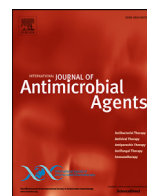




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



## Hot Topic

## Arguments in favour of remdesivir for treating SARS-CoV-2 infections

Wen-Chien Ko<sup>a,b</sup>, Jean-Marc Rolain<sup>c,d</sup>, Nan-Yao Lee<sup>a,b</sup>, Po-Lin Chen<sup>a,b</sup>, Ching-Tai Huang<sup>e</sup>,  
Ping-Ing Lee<sup>f</sup>, Po-Ren Hsueh<sup>g,h,\*</sup>



<sup>a</sup> Department of Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan

<sup>b</sup> Center for Infection Control and Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan

<sup>c</sup> Aix-Marseille Université, Institut de Recherche pour le Développement (IRD), Assistance 7 Publique-Hôpitaux de Marseille (AP-HM), MEPHI, 27 boulevard Jean Moulin, 13005 8 Marseille, France

<sup>d</sup> IHU Méditerranée Infection, 19–21 boulevard Jean Moulin, 13005 Marseille, France

<sup>e</sup> Department of Infectious Diseases, Chang Gung Memorial Hospital, Taoyuan, Taiwan

<sup>f</sup> Department of Pediatrics, National Taiwan University Children's Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

<sup>g</sup> Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

<sup>h</sup> Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

## ARTICLE INFO

## Article history:

Received 16 February 2020

## Keywords:

Remdesivir

Betacoronavirus

SARS-CoV-2

Coronavirus disease 2019

COVID-19

Wuhan pneumonia

## 1. Introduction

Since the end of 2019, an increasing number of cases of pneumonia were reported in Wuhan, followed by other cities and provinces in China and many other countries [1–7], and the 2019 novel coronavirus (2019-nCoV) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [8], a new human pathogen, was identified as the cause of Wuhan pneumonia. The disease spectrum of SARS-CoV-2 infection, so-called coronavirus disease 2019 (COVID-19), was known to be diverse in severity, ranging from asymptomatic carriage to mild respiratory tract infection and severe or fatal pneumonia. Moreover, SARS-CoV-2 can be transmitted within the family, in the community, among cruise passengers and in hospitals, and has become a public-health emergency of international concern (PHEIC), declared by the World Health Organization (WHO) on 30 January 2020. As of 28 February 2020, laboratory-confirmed cases of COVID-19 have been reported in 56 countries and territories with more than 83 382 cases reported

globally; more than 78 832 of these cases were reported from China (<https://www.worldometers.info/coronavirus/>).

In the view of virologists, human and zoonotic coronaviruses belong to the family Coronaviridae in the order Nidovirales. Currently, there are four genera in the subfamily Coronavirinae of the family Coronaviridae: *Alphacoronavirus*, *Betacoronavirus*, *Deltacoronavirus* and *Gammacoronavirus*. Before the current COVID-19 epidemic, there were six recognised human respiratory coronaviruses, including HCoV-229E (*Alphacoronavirus*), HCoV-OC43 (*Betacoronavirus*), HCoV-NL63 (*Alphacoronavirus*) and HKU1 (*Betacoronavirus*) that often cause mild respiratory tract infection as well as SARS-CoV and MERS-CoV that in contrast can lead to severe or even fatal lower respiratory tract disease [9]. The seventh human coronavirus, SARS-CoV-2, belongs to the genus *Betacoronavirus*, which also contains SARS-CoV and MERS-CoV.

So far, no drugs, monoclonal antibodies or vaccines have been approved to treat human infections due to coronaviruses. Several pre-existing and potential drug candidates, including chloroquine and remdesivir, have been considered [10–12]. The discovery and marketing of new compounds often require months to years. However, in the face of the global spread of COVID-19, effective interventions for severe cases of COVID-19 are urgently required. Although little is known about SARS-CoV-2, several insights may

\* Corresponding author. Present address: Departments of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, Number 7, Chung-Shan South Road, Taipei 100, Taiwan.

E-mail address: [hsoren@ntu.edu.tw](mailto:hsoren@ntu.edu.tw) (P.-R. Hsueh).

be gained from its more well-known family member, SARS-CoV [11]. Here we review the literature on an existing but not approved antiviral agent, remdesivir, which exhibits promising in vitro antiviral activity and preliminary clinical experiences in the treatment of COVID-19.

