Pediatric RESEARCH

CORRESPONDENCE

COVID-19 and remdesivir in pediatric patients: the invisible part of the iceberg

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Remdesivir, a nucleotide analog prodrug that inhibits viral RNA polymerases, resulting in delayed chain termination during viral RNA replication, has shown in vitro and in vivo activity against novel coronavirus disease (SARS-CoV-2).[1] According to a recent case report, in a pediatric patient with severe COVID-19 presenting with respiratory failure and severe thrombocytopenia, a temporal clinical improvement was observed after tocilizumab and remdesivir coadministration.[2] A novel broad-spectrum antiviral, the prodrug nucleotide analog remdesivir, has also been shown to be effective in congenital Ebola virus infection in a newborn baby without any evidence of drug-related toxicity.[3] Although recent reports show that acute symptomatic SARS-CoV-2 infection is relatively rare in pediatrics and much less severe than adults, parenteral remdesivir, which has been approved also for pediatric patients by the US Food and Drug Administration and for adolescent patients (≥12 years) by European Medicines Agency, has been proven to offer potential benefits.[4] Nonetheless, some limitations may appear in terms of administering and close monitoring of remdesivir in neonatal intensive care unit (NICU) and pediatric intensive care unit (PICU) patients with severe disease ($SpO_2 \leq 94\%$ on room air or requiring oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)).

COVID-19 infection causes acute kidney injury, and continuous renal replacement therapy (CRRT) is the most used blood purification technique when needed. Remdesivir use is not recommended in pediatric patients whose estimated GFR <30 mL/min (older than 28 days), and full-term neonates with serum creatinine level 1 mg/dl or greater. The formulation contains the excipient, 3 g of sulfobutylether-beta-cyclodextrin sodium salt (SBECD) per 100 mg of remdesivir, which may accumulate in pediatric patients with kidney impairment and receiving renal replacement therapies (e.g., hemodialysis, peritoneal dialysis, and CRRT). The accumulation of SBECD may trigger kidney impairment.[5] In addition, if pediatric patients require mechanical ventilation/ECMO, treatment duration of remdesivir can be extended to 10 days. The interaction between the ECMO circuit and the physicochemical properties of remdesivir (e.g., circuit factors, physicochemical characteristics, increased volume of distribution, and clearance) may lead to significant changes in the pharmacokinetics of COVID-19 treatment and so required dose adjustments.[6] Besides, since remdesivir increases liver aminotransferase levels (adverse-effect incidence, 11.7%), its use is not recommended in pediatric patients having hepatic impairment and hepatotoxicity with baseline ALT ≥ 5 times the upper limits of normal.[5] In a 5-year-old child who received remdesivir during induction chemotherapy for newly diagnosed pediatric acute lymphoblastic leukemia with concomitant SARS-CoV-2 infection, remdesivir was well tolerated with no adverse effects, except for the expected increase in ALT secondary to induction chemotherapy.[7] Just in case, using the Child–Pugh score (total bilirubin, albumin, INR, and the presence of ascites and encephalopathy) and pediatric end-stage liver disease (PELD) score (age, bilirubin, albumin, INR, and history of growth failure) for dose adjustment in COVID-19 patients with hepatic impairment should be considered by clinicians. On the other hand, according to a case series, a total of seven doses of remdesivir, which were well tolerated by stable creatinine and liver function tests throughout therapy, were successfully administered to a 19-day-old full-term infant.[8] As a result, lack of safety or pharmacokinetic data increases the need for clinical trials for pediatric patients with hepatic or kidney impairment (including renal replacement therapies) or ECMO requirement day by day.

When the administration during lactation is examined, remdesivir is given intravenously because of poor oral absorption; therefore, infants are not likely to absorb clinically important amounts of the drug through breastfeeding. Given this limited information, it does not appear that mothers receiving remdesivir need to avoid nursing, but until more clinical trials are available, remdesivir should be used with careful infant monitoring during breastfeeding.[9]

Finally, the combination of P-glycoprotein inhibitors (e.g., hydroxychloroquine, azithromycin, cyclosporine, tacrolimus, and amiodarone) with remdesivir may have increased the intrahepatocellular concentration above the toxicity threshold that caused the hepatocellular toxicity for drug–drug interactions (DDIs). Another point to be mentioned is since hydroxychloroquine (30–60 days) and amiodarone (26–107 days) have very long half-lives, DDIs may occur even after discontinuation of treatment.[10] Hydroxychloroquine exhibits an antagonistic effect on the intracellular metabolic activation and antiviral activity of remdesivir. Due to this antagonism observed in vitro and the possibility of reduced efficacy of remdesivir, concomitant use of remdesivir and hydroxychloroquine is not recommended in pediatric patients. NICU and PICU patients with COVID-19 are expected to have clinical or subclinical acute symptomatic seizures, and these patients may have epilepsy comorbidity. Therefore, when antiepileptic drugs (AEDs) are concomitantly prescribed with remdesivir, the serum concentration of remdesivir may be significantly reduced due to strong induction by AEDs (e.g., carbamazepine, phenobarbital, phenytoin, and primidone) with CYP3A4 and CYP2C9 enzymes.[5]

In view of such information, a clear understanding of the clinical pharmacokinetics and clinical significance of potential DDIs for remdesivir is needed to provide patient-centered care for NICU and PICU patients in the ongoing pandemic.

ADDITIONAL INFORMATION

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