FAQ: Remdesivir Formulation and Adverse Events

This FAQ is meant to inform the reader weighing the risk vs benefit of remdesivir in their patients, but should not supersede any guidance given by their respective State department of health or authority allocating their remdesivir supply.

What do we need to know about remdesivir administration under the EUA in regard to alternate formulations, cyclodextrin-related adverse effects, and hepatotoxicity? What should the hospital do if a patient experiences an adverse event or death while receiving remdesivir?

Remdesivir has been distributed to hospitals across the country over the past few weeks under the FDA's Emergency Use Authorization (EUA). As hospitals obtain a supply of this agent, DASON has received questions related to the drug formulation, its stability and wording in the EUA related to renal impairment and hepatotoxicity. We hope this FAQ will address some of these commonly asked questions and assist you with better understanding some of the criteria for administration.

Reconstitution and Drug Formulations:

The EUA for remdesivir includes a fact sheet for healthcare providers that serves as the package insert for the agent under its current approval status. This document contains detailed information for clinicians on reconstituting and administering each of the two currently available drug formulations: remdesivir for injection (100 mg) lyophilized powder and remdesivir injection (5 mg/mL) concentrated solution. There are important distinctions between these formulations in regards to appropriate patient populations and drug storage: [1,2]

1. Pediatric patients who weigh between 3.5 kg - 40 kg may only receive the lyophilized powder formulation of remdesivir. Patients ≥40 kg may use either lyophilized powder or concentrated solution remdesivir.[1] The current federal remdesivir distributions do include limited amounts of the lyophilized powder, although not all sites are receiving this formulation.
2. Lyophilized powder vials may be stored at room temperatures up to 30°C (86°F) until reconstitution; whereas, concentrated solution requires refrigeration at temperatures (2°C to 8°C [36°F to 46°F]). The EUA contains more detailed storage requirements.[1,2]

Cyclodextrin and Renal Function:

The EUA fact sheet states that remdesivir is not recommended in adults with an eGFR < 30 mL/min unless the potential benefit outweighs the potential risk. It is important to fully understand the rationale behind cautioning drug administration in this patient population.[1] The recommendation is based on two factors: limited data in these patients and the presence of an inactive ingredient in remdesivir, sulfobutylether-β-cyclodextrin (SBECD) sodium salt, which can accumulate in patients with impaired renal function.[1,3] SBECD is a substance used improve the aqueous solubility and dissolution rates of therapeutic agents, including voriconazole and amiodarone.[1,4-6] It is renally excreted and its clearance is linearly correlated with creatinine clearance.[11,14] In vivo animal studies have raised concerns about SBECD related nephrotoxicity. For example, mild toxicity in the kidney and liver occurred in rats at the maximum dose of 3000 mg/kg, which is approximately 50-fold greater than the SBECD dose typically administered in humans.[7] In a dog kidney model, doses up to 1500 mg/kg produced no histopathological evidence of toxicity.[7]

Reviewed on 5/29/20.

Much of the available human data on SBECD in patients with compromised renal function comes from studies in patients on voriconazole. We feel 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).[1,8,9] 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.[10] 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.[11]

A critical point to remember is that treatment with remdesivir itself is not 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. For this reason, serum creatinine concentrations should be monitored daily in subjects with renal compromise receiving multiple doses of SBECD as directed in the EUA documents provided with remdesivir.

Remdesivir and Hepatotoxicity:

The EUA fact sheet for healthcare providers also states that remdesivir should be used in patients with hepatic impairment only if the benefits outweigh the risks. The guidance further specifies "Remdesivir should be discontinued in patients who develop ALT ≥ 5 times the upper limit of normal during treatment with remdesivir or ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR. Remdesivir may be restarted when ALT is < 5 times the upper limit of normal."[2] In the studies reported by Gilead in healthy adults, all liver enzyme abnormalities returned to normal with cessation of the drug.[2] It is important to note that there is an increased risk of transaminase elevation with remdesivir, observed in both healthy volunteers and patients with COVID-19. Experience thus far in the Gilead sponsored study of 397 patients with severe COVID-19 (Study GS-US-540-5773) is reported in the EUA Fact Sheet for Healthcare Providers. Grade 3 hepatic lab abnormalities were seen in 5% and Grade 4 in 2% of patients, but there was no comparator group. In a recently published study, Wang et al showed that hepatic enzyme elevation leading to discontinuation only occurred in 2 of 155 patients in the remdesivir arm.[12] It is also notable that in the experience in the PALM study involving 175 patients with Ebola virus who received remdesivir, no adverse events of transaminase elevations or hepatic events were noted.[13] While the mechanism of hepatoxicity is currently unknown, there may an increased risk in COVID-19 patients, thus we recommend daily monitoring of liver enzymes and liver function as recommended by the EUA of remdesivir.

