European Journal of Pediatrics (2021) 180:1317–1322
https://doi.org/10.1007/s00431-020-03876-1

SHORT COMMUNICATION

Compassionate use of remdesivir in children with COVID-19

Ana Méndez-Echevarría[1] · Antonio Pérez-Martínez[2] · Luis Gonzalez del Valle[3] · María Fátima Ara[4] · Susana Melendo[5] · Marta Ruiz de Valbuena[6] · Jose Luis Vazquez-Martinez[7] · Antonio Morales-Martínez[8] · Agustín Remesal[9] · Kinga Amália Sándor-Bajusz[10] · Fernando Cabañas[11] · Cristina Calvo[1]

Received: 30 May 2020 / Revised: 5 November 2020 / Accepted: 11 November 2020 / Published online: 16 November 2020

Abstract

Children represent a minority of total COVID-19 cases, but studies have reported severe disease and death in pediatric patients. Remdesivir (RDV) has recently demonstrated promising results in adults with COVID-19, but few data have been reported to date in children.

A nationwide multicenter observational study was conducted on children with confirmed SARS-CoV-2 receiving compassionate treatment with RDV in Spain. Eight patients were included in the study, four infants and four older children [median age 5 years old; IQR 4 months–11.6 years old]. Half of them had complex underlying medical conditions, and the rest were mostly infants (3/4). Six out of eight children needed Pediatric Intensive Care Unit Admission. No RDV-related adverse outcomes were observed in our patients. Seven have reached successful clinical outcome, but one patient with serious clinical status died due to complications. However, she received RDV very late after the first COVID-19 symptom.

Conclusions: In our cohort, most of the patients achieved successful clinical outcome, without observing adverse events. Clinical trials of RDV therapy for children with COVID-19 are urgently needed, to assess the safety, tolerability, efficacy, and pharmacokinetics of RDV in children, as this could be an effective treatment in severe cases.

What is Known:
- *Remdesivir has not been approved to treat COVID-19 in children under 12 years old, although the drug is currently being prescribed in critically ill children.*
- *Remdesivir has recently demonstrated promising results in adults with COVID-19, but few data have been reported to date in paediatric population.*

What is New:
- *We report a multicentre cohort of children with confirmed SARS-CoV-2 and severe COVID-19 disease receiving remdesivir during the first month of the pandemic in Spain.*
- *No remdesivir-related adverse outcomes were observed in most of the cases. Seven patients reached successful clinical outcome, and one died due to complications (bacterial sepsis).*

Communicated by Nicole Ritz

✉ Ana Méndez-Echevarría
amendezes@yahoo.es

Antonio Pérez-Martínez
aperezmartinez@salud.madrid.org

Luis Gonzalez del Valle
lgvalle@salud.madrid.org

María Fátima Ara
fatiaramon@gmail.com

Susana Melendo
susanamelendo@upiip.com

Marta Ruiz de Valbuena
martaruizde@hotmail.com

Jose Luis Vazquez-Martinez
jvazquezm@salud.madrid.org

Antonio Morales-Martínez
moralesmartinezantonio@gmail.com

Agustín Remesal
agusremesal@hotmail.com

Kinga Amália Sándor-Bajusz
sandor.kinga@pte.hu

Fernando Cabañas
fernando.cabanas@quironsalud.es

Cristina Calvo
ccalvorey@gmail.com

Extended author information available on the last page of the article

Keywords SARS-CoV-2 · COVID-19 · Remdesivir · Children · Infant

Introduction

Remdesivir (RDV) may be a potential drug to treat COVID-19. Preliminary data from China reported that RDV was not associated with clinical benefits in adult patients treated with the drug [1]. However, recent results of clinical trials including more than 1000 adults observed a shorter time to recovery with RDV compared to placebo [2].