## 2. Mode of action of remdesivir: a nucleotide analogue inhibitor of RNA-dependent RNA polymerases

Although SARS-CoV and SARS-CoV-2 share only 82% RNA sequence identity, their RNA-dependent RNA polymerase (RdRp) shares 96% sequence identity [11]. Therefore, drugs targeting viral RdRp proteins of SARS-CoV are likely to be effective for SARS-CoV-2. For the RdRp target in the genus *Betacoronavirus*, there are several potential drugs or compounds, including favipiravir, ribavirin, penciclovir, galidesivir, remdesivir, 6'-fluorinated aristeromycin analogues and acyclovir fleximer analogues [12]. Remdesivir (GS-5734), the phosphoramidate prodrug of an adenosine C-nucleoside [13], has a similar structure to tenofovir alafenamide, which is a nucleotide analogue of adenosine 5-monophosphate with antiviral activity against hepatitis B virus and human immunodeficiency virus (HIV). It was developed by Gilead Science Inc. and has not been licensed or approved anywhere so far. Moreover, GS-441524 has been recommended for the treatment of cats with feline infectious peritonitis, which is uncommon but fatal and is caused by a feline coronavirus [14].

The chemical formula of remdesivir, with a molecular mass of 602.6, is  $C_{27}H_{35}N_6O_8P$ . Remdesivir can be effectively metabolised to active nucleoside triphosphate in several human cell lines [15]. An in vitro study has demonstrated that nucleoside triphosphate works as an incorporation competitor with adenosine triphosphate, confuses viral RdRp, acts as a delayed RNA chain terminator against Ebola virus [15,16], evades proofreading by viral exoribonuclease, and causes a decrease in viral RNA production [17]. Recently, the antiviral activity of remdesivir was demonstrated at the stage after virus entry into Vero E6 cells, supporting its antiviral mechanism as a nucleotide analogue [18].

## 3. In vitro efficacy of remdesivir for different viruses

In 2016, remdesivir (GS-5734) was reported to be active against Ebola virus in multiple human cell types, including primary macrophages and human endothelial cells, with low half-maximal effective concentration ( $EC_{50}$ ) values of 0.06–0.14  $\mu M$  [15]. In addition, remdesivir was reported to exhibit antiviral activity in vitro against Marburg virus [15], Paramyxoviridae (such as parainfluenza type 3 virus, Nipah virus, Hendra virus, and measles and mumps viruses) and Pneumoviridae (such as respiratory syncytial virus) [19].

In primary human airway epithelial cell culture, a biologically relevant in vitro model of pulmonary infection, remdesivir was shown to inhibit SARS-CoV [half-maximal inhibitory concentration ( $IC_{50}$ ) = 0.069  $\mu M$ ] and MERS-CoV ( $IC_{50}$  = 0.074  $\mu M$ ) replication [20]. In addition, remdesivir was effective against many human and zoonotic coronaviruses, including HCoV-NL63, HCoV-OC43, HCoV-229E, mouse hepatitis virus (MHV) (*Betacoronavirus*), SARS-CoV and related bat coronaviruses WIV1 and SHC014 (*Betacoronavirus*), MERS-CoV and related bat coronavirus HKU5, and porcine deltacoronavirus (*Deltacoronavirus*) [17,20,21]. A recent study reported the in vitro antiviral activity of remdesivir against the causative aetiological pathogen of Wuhan pneumonia, nCoV-2019/BetaCoV/Wuhan/WIV04/2019. The  $EC_{50}$  of remdesivir in Vero E6 cells was 0.77  $\mu M$  and the  $EC_{90}$  was 1.76  $\mu M$  [18]. Therefore, remdesivir is regarded to have 'broad-spectrum' anti-coronavirus activity.

Even before approval and clinical use, the concern of antiviral resistance against remdesivir has been studied. Using MHV as the tested coronavirus, two of three lineages of wild-type MHV in the presence of increased concentrations of GS-441524 were lost after 17 and 20 repeated passages, and only one lineage after 23 passages selected a low-level resistant mutant, conferring a 5.6-fold increase in the  $EC_{50}$  [17]. Two amino acid substitutions (F467L and V553L) were noted in non-structural protein (nsp) 12, the RdRp of MHV, and also resulted in a 6-fold increase in the  $EC_{50}$  in SARS-CoV. However, the remdesivir-resistant MHV with F476L and V553L mutations was outcompeted by wild-type MHV in the absence of GS-5734, suggestive of the effect of remdesivir resistance on decreased viral fitness. Of note, in the mouse model of SARS-CoV infection, the remdesivir-resistant SARS-CoV-infected mice lost less weight and had a more evident decline in pulmonary viral loads by 4 days after infection than wild-type SARS-CoV-infected mice, indicative of attenuated pathogenicity of remdesivir-resistant SARS-CoV. The above findings indicate a high genetic barrier for remdesivir to develop resistance as well as decreased fitness and pathogenicity in remdesivir-resistant mutants, and further encourage the therapeutic potential of remdesivir in the treatment of newly emerging COVID-19.

## 4. Clinical efficacy and tolerance of remdesivir in human and animal diseases

With the favourable in vitro antiviral activity of remdesivir, it has been further tested in animal models of different viral infections. In a rhesus monkey model of Ebola virus disease, daily administration of 10 mg/kg remdesivir for 12 days profoundly suppressed the replication of Ebola virus