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Review

Use of remdesivir in children with COVID-19 infection: a quick narrative review

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Abstract. SARS-CoV-2 infection has a severe course in a small percentage of children. Remdesivir has shown promising results in reducing hospitalisation time in adults, but data on mortality rate are conflicting and few studies are available on its use use in antivirals in children. We performed a quick narrative review of the available literature data regarding the usage of remdesivir in children and neonates. In children, remdesivir showed good safety profile, however bradicardia events have been reported in children. Remdesivir is currently recommended by several guidelines in some subgroups of children with severe COVID-19, and should also be considered in critically ill patients, always in the context of the overall clinical picture and drug availability. (www.actabiomedica.it)

Key words: COVID-19, SARS-CoV-2, remdesivir, children

Introduction

COVID-19 disease occurs in a mild form in most majority of children. Most of children with COVID-19 can be managed with supportive care alone. A small percentage of children (about 1%) develop severe or critical illness, requiring assisted ventilation and admission to intensive care units during the infection (1) while a post-infectious inflammatory syndrome related to SARS-CoV-2 (MIS-C) generally occurring 4 weeks after the infection can cause a life-threatening multi-organ failure (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological).

Therapies for COVID-19 includes two broad categories of drugs: agents that limit viral replication (i.e. remdesivir and monoclonal antibodies) and agent that regulate the hyperinflammatory immune response (i.e. steroids and Tocilizumab). Current guidelines recommend use of antivirals in well selected subgroups of children as reported in Table 1 (2). However, most recommendation rely on adult data pending results from ongoing pediatric clinical trials. Currently, remdesivir is the only antiviral drug recommended in children with severe or critical SARS-CoV-2 disease.

Remdesivir (Veklury®) is a nucleotide analogue pro-drug that binds to viral RNA-dependent RNA polymerase of SARS-CoV-2 and other coronaviruses (including SARS-CoV and MERS-CoV), inhibiting viral replication through abnormal termination of RNA transcription after undergoing to metabolic activation to form the intracellular active triphosphate. It is administered intravenously (3).

The results of nonclinical evaluations suggested that RDV is primarily metabolized (80% of total metabolism) in the liver and then primarily eliminated in urine

Table 1. Pharmacologic therapies for coronavirus disease 2019.

	Mechanism of action	NIH indications (from….)
I.Antiviral therapies		
Remdesivir	Nucleoside analog prodrug, binds viral RNA polymerase and leads to termination of the RNA chain.	Hospitalized children aged ≥12 years with COVID-19 who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen (BIII). Hospitalized children aged ≥16 years with COVID-19 who have an emergent or increasing need for supplemental oxygen regardless of whether they have risks factors for severe disease In consultation with a pediatric infectious disease specialist, remdesivir can be considered for hospitalized children of all ages with COVID-19 who have an emergent or increasing need for supplemental oxygen
Bamlanivimab-etesevimab and Casirivimab-indevimab	Monoclonal Antibodies that bind the receptor binding domain of the SARS-CoV-2 spike protein, preventing viral attachment to human cells	Insufficient evidence for the Panel to recommend either for or against the use of anti-SARS-CoV-2 monoclonal antibody products for children with COVID-19 who are not hospitalized but who have risk factors for severe disease. Based on adult studies, bamlanivimab plus etesevimab or casirivimab plus imdevimab may be considered on a case-by-case basis for nonhospitalized children who meet Emergency Use Authorization (EUA) criteria for high-risk of severe disease, especially those who meet more than one criterion or are aged ≥16 years.
High-Titer convalescent plasma	Plasma containing high titers of ant-SARS-CoV-2 antibodies	The Panel recommends against the use of convalescent plasma for hospitalized children with COVID-19 who do not require mechanical ventilation, except in a clinical trial (AIII). The Panel recommends against the use of convalescent plasma for pediatric patients with COVID-19 who are mechanically ventilated (AIII). In consultation with a pediatric infectious disease specialist, high-titer convalescent plasma may be considered on a case-by-case basis for hospitalized children who meet the EUA criteria for its use.
II.Immunomodulatory agents		
Dexamethasone	Anti-inflammatory	Hospitalized children with COVID-19 who require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation
Tocilizumab	Monoclonal antibody IL-6 receptor blockade	Insufficient evidence for the Panel to recommend either for or against the use of tocilizumab in hospitalized children with COVID-19 or multisystem inflammatory syndrome in children (MIS-C)
Baricitinib	Anti-inflammatory through JAK inhibition	Emergency use in combination with remdesivir in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or ECMO
Intravenous immune globulin (IVIG)	Anti-inflammatory	MIS-C first-line treatment
Anti IL-1 molecules (Anakinra)	Monoclonal antibody IL-1 receptor blockade	MIS-C second-line treatment