RDV has received emergency approval for treating COVID-19, although few data in children are available, as most clinical trials have focused on adult patients [1, 2]. In addition, pediatric pharmacokinetics of RDV that analyze the association between drug dose, plasma exposure, and intracellular drug exposure is currently unavailable [3]. However, RDV use is recommended in children with severe COVID-19 [4], the only antiviral drug that has shown some effectiveness in clinical trials [2].

Young infants and children with underlying medical conditions are at higher risk for developing severe disease, and deaths as previously reported [5, 6]. For these reasons, data of RDV use in the pediatric population is needed, as the drug is currently being prescribed in critically ill children.

Patients and methods

We conducted a nationwide observational study of children under 16 years of age with COVID-19 who received compassionate treatment with RDV in Spain during March 2020. Informed consent was obtained prior to drug administration and study inclusion.

A formal request for RDV was made to *Gilead Science* through a web platform completing an assessment form with patient's clinical status information. The drug administration was approved by the Spanish Agency of Medicines/Medical Devices. The formulation and administration of the drug was performed in compliance with the manufacturer's instructions.

Children who weighed 40 Kg or more at screening received a single 200 mg dose on day one, following by a daily 100-mg dose from day 2 up to 10 days. For the rest of the children, a single dose of 5 mg/kg on day one was prescribed, followed by a daily dose of 2.5 mg/kg from day 2 up to 10 days.

Results

Eight patients were included. The clinical characteristics of the patients are detailed in Table 1 (some data partially published [7, 8]).

Four patients were previously healthy children and the other four had underlying medical conditions. The mean age was 5 years (IQR 0.3–11), although children with underlying conditions were older [mean age 10.3 years (IQR 3–14.2)] than the previously healthy children [mean age 0.38 years (IQR 0.19–8)].

All patients presented hypoxemia, six of them requiring Pediatric Intensive Care Unit (PICU) admission, five mechanical ventilation (14 to 23 days), and one case noninvasive ventilation subsequently followed by high-flow oxygen therapy and prone position (*Supplementary File*). Four patients required inotropic drug support (2 to 13 days). Clinical features other than respiratory symptoms are collected in Table 1.

Two infants presented with a coinfection (respiratory syncytial virus and metapneumovirus, respectively). One older child had just been treated for a *P. jirovencii* pneumonia when COVID-19 was diagnosed (*Patient 8*).

Three patients presented a previously negative SARS-CoV-2 PCR; two of these tests were performed 1 to 3 days before the first positive result (nasopharyngeal swab). In the third patient (*Patient 8*), SARS-CoV-2 PCR test was requested twice on respiratory samples obtained from tracheal aspirates, both with negative results. A lack of therapeutic response was therefore confirmed and a bronchoalveolar lavage was performed with a third PCR test, which was positive 4 days after the first test.

All patients received hydroxychloroquine 2 to 6 days prior to RDV administration. Six patient received azithromycin (2 to 8 days before RDV therapy), four lopinavir/ritonavir (2 to 5 days before RDV therapy), and five corticosteroids (four of them 3–6 days after RDV and 1 to 3 days before RDV administration). Four patients were treated with tocilizumab 1 to 3 days before RDV (Table 1).

Mean RDV treatment duration was 7.1 ± 0.89 days. Median time from first COVID-19 symptoms to RDV administration was 8 days (IQR; 7.25–11.75), from PICU admission to RDV administration 5.5 days (IQR; 2.75–9.25), and from first positive polymerase-chain-reaction (PCR) result 6.5 days (IQR; 4.5–7).

The PCR was monitored on six children after starting treatment. Mean days from RDV initiation to clearance of SARS-CoV-2 was 9.5 days (IQR: 4.25 to 29–25). One immunocompromised girl presented prolonged virus excretion (72 days).

Liver enzymes were monitored every 2 or 3 days in all the patients while they received the drug. None of the patients had elevated liver enzymes. *Patient 8* presented a multifactorial renal impairment due to multiple organ failure and nephrotoxic drugs (voriconazole and liposomal amphotericin B). No clinical or other laboratory toxicity was observed.

