Remdesivir in Patients with Acute or Chronic Kidney Disease and COVID-19

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On May 1, 2020, after review of yet unpublished data from available clinical trials, the US Food and Drug Administration issued an emergency use authorization (EUA) to permit the use of remdesivir, a nucleotide analog that inhibits viral RNA-dependent RNA polymerase (RDRP), for treatment of adults and children hospitalized with severe coronavirus disease 2019 (COVID-19). EUA was granted after an interim analysis of 606 recoveries in the randomized, placebo-controlled National Institute of Allergy and Infectious Diseases Adaptive Covid-19 Treatment Trial ($n=1063$ participants from 47 United States sites and 21 international sites). Remdesivir reduced the median time to recovery (11 versus 15 days; hazard ratio, 1.31; 95% confidence interval, 1.12 to 1.54; $P<0.001$) compared with placebo, and overall mortality among patients treated with remdesivir was 8.0% compared with 11.6% among those treated with placebo ($P=0.59$).[1] Notably, patients with severe AKI and ESKD were excluded from this and all other remdesivir trials on the basis of eGFR cutoffs (either 50 or 30 ml/min per 1.73 m^2) (Table 1). As a result, the EUA fact sheet for health care providers states the following.[1]

> The pharmacokinetics of remdesivir have not been evaluated in patients with renal impairment. Adult and pediatric patients (>28 days old) must have creatinine clearance determined and full-term neonates (≥7 days to ≤28 days old) must have serum creatinine determined before dosing. Remdesivir is not recommended in adults and pediatric patients (>28 days old) with eGFR less than 30 mL per minute or in full-term neonates (≥7 days and ≤28 days old) with serum creatinine ≥1 mg/dL *unless the potential benefit outweighs the potential risk.* (emphasis added)

Severe COVID-19 infection leads to AKI in up to 20%–40% of critically ill patients, and the ESKD population has a higher risk for exposure and is at increased risk for severe infection. Yet, many of these patients may not be considered for treatment with this potentially beneficial agent. Here, we review what is known about remdesivir and the potential risks of its administration in patients with impaired kidney function.

REMDESIVIR

Replication of the single-stranded RNA genome of severe acute respiratory syndrome coronavirus 2 depends on an RDRP. Remdesivir is a prodrug that, after metabolized to remdesivir triphosphate, acts as an analog of ATP, competing for incorporation by RDRP and interfering with viral RNA replication (Figure 1). Originally developed as an investigational agent for Ebola, it has activity against severe acute respiratory syndrome coronavirus 2 *in vitro* and in animal models.[4,5] Remdesivir has a molecular weight of 602.6 g/mol with limited water solubility. It is administered intravenously at a dose of 200 mg once followed by 100 mg daily for a total of 5–10 days in adults and children ≥40 kg. Pharmacokinetic data among individuals with normal kidney function demonstrated that remdesivir and its active metabolite are predominantly (74%) renally eliminated. The plasma $t_{1/2}$ of parent remdesivir is short (1–2 hours), but the $t_{1/2}$ of the active metabolite remdesivir triphosphate is approximately 20–25 hours,[4] with wide distribution to most tissues.[6,7] Concerns about the drug's potential toxicity in patients with kidney disease relate both to remdesivir's actions and to the potential accumulation of its sulfobutylether-β-cyclodextrin (SBECD) carrier.

RISKS OF REMDESIVIR

Because remdesivir triphosphate is a weak inhibitor of mammalian DNA and RNA polymerases, it is considered to have low potential for mitochondrial toxicity.[1] Although other nucleotide/nucleoside antivirals (*i.e.*, tenofovir) can lead to mitochondrial injury in renal tubular epithelial cells, kidney

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Table 1. Summary of available clinical trial data

Trial Name/NCT No.	Study Design	*N*, Population	eGFR Cutoff	Remdesivir Duration, d	Outcomes
NIAID ACTT-1 study	Double-blind, placebo-controlled RCT	1063 hospitalized adult patients, international	30	10	Interim analysis: median time to recovery 11 versus 15 d; $P<0.001$; mortality 8% versus 11.6%; $P=0.06$
NCT04292899	Randomized, open-label trial	197 adults with severe COVID-19, international	50	5 versus 10	70% clinical recovery and 59% clinical recovery by 14 d in 5- and 10-d groups
Compassionate use program	Open label, multicenter, nonrandomized	>1200 adults, 76 children with COVID-19, international	30	10	Report of 61 treated patients, 8 lost to follow-up; 36 of 53 improved at a median follow-up of 18 d[2]
NCT04257656	Double-blind, placebo-controlled RCT	237 adults with severe COVID-19, China	30	10	No difference in time to clinical improvement; equivalent number of renal AEs in placebo and remdesivir arms[3]

In all cases, remdesivir dosing begins with a 200-mg intravenous loading dose followed by 100 mg intravenously daily. Currently available clinical trial data supporting remdesivir use are shown. NCT, national clinical trial; NIAID ACTT-1, National Institute of Allergy and Infectious Diseases Adaptive Covid-19 Treatment Trial; RCT, randomized, controlled trial; AE, adverse event.

toxicity occurs after prolonged exposure and therefore, would be extraordinarily rare to occur within a 5- or 10-day therapy course.[8] Notably, toxicology studies in rhesus monkeys showed kidney injury and casts at doses of 5, 10, and 20 mg/kg for 7 days, considerably higher than the EUA dose.[1] Available data from a single randomized, controlled trial in COVID-19 did not demonstrate an increased risk of renal adverse events in patients randomized to receive remdesivir.[3] In addition, significant renal adverse events were not reported when remdesivir was used in a clinical trial for Ebola.[9]

Transaminase elevations have been reported in healthy volunteers and COVID-19–infected patients receiving remdesivir. Under the EUA, liver function tests must be monitored daily, and remdesivir is discontinued in patients with alanine aminotransferase more than five times the upper limit of normal.[1] Infusion-related reactions have also been reported.