as the nucleoside metabolite. Remdesivir has low predicted drug–drug interaction based on in vitro data (4).

Simulations through a physiologically –based on pharmacokinetic model (5) and data from a trial on the remdesivir regimen for treatment of Ebola in children (6) indicated that to maintain therapeutic exposures of remdesivir and its metabolites, it has to be use a dosage regimen as following: on the first day, a loading dose of 5 mg/kg (maximum dose 200 mg) is administered; on subsequent days, the recommended dose is 2.5 mg/kg every 24 hours (maximum daily dose 100 mg).

Hereby we performed a quick narrative review summarizing efficacy and safety published data concerning the use of remdesivir in children.

Methods

A search of the literature contained in the MEDLINE database, including studies published in English from 01/01/2019 to 17/07/2021 (all types), was performed. Pertinent articles from the references of the studies selected were also considered. An additional review of the literature was performed prior to final drafting.

Results

Several observational studies and series of pediatric clinical cases reporting the use of different molecules for antiviral purposes in children in different countries where retrieved by literature searches. Several case series collecting data on clinical presentation and management of children hospitalized with COVID 19 infection in the "real world" settings reported a quite common use of remdesivir, but specific detailed results regarding clinical outcomes by treatment group are not available.

Efficacy

Trials in adults have shown a possible role for remdesivir in decreasing median recovery time with a more likable clinical improvement at day 15, in severe but non-critical patients. One of the trials that gave the clearest indications in this sense was the US trial, ACTT-1 trial (Adaptive COVID-19 Treatment Trial 1) (7). A subsequent trial including evaluated different courses of remdesivir (5 vs. 10 days), the subjects who had received a 5 days regimen showed significantly higher odds of reaching an improvement of clinical status, (8) this trial included children aged ≥ 12 years with severe COVID-19 disease who did not require mechanical ventilation at baseline. The SOLIDARITY trial (9), an ongoing multicentre randomised clinical trial conducted by the World Health Organization (WHO), assessed four different molecules (remdesivir, hydroxychloroquine, Lopinavir/Ritonavir, and interferon β1a) for the treatment of COVID-19. The trial included 11330 adult patients in 30 countries, randomly assigned to receive one of the four experimental treatments or the care standard, with open control. To date, none of these drugs has been proven to clearly benefit the course of the disease and mortality. In a systematic review (10) and meta-analysis of 52 RCTs and 4 studies with total of 7324 patients. No mortality benefit was observed with remdesivir versus control group. Significantly higher rates of clinical improvement and faster time to clinical improvement was observed in the remdesivir group versus control group. Considering the above data, remdesivir was approved by both the Food and Drug Administration(FDA) and the EMA for the treatment of adults and children (aged at least 12 and weighing at least 40 kg) with COVID-19 requiring hospitalisation and oxygen therapy, but not ventilatory support. It is also available for emergency use for the treatment of COVID-19 in hospitalized children under the age of 12 and weighing at least 3.5 kg. With regard to the effect of remdesivir on currently known SARS-CoV-2 variants such as B.1.1.7 and B.1.351 (known as the "UK" and "South African" variants respectively), a recent study of more than 9,000 virus isolates from around the world that included these variants showed low variability and high genetic stability of the viral RNA replication complex, so the risk of these variants exhibiting intrinsic resistance to remdesivir was considered minimal by the authors. Data on actual remdesivir efficacy on children come from 2 observational studies:

- a Spanish multicenter observational study on 8 children under 16 years of age who received compassion-

ate treatment with remdesivir that achieved successful clinical outcome, without observing adverse events.