Reporting of Death and Serious Adverse Events to FDA Medwatch:

The remdesivir EUA clearly states that the prescribing healthcare provider or their designee is responsible for reporting medication errors, death, and serious adverse events considered to be potentially attributed to remdesivir during treatment to FDA Medwatch within 7 calendar days of event onset. Serious adverse events include: "death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly/birth defect, a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly." The report may be submitted online or by mailing a postage-paid Form FDA 3500. Gilead also requires hospitals to share a copy of the submitted form with the company via fax or email. We encourage our hospitals to educate providers on this process and to establish a process to review charts of patients receiving remdesivir under the EUA to ensure this important requirement of the EUA is met by the facility.[15]

References:

1. Gilead Pharmacy Guide
2. Emergency Use Authorization (EUA) of Remdesivir (GS-5734™) Fact Sheet for Health Care Providers
3. Lexicomp Online, General Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; May 21, 2020.
4. L.-P. Ruan, B.-Y. Yu, G.-M. Fu, and D.-N. Zhu, "Improving the solubility of ampelopsin by solid dispersions and inclusion complexes," Journal of Pharmaceutical and Biomedical Analysis, vol. 38, no. 3, pp. 457–464, 2005. 12 BioMed Research International
5. M. Radtke, "Pure drug nanoparticles for the formulation of poorly soluble drugs," New Drugs, vol. 3, Article ID 68, pp. 62– 68, 2001.
6. R. H. Muller, C. Jacobs, and O. Kayser, "Nanosuspensions as ¨ particulate drug formulations in therapy: rationale for development and what we can expect for the future," Advanced Drug Delivery Reviews, vol. 47, no. 1, pp. 3–19, 2001.
7. Luke DR, Tomaszewski K, Damle B, Schlamm HT. J Pharm Sci. 2010 Aug; 99(8):3291-301.
8. VFEND package insert. http://labeling.pfizer.com/ShowLabeling.aspx?id=618
9. Yasu T. Antimicrob Agents Chemother. 2018 Aug 27;62(9):e00507-18. doi: 10.1128/AAC.00507-18. Print 2018 Sep.
10. von Mach MA, Burhenne J, Weilemann LS. Accumulation of the solvent vehicle sulphobutylether beta cyclodextrin sodium in critically ill patients treated with intravenous voriconazole under renal replacement therapy. *BMC Clin Pharmacol*. 2006;6:6.
11. Hafner V, Czock D, Burhenne J, et al. Pharmacokinetics of Sulfobutylether-Beta-Cyclodextrin and Voriconazole in Patients with End-Stage Renal Failure during Treatment with Two Hemodialysis Systems and Hemodiafiltration. *Antimicrobial Agents and Chemotherapy*. 2010;54(6):2596-2602.
12. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet*. 2020;395(10236):1569-1578.
13. Mulangu S, Dodd LE, Davey RT, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. *New England Journal of Medicine*. 2019;381(24):2293-2303.
14. Abel S, Allan R, Gandelman K, Tomaszewski K, Webb DJ, Wood ND. Pharmacokinetics, safety and tolerance of voriconazole in renally impaired subjects: two prospective, multicentre, open-label, parallel-group volunteer studies. *Clin Drug Investig*. 2008;28(7):409-420.
15. Remdesivir EUA. Gilead. Accessed 29 May 2020 at: https://www.gilead.com/-/media/files/pdfs/remdesivir/eua-fact-sheet-for-hcps_01may2020.pdf