RISK OF SBECD CARRIER ACCUMULATION

Because remdesivir has limited water solubility, the intravenous preparation contains the vehicle SBECD. SBECD is a large, cyclic oligosaccharide that is predominantly excreted through glomerular filtration with a $t_{1/2}$ of elimination of <2 hours in patients with normal kidney function.[10] Animal studies have associated SBECD accumulation with liver necrosis and renal tubule obstruction,[11] which occurred in animals at doses 50- to 100-fold higher than expected for a 5- to 10-day remdesivir course. Each 100 mg of lyophilized powder and solution of remdesivir contain 3 and 6 g of SBECD, respectively, well below the maximum recommended safety threshold dose of 250 mg/kg per day of SBECD.

Much of what is known about the pharmacokinetics and clinical effects of SBECD in kidney failure is gleaned from literature of intravenous voriconazole, which also uses this carrier. Although oral voriconazole is preferred for patients with renal failure, intravenous therapy may be necessary in patients with invasive fungal infections who are critically ill with poor gut perfusion that limits oral absorption. In this setting, short courses are generally well tolerated, without significant adverse events noted despite documented accumulation of SBECD above levels in patients with normal kidney function.[10–14] Further, SBECD is readily removed by continuous RRT and hemodialysis, and significant accumulation only occurs in

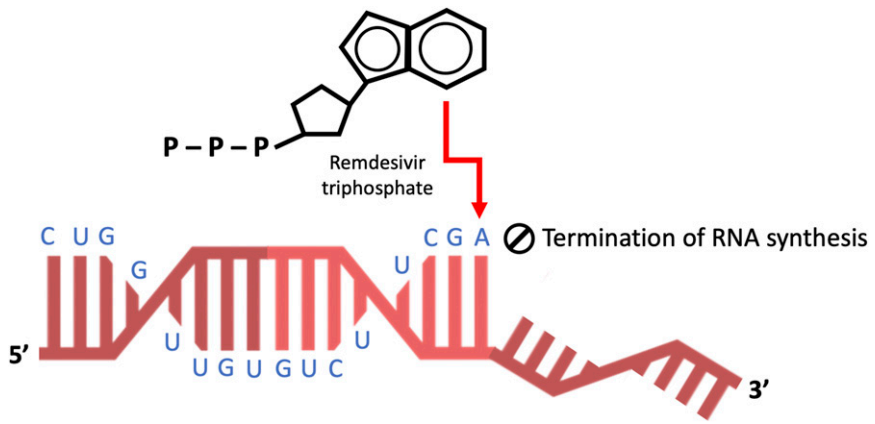

Figure 1. Mechanism of action of remdesivir. Remdesivir triphosphate leads to delayed chain termination after three additional bases have been added.

patients when dialysis is held for prolonged periods.[12] Although SBECD exposure is higher than in patients with normal kidney function, RRT seems to keep this exposure within a limit that is generally considered safe. Although numbers are limited, liver function test elevation attributed to SBECD use in patients with kidney failure was rare and transient.[10,13]

Conclusive data on the safety of remdesivir among individuals with eGFR<30 ml/min per 1.73 m^2 are lacking. Nevertheless, the limited duration of treatment (5–10 days) and relatively low concentration of SBECD carrier suggest that its benefits may outweigh risk in select patients with eGFR<30 ml/min per 1.73 m^2. Patients without underlying liver disease who are expected to undergo continuous or intermittent dialysis or those with AKI expected to be transient may be the best initial candidates to receive remdesivir. Ultimately, patients or their surrogates should be informed of the lack of information in patients with eGFR<30 ml/min per 1.73 m^2 and should consent for use in this emergency setting.

Evaluating treatments for patients with COVID-19 who have AKI and ESKD is a major unmet clinical need given that these patients are at high risk of suffering excess morbidity and mortality. Of note, favipiravir, another RDRP inhibitor under investigation for treatment of COVID-19, is also predominantly excreted through the urine; thus, patients with eGFR<20 ml/min per 1.73 m^2 are also excluded from clinical trials (NCT04358549). Although the World Health Organization's Solidarity trial, which allows clinician discretion in enrolling patients,[15] may include some patients with kidney disease, an urgent need remains for dedicated trials in patients with COVID-19 who have eGFR<30 ml/min per 1.73 m^2. Although this is not a unique example of the exclusion of patients with kidney disease from clinical trials assessing critical treatments,[16] the magnitude and pace of the current pandemic and the vulnerability of these patients create an immediate call to action for trials and systematic retrospective studies that can inform clinical decision making and increase access to a potentially life-saving therapy in this patient population.

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A. Kim has served on an advisory board for Biomarin, Inc. (gene therapy). M. Sise discloses personal fees and participation in scientific advisory boards for Gilead in the area of viral hepatitis. All remaining authors have nothing to disclose.

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