Accepted Article

DR. MELIS DENIZ (Orcid ID : 0000-0002-9740-4196)

Article type : Short Commentary

Drugs being investigated for children with COVID-19

Melis Deniz, Anıl Tapısız, Hasan Tezer

Department of Pediatric Infectious Diseases, Faculty of Medicine, Gazi University, Ankara, Turkey

Corresponding author: Dr. Melis Deniz (ORCID ID: 0000-0002-9740-4196)

Department of Pediatric Infectious Diseases, Faculty of Medicine, Gazi University, Emniyet Mah. Mevlana Bulv. No: 29 Yenimahalle, Ankara, Turkey

E – mail address: mlsdnz@gmail.com

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/APA.15399

This article is protected by copyright. All rights reserved

Accepted Article

We were interested to read the review paper on COVID-19 by Ludvigsson in *Acta Paediatrica* (1). The author mentioned that COVID-19 appeared to be milder in children than in adults but said there was a knowledge gap about antiviral treatment in severely ill patients. We would like to provide some comments about the experimental drugs that are being considered to treat children with the disease.

Although the course of COVID-19 is milder in children, the use of experimental drugs for severely ill patients is still being debated. Remdesivir, which has shown promise in treating COVID-19 in adults, is a nucleotide analogue that inhibits viral ribonucleic acid (RNA) polymerase. The effectiveness of the drug was shown during the outbreaks of Ebola, severe acute respiratory syndrome coronavirus (SARS) and Middle-East syndrome related coronavirus (MERS). It has also been shown to be effective *in vitro* against SARS-CoV-2, which is the virus that causes COVID-19 (2). Despite the absence of data on children with COVID-19, no adverse effects were observed when a baby who was diagnosed with Ebola was followed up after being treated with remdesivir at 19 days of life (3). The paediatric dose was specified according to the infant's body weight, based on Ebola studies and adult tests. For children under 40 kg this was 5 mg/kg/dose as a single loading dose on day one, intravenously infused over 30 minutes. This was then followed by a 2.5 mg/kg/dose intravenously once a day. For children over 40 kg the respective doses were 200 mg and 100 mg, delivered in exactly the same way (4). The American Food and Drug Administration has approved the emergency use of remdesivir for treating hospitalised children with severe COVID-19. Severe disease has been defined as having an oxygen saturation of up to 94% room air and requiring supplementary oxygen, mechanical ventilation or extracorporeal membrane oxygenation (5). Phase three trials are currently evaluating the effectiveness of remdesivir on treating COVID-19 in adults and in children above 12 years of age (6).

Favipiravir, which is an RNA-dependent RNA polymerase inhibitor, is another drug that is being assessed as a potential treatment for COVID-19. It was effective during the 2014-2016 Ebola outbreak and the 2009 influenza outbreak. When it was tested on COVID-19 patients above 16 years of age, it demonstrated faster viral clearance and higher recovery rates than lopinavir and ritonavir (7). The treatment options for children were reviewed as soon as COVID-19 emerged, as the case fatality rate had been high in children during the Ebola outbreak. The paediatric use of

This article is protected by copyright. All rights reserved

favipiravir is of interest because it can be well tolerated by adults and the tablets can be ground up and taken with food or liquids. A dose scheme has been created for the drug, based on the body weight of children above 10 kg (8).

In conclusion, the efficacy and safety of the drugs we have discussed are still being debated. There appear to be experimental drugs that, based on the experiences in the SARS, MERS, Ebola and influenza outbreaks, could be used for severely ill children with COVID-19 who do not respond to other treatment options.

ABBREVIATIONS

RNA, ribonucleic acid; SARS, severe acute respiratory syndrome coronavirus; MERS, Middle-East syndrome related.

FUNDING

None.

CONFLICTS OF INTEREST

None.

REFERENCES

1) Ludvigsson J. Systematic Review of COVID-19 in Children Shows Milder Cases and a Better Prognosis Than Adults. *Acta Paediatr* 2020 Jun;109(6):1088-1095.
2) Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *N Engl J Med*. 2020 Apr 10; NEJMoa2007016. https://doi: 10.1056/NEJMoa2007016
3) Dörnemann J, Burzio C, Ronsse A, Sprecher A , De Clerck H, Van Herp et al. First Newborn Baby to Receive Experimental Therapies Survives Ebola Virus Disease. *J Infect Dis* 2017 Jan 15;215(2):171-174.
4) WHO. Deliberations on design options for randomized controlled clinical trials to assess the safety and efficacy of investigational therapeutics for the treatment of patients with Ebola virus disease. 2018, Geneva. Available from: URL : www.who.int/ebola/drc-2018/summaries-of-evidence-experimental-therapeutics.pdf?ua=1. Accessed on April 13,2020.
5) US Food and Drug Administration. Remdesivir letter of Emergency Use Authorization ,2020. Available from: URL: www.fda.gov/media/137564/download. Accessed on May 11, 2020.

This article is protected by copyright. All rights reserved

6) ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier: NCT04292899, Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants With Severe Coronavirus Disease (COVID-19); March 3,2020. Available from : URL: https://www.clinicaltrials.gov/ct2/show/NCT04292899?cond=covid19+remdesivir&draw=2&rank=4. Accessed on April 16, 2020.
7) Cai Q., Yang M., Liu D., Chen J., Shu D., Xia J. et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study, *Engineering (Beijing)* 2020 Mar 18. https://doi: 10.1016/j.eng.2020.03.007.
8) Bouazza N, Treluyer JM, Foissac F, Mentré F, Taburet AM, Guedj J et al. Favipiravir for children with Ebola. *Lancet.* 2015 Feb 14;385(9968):603-604

Accepted Article

This article is protected by copyright. All rights reserved