- an observational study (11) conducted on 77 children treated with remdesivir for severe COVID-19 showed that most of patients recovered and the rate of serious adverse events was low. At baseline, 90% of children required supplemental oxygen and 51% required invasive ventilation. At day 28, 88% of patients decreased oxygen-support requirement, 83% recovered, and 73% were discharged. In the group of children requiring invasive ventilation at baseline, 90% were extubated, 80% recovered, and 67% were discharged. There were 4 deaths, of which 3 were attributed to COVID-19.

Little information is available on the use of remdesivir during the neonatal period. Only two clinical cases are reported, the first one in a full-term neonate with severe COVID-19 and the second one in a five-week-old ex-preterm infant with critical illness, both infants recovered completely and the drug was well tolerated (12). Given the lack of data related to children, in February 2021, the Pediatric Infectious Diseases Society (13) in the United States published interim guidance to establish criteria for the use of remdesivir in children with COVID-19. Similar documents have been published in other countries, including Italy.

Recommendations

The most important criterion is disease severity, defined by the need for oxygen therapy, ventilatory support and clinical stability (Table 2).

Patients with mild to moderate illness, those that did not require Oxygen therapy, should be managed with supportive care alone without requiring further intervention. Those requiring supplemental oxygen therapy but not ventilatory support are the selected subgroup that could benefit from therapy with remdesivir; a case-by-case assessment is still essential based on the severity and course of symptoms, drug availability, and other possible risk factors due to poor prognosis. Children who have history of medical complexity (e.g., due to neurologic impairment, developmental delays, or genetic syndromes including trisomy 21), obesity, chronic cardiopulmonary disease, severe immunodeficiency and age >12 yo may be at risk for severe disease. It is also preferable to administer the drug in the early stages of the illness.

The treatment should last to a maximum of five days in severe cases and five-ten days in critical cases; in this case, the drug is initially administered for five days, with subsequent extension to no more than ten days if there is no response.

Adverse events

The most common adverse events of remdesivir are the following: hypertransaminasemia (32.1%), renal impairment (14.4%), increased creatinine (11.2%) and respiratory failure (6.4%) (14), in the recent meta-analysis by Lai et al., no increased risk of adverse events was found compared with the control group. So, it is mandatory to monitor renal and hepatic function

Table 2. Management of COVID-19 based on disease severity (adapted from Chiotos et al (13).
An important fact for the clinician is that remdesivir is not currently recommended or authorised by Agenzia Italiana del Farmaco (AIFA) for use in critically ill patients on assisted ventilation, who are therefore currently excluded from treatment.

	Mild	**Moderate**	**Severe**	**Critical**
Respiratory support required	No need for additional oxygen therapy, upper airway involvement	No need for additional oxygen therapy, lower airway involvement	New or increased oxygen demand compared to baseline, *WITHOUT* the need for invasive or non-invasive ventilatory support	Need for invasive or non-invasive ventilatory support, multi-organ failure *OR* rapid clinical deterioration that does not yet meet these criteria
Treatment	Supportive therapy	Supportive therapy	Remdesivir up to five days recommended (unless contraindicated)	The use of remdesivir 5-10 days should be considered in selected critical patients unless contraindicated*
			3.5-40 kg: Loading dose on day one at 5 mg/kg intravenously, followed by 2.5 mg/kg intravenously every 24 hours	
			>40 kg: Loading dose on day one at 200 mg intravenously, followed by 100 mg intravenously every 24 hours	

during treatment, and the main contraindications to the use of remdesivir are the presence of hepatic damage or renal failure. In particular, the drug should not be administered in the following situations:

