on IV voriconazole, which also contains this inactive ingredient. The voriconazole studies can be readily extrapolated to the remdesivir population since the amount of SBECD exposure in patients taking remdesivir (lyophilized vials contain 3 g SBECD per 100 mg vial and concentrated solution contains 6 g SBECD per 100 mg vial) is similar to a standard exposure from a daily dose of voriconazole (3.2 g of SBECD in each 200 mg vial for a 6.4 g total daily dose). von Mach et al, characterized the levels of SBECD in 4 patients receiving voriconazole who were undergoing renal replacement therapy, and despite accumulation reaching levels seen in the original toxicology studies, there were no deleterious effects seen in the patients.[4] To be further noted, Hafner et al has shown SBECD is extensively and rapidly eliminated with renal replacement therapy or approximately 67% removal by the 6-hour renal replacement therapy as measured by the amount recovered in the dialysate.[1]

There are also two other factors to consider. The prodrug of remdesivir GS-441524 and the intermediate metabolite, GS-704277 has also been shown to accumulate in patients with renal dysfunction, but it is unclear if the potential accumulation increases the risk of any adverse effects. Le et al. report a case of a double lung transplant where the authors assert the possibility that GS-441524 and SBECD contributed to the patients renal failure and that hemodialysis is a viable option to prevent this nephrotoxicity.[5] However, this assertion regarding GS-441524 was largely refuted in a reply by Yan and Muller, who noted that the numerous other known causes of renal injury in this patient likely contributed more, such as tacrolimus, critical illness, and the SARS-CoV-2 virus itself.[6] They also discuss a very small study published by Tempestelli et al, showing rate of clearance remained similar in those with renal injury vs those without renal injury.[7] Regarding the accumulation of GS-704277, there were toxicity studies in rats performed by Gilead Sciences is an effective substrate of OAT1/3 (drug transporter in proximal tubule) and likely contributes to renal adverse events in rats. However, according to the European Medicine Agency assessment report (EMA/357513/2020), the role of intermediate L-alanine metabolite (GS-704277) in renal toxicity in rats is unlikely to be replicated in humans, because the active transport of this metabolite by human renal OAT1/3 transporters has never been detected, its rate of metabolism by plasma esterase is lower, and therefore much less GS-704277 is formed in humans.

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Real world clinical data comparing risk for safety outcomes associated with renal injury and remdesivir are sparse. The Gilead sponsored trial by Beigel et al. excluded patients with stage 4 CKD and those receiving dialysis.[8] One case series of patients on a renal unit in Mumbai, India, reviewed 46 patients with COVID who received remdesivir despite the national recommendation not to use in patients with eGFR <30 ml/min/1.73 m^2 or when there is a need for hemodialysis.[9] Thirty-six patients were on dialysis when remdesivir was initiated (16 ESRD and 20 for AKI) and the others were stage 1, 2, or 3 AKI. Eight of these patients who were not on dialysis were also renal transplant recipients. There were no adverse events from the remdesivir other than mild elevation of the hepatic enzymes. Given the majority of patients in the study were on dialysis, and a typical 4 hour intermittent dialysis session removes half of accumulated SBECD, the study is not able to comment on patients with severe renal impairment who are not yet on dialysis.[3] However, a second retrospective chart review, from the Yale New Haven Health System, compared risk of safety outcomes between COVID patients with an eCrCl < 30mL/min to those with eCrCl ≥ 30mL/min and excluded patients who were already on dialysis at time of initiation.[10] They reviewed 40 patients with an eCrCl < 30mL/min and 307 patients with eCrCl > 30mL/min. Despite the fact the renal failure group were older (median 80 yrs vs 62; p<0.001), more likely to be on vasopressors on day of initiation (30% vs 12.7%; p=0.003), and more likely to be mechanically ventilated on initiation (27.5% vs 12.4%; p=0.01), there was no significant difference in the frequency of end of therapy AKI (5% vs 2.3%; p=0.283). Of the 2 patients in the < 30mL/min group who developed AKI, one was deemed to have been from hypotension and the other from tacrolimus toxicity or contrast induced nephropathy.

A critical point to remember is that treatment with remdesivir itself is not clearly known to cause nephrotoxicity, however, SBECD may accumulate in patients with renal impairment and further potentiate the risk for nephrotoxicity. While this risk is low, the risk potentially increases with total dose and level of renal impairment.[11] For this reason, serum creatinine levels should be monitored in subjects with renal compromise receiving multiple doses of SBECD.

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