Patient 8 died due to COVID-19 and severe complications 10 days after initial RDV administration (Table 1). The rest of

Table 1 Main clinical characteristics of pediatric patient's compassionately treated with RDV

	Previously healthy patients				Patients with underlying diseases			
Patient	1	2	3	4	5	6	7	8
Age	11 years	1.5 months	5 months	4.5 months	1 years	15 years	9 years	11 years
Sex	M	M	M	M	F	F	M	F
Underlying medical condition	NO	NO	NO	NO	Premature (GA 29 weeks) ILD	CTLA-4 haploinsufficiency HSCT BOOP Lobectomy	T-ALL (complete remission)	AntiMDA5-associated dermatomyositis ILD
Duration of hospital stay (days)	10	16	28	22	22	11	20	32 (until death)
Days in PICU	5	14	23	22	13	0	0	23 (until death)
Days from first positive PCR result to start of RDV	3	6	7	6	7	4	8	7
Main clinical symptoms	Multilobar pneumonia Respiratory insufficiency	Multilobar pneumonia Respiratory insufficiency Anemia	Lobar pneumonia Respiratory Insufficiency Coagulopathy Pericardiac/pleural effusion Hypopnea-apnea Low level of consciousness	Multilobar pneumonia Respiratory insufficiency Sepsis-like disease (culture -)	Multilobar pneumonia Respiratory insufficiency Sepsis-like (culture -)	Respiratory insufficiency	Febrile syndrome Respiratory insufficiency HLH	Multilobar pneumonia Respiratory insufficiency Myocarditis Pneumothorax Pneumomediastinum Pneumoretroperitoneum HLH
Basic therapy for underlying medical condition prior to COVID-19	NO	NO	NO	NO	Oxygen HCQ AZM	Oxygen Corticoids TPM-SMX Voriconazole Spironolactone Intermittent home oxygen support	6-Mercaptopurine Methotrexate	Cyclophosphamide Tacrolimus Tofacitinib TPM-SMX Corticoids
Treatment for COVID-19	HQC AZM L/R TCZ RDV	HQC AZM RDV	HQC AZM Corticosteroids L/R TCZ RDV	HQC Corticosteroids L/R RDV	HQC AZM Corticosteroids IVIG α-IFN L/R RDV	HQC RDV	HQC AZM Corticosteroids TCZ RDV	HQC AZM Corticosteroids TCZ Plasmapheresis RDV
Reason for RDV prescription	ICU admission Worsening respiratory status	ICU admission Worsening respiratory status	ICU admission Worsening respiratory status	ICU admission Worsening respiratory status	ICU admission Worsening respiratory status	Underlying condition Hypoxemia	Underlying condition Hypoxemia Severe lymphopenia ⇑ Inflammatory parameters	ICU admission Worsening respiratory status

Table 1 (continued)

	Previously healthy patients				Patients with underlying diseases			
Patient	1	2	3	4	5	6	7	8
Respiratory support	NIV	IMV	IMV	IMV	IMV	Oxygen	Oxygen	IMV
Inotropic support		Dopamine Noradrenaline	Noradrenaline		Milrinone Adrenaline			Noradrenaline
SARS-CoV-2 PCR monitorization after starting RDV	Not performed	Negative 2 days after RDV	Not performed	Positive 4 and 8 days after RDV Negative 15 days after RDV	Negative 8 days after RDV	Positive 6, 21 and 65 days after RDV Negative 72 days after RDV	Negative 11 days after RDV	Negative 5 days after RDV
Clinical complications			Sepsis due to MSSA	Ventilation-associated pneumonia *(P. aeruginosa)*				Sepsis (*E. faecimum*) Thrombotic microangiopathy Coagulopathy Multiorgan dysfunction syndrome Death

α-IFN, alpha interferon; *AZM*, azythromycin; *BOOP*, bronchiolitis obliterans organizing pneumonia; *F*, female; *GA*, gestational age; *HLH*, hemophagocytic histiolymphocytosis; *HSCT*, hematopoietic stem cell transplantation; *HQC*, hydroxychloroquine; *ILD*, interstitial lung disease; *IMV*, invasive mechanical ventilation; *IVIG*, intravenous immune globulin; *L/R*, lopinavir/ritonavir; *M*, male; *MSSA*, Meti-sensitive *S. aureus*

NIV, non-invasive ventilation; *PICU*, pediatric intensive care unit; *RDV*, remdesivir; *T-ALL*, T cell acute lymphoblastic leukemia; *TCZ*, tocilizumab; *TPM-SMX*, Trimethoprim/sulfometoxazole

the patients presented a good clinical outcome and were discharged [mean hospital stay of 20 days (IQR; 11–22)].

Discussion

We report a cohort of children with severe COVID-19 compassionately treated with RDV during the first month of the pandemic in Spain. Seven out of eight patients achieved successful clinical outcome. The last child died, although RDV was started 11 days after the first probable COVID-19 symptom.

During the first weeks of the epidemic in Madrid, 10% of confirmed COVID-19 children required PICU admission [9]. Large case series of children diagnosed with COVID in Europe and the USA during the initial peak of the pandemic demonstrated that younger age and pre-existing medical conditions were associated with worse clinical outcomes [5, 6] as we have also observed in our cohort. Although most children did not required hospital admission [6], the rate of PICU admission was considerably high among those who require hospitalization (8 to 33%) [5, 6]. Despite of this, only 4.5% of the 569 hospitalized children reported in these series received RDV [5, 6].

Clinical trials including more than 1000 adults treated with RDV observed a shorter recovery time in these patients compared to placebo [2]. Although children were not included in this trial, the benefits of RDV were observed among the youngest patients [2].

RDV is a promising treatment in the early course of the illness, when the virus is multiplying in the host's tissues [10]. However, patients usually received RDV in a mean of 9 days from symptoms onset to drug administration [2], as we have observed in our cohort. In addition, the benefit of RDV has been observed only in patients with mild disease [2]. Therefore, it is important to prescribe the drug early in the course of the disease, especially in children with risk factors for worse clinical outcome.

However, early RDV administration in children with COVID-19 is a challenge. False-negative PCR results has been reported [11], as we have reported in three cases. In addition, RDV must be compassionately use in children under 12 years of age, formally requested and approved before its clinical use. This could delay the drug administration.

Clinical trials and research efforts during this pandemic have focused on adult care [2, 3]. However, pediatricians must try to provide the best care for children, an especially vulnerable population, even in such a critical situation as the pandemic. Few data regarding safety, tolerability, efficacy, and pharmacokinetics of RDV in children below 12 years of age are currently available [3], but the use of RDV in this population must be considered in cases of severe COVID-19 [4].

Interpretation of our data is limited by the small size of the cohort and the lack of a randomized control group. Many of our patients received the drug when the disease had progressed. Clinical trials of RDV therapy for children with COVID-19 are urgently needed in order to evaluate the safety, tolerability, efficacy, and pharmacokinetics of RDV in children.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00431-020-03876-1.

Acknowledgments We acknowledge Pilar Guerra García, David Moreno, Blanca Rosich, Antoni Soriano-Arandes, and Cesar Perez-Caballero for their substantial contribution to this manuscript.

Authors' contributions AME was responsible for study design, methodology, supervision, and oversight of the study.

APM, SM; MRdV; JLVM; AR; MFA: They were responsible for data collection. They reviewed and approved the final manuscript. AME, KSB, LGDV: They wrote the initial draft of the manuscript.

FC and CC: They were responsible for supervision. They reviewed the manuscript and approved the final manuscript. All authors have made substantial contributions, critically review the manuscript, approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data Availability N/A

Compliance with ethical standards

Conflicts of interest The corresponding author (Ana Mendez-Echevarria) is the principal investigator in La Paz Hospital of the Clinical Trial GS-US-540-5823 (Promoter: GILEAD®). The corresponding author has been parted of the Advisory Board COVID-19 of GILEAD®.

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors. In this retrospective study, patients remain unidentifiable and in consultation with the Ethic Committee of La Paz University Hospital, no consent for publication was required.

Consent to participate Signed informed consent was obtained from all participants included in the study.

Consent for publication Signed informed consent for data publication was obtained from all participants included in the study.

Code availability N/A

References

1. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y et al (2020) Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 395:1569–1578
2. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T,

Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC (2020) Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 383: 1813–1826. https://doi.org/10.1056/NEJMoa2007764

3. Maharaj AR, Wu H, Hornik CP, Balevic SJ, Hornik CD, Smith PB et al (2020) Simulated assessment of pharmacokinetically guided dosing for investigational treatments of pediatric patients with coronavirus disease 2019. JAMA Pediatr 174:e202422
4. Chiotos K, Hayes M, Kimberlin DW, Jones SB, James SH, Pinninti SG, Yarbrough A, Abzug MJ, MacBrayne CE, Soma VL, Dulek DE, Vora SB, Waghmare A, Wolf J, Olivero R, Grapentine S, Wattier RL, Bio L, Cross SJ, Dillman NO, Downes KJ, Oliveira CR, Timberlake K, Young J, Orscheln RC, Tamma PD, Schwenk HT, Zachariah P, Aldrich ML, Goldman DL, Groves HE, Rajapakse NS, Lamb GS, Tribble AC, Hersh AL, Thorell EA, Denison MR, Ratner AJ, Newland JG, Nakamura MM (2020) Multicenter interim guidance on use of antivirals for children with COVID-19/SARS-CoV-2. J Pediatric Infect Dis Soc. https://doi.org/10.1093/jpids/piaa115
5. Götzinger F, Santiago-García B, Noguera-Julián A, Lanaspa M, Lancella L, Calò Carducci FI, Gabrovska N, Velizarova S, Prunk P, Osterman V, Krivec U, Lo Vecchio A, Shingadia D, Soriano-Arandes A, Melendo S, Lanari M, Pierantoni L, Wagner N, L'Huillier AG, Heininger U, Ritz N, Bandi S, Krajcar N, Roglić S, Santos M, Christiaens C, Creuven M, Buonsenso D, Welch SB, Bogyi M, Brinkmann F, Tebruegge M, Pfefferle J, Zacharasiewicz A, Berger A, Berger R, Strenger V, Kohlfürst DS, Zschocke A, Bernar B, Simma B, Haberlandt E, Thir C, Biebl A, vanden Driessche K, Boiy T, van Brusselen D, Bael A, Debulpaep S, Schelstraete P, Pavic I, Nygaard U, Glenthoej JP, Heilmann Jensen L, Lind I, Tistsenko M, Uustalu Ü, Buchtala L, Thee S, Kobbe R, Rau C, Schwerk N, Barker M, Tsolia M, Eleftheriou I, Gavin P, Kozdoba O, Zsigmond B, Valentini P, Ivaškeviciene I, Ivaškevicius R, Vilc V, Schölvinck E, Rojahn A, Smyrnaios A, Klingenberg C, Carvalho I, Ribeiro A, Starshinova A, Solovic I, Falcón L, Neth O, Minguell L, Bustillo M, Gutiérrez-Sánchez AM, Guarch Ibáñez B, Ripoll F, Soto B, Kötz K, Zimmermann P, Schmid H, Zucol F, Niederer A, Buettcher M, Cetin BS, Bilogortseva O, Chechenyeva V, Demirjian A, Shackley F, McFetridge L, Speirs L, Doherty C, Jones L, McMaster P, Murray C, Child F, Beuvink Y, Makwana N, Whittaker E, Williams A, Fidler K, Bernatoniene J, Song R, Oliver Z, Riordan A (2020) COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health 4:653–661
6. Kim L, Whitaker M, O'Halloran A, Kambhampati A, Chai SJ, Reingold A et al (2020) Hospitalization rates and characteristics of children aged <18 years hospitalized with laboratory-confirmed COVID-19 - COVID-NET, 14 States, March 1-July 25, 2020. Morb Mortal Wkly Rep 69:1081–1088
7. Pérez-Martinez A, Guerra-García P, Melgosa M, Frauca E, Fernandez-Camblor C, Remesal A, Calvo C (2020) Outcome of SARS-CoV-2 infection in immunosuppressed children in Spain. Eur J Pediatr. https://doi.org/10.1007/s00431-020-03793-3
8. Quintana-Ortega C, Remesal A, Ruiz de Valbuena M, de la Serna O, Laplaza-González M, Álvarez-Rojas E, Udaondo C, Alcobendas R, Murias S (2020) Fatal outcome of anti-MDA5 juvenile dermatomyositis in a paediatric COVID-19 patient: a case report. Mod Rheumatol Case Rep 20:1–7
9. Tagarro A, Epalza C, Santos M, Sanz-Santaeufemia FJ, Otheo E, Moraleda C, Calvo C (2020) Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid. JAMA Pediatr 8: e201346. https://doi.org/10.1001/jamapediatrics.2020.1346
10. Siddiqi HK, Mehra MR (2020) COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplant 39(5):405–407. https://doi.org/10.1016/j.healun.2020.03.012
11. Xiao AT, Tong YX, Gao C, Zhu L, Zhang YJ, Zhang S (2020) Dynamic profile of RT-PCR findings from 301 COVID-19 patients in Wuhan, China: a descriptive study. J Clin Virol 127:104346. https://doi.org/10.1016/j.jcv.2020

Affiliations

Ana Méndez-Echevarría[1] · Antonio Pérez-Martínez[2] · Luis Gonzalez del Valle[3] · María Fátima Ara[4] · Susana Melendo[5] · Marta Ruiz de Valbuena[6] · Jose Luis Vazquez-Martinez[7] · Antonio Morales-Martínez[8] · Agustín Remesal[9] · Kinga Amália Sándor-Bajusz[10] · Fernando Cabañas[11] · Cristina Calvo[1]

[1] Paediatric Infectious Diseases Department, Translational Research Network in Paediatric Infectious Diseases (RITIP), La Paz University Hospital, Paseo de la Castellana 261, 28046 Madrid, Spain

[2] Paediatric Hemato-Oncology Department, Translational Research in Pediatric Oncology, Hematopoietic Transplantation and Cell Therapy, La Paz University Hospital, La Paz Institute for Health Research (IdiPAZ), Madrid, Spain

[3] Pharmacy Department, La Paz University Hospital, Madrid, Spain

[4] Department of Paediatrics and Neonatology, Quironsalud Madrid University Hospital, Madrid, Spain

[5] Paediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron (HUVH). Vall d'Hebron Research Institute (VHIR), Barcelona, Spain

[6] Pediatric Pulmunology Unit, La Paz University Hospital, Madrid, Spain

[7] Paediatric Intensive Care Unit, Ramon y Cajal Universitary Hospital, Madrid, Spain

[8] Paediatric Intensive Care Unit, Universitary Regional Málaga Hospital, Málaga, Spain

[9] Paediatric Rheumatology Unit, La Paz University Hospital, Madrid, Spain

[10] Department of Paediatrics, University of Pécs Medical School, Pécs, Hungary

[11] Department of Neonatology, Quironsalud Madrid University Hospital and Biomedical Research Foundation, La Paz University Hospital Madrid, Madrid, Spain