- alanine transaminase (ALT) values ≥ five times the upper limit
- ALT increase associated with conjugated hyperbilirubinemia, increased alkaline phosphatase or extension of the International Normalized Ratio (INR)
- infants aged > 28 days with a glomerular filtration rate < 30ml/min
- full-term infants aged 7-28 days with creatinine ≥ 1 mg/dL

Moreover cardiovascular adverse effects are reported in 2 case series such as marked sinus bradycardia that began acutely on initiation of remdesivir and resolved almost immediately on cessation of the drug (15).

Conclusion

The extent of the benefit of using remdesivir in clinical practice, also in adults, is the subject of much debate and discussion. To date, remdesivir has not been shown to be associated with a significant reduction in mortality in patients with COVID-19 or a marked reduction in the length of hospitalisation, despite promising results from the ACTT-1 trial.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Manti S, Licari A, Montagna L, et al. SARS-CoV-2 infection in pediatric population. Acta Biomed 2020;91:e2020003.
2. Levy ER, Blumenthal J, Chiotos K. Coronavirus disease 2019 in children. Curr Opin Infect Dis 2021. Epub ahead of print.
3. Garazzino S, Lo Vecchio A, Pierantoni L, et al. Epidemiology, clinical features and prognostic factors of pediatric SARS-CoV-2 infection: results from an italian multicenter study. Front Pediatr 2021;9:649358.
4. Humeniuk R, Mathias A, Kirby BJ, et al. Pharmacokinetic, pharmacodynamic, and drug-interaction profile of remdesivir, a SARS-CoV-2 replication inhibitor. Clin Pharmacokinet 2021;60:569-583.
5. Lutz JD, Mathias A, German P, Pikora C, Reddy S, Kirby BJ. Physiologically-based pharmacokinetic modeling of remdesivir and its metabolites to support dose selection for the treatment of pediatric patients with COVID-19. Clin Pharmacol Ther 2021;109:1116-1124.
6. Mulangu S, Dodd LE, Davey RT Jr, et al.A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med 2019; 381:2293–303.
7. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - final report. N Engl J Med 2020;383:1813-26.
8. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med 2020;383:1827-37.
9. Pan H, Peto R, Henao-Restrepo AM, et al. Repurposed antiviral drugs for Covid-19 - interim WHO solidarity trial results. N Engl J Med 2021;384:497-511.
10. Singh S, Khera D, Chugh A, Khera PS, Chugh VK. Efficacy and safety of remdesivir in COVID-19 caused by SARS-CoV-2: a systematic review and meta-analysis. BMJ Open 2021;11:e048416.
11. Goldman DL, Aldrich ML, Hagmann SHF, et al. Compassionate use of remdesivir in children with severe COVID-19. Pediatrics 2021;147:e2020047803.
12. Wardell H, Campbell JI, VanderPluym C, Dixit A. Severe acute respiratory syndrome Coronavirus 2 infection in febrile neonates. J Pediatric Infect Dis Soc 2020;9:630-5.
13. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter interim guidance on use of antivirals for children with Coronavirus disease 2019/Severe Acute Respiratory Syndrome Coronavirus 2. J Pediatric Infect Dis Soc 2021;10:34-48.
14. Charan J, Kaur RJ, Bhardwaj P, et al. Rapid review of suspected adverse drug events due to remdesivir in the WHO database; findings and implications. Expert Rev Clin Pharmacol 2021;14:95-103.
15. Gubitosa JC, Kakar P, Gerula C, Nossa H, Finkel D, Wong K, Khatri M, Ali H. Marked sinus bradycardia associated with remdesivir in COVID-19: a case and literature review. JACC Case Rep 2020;2:2260-2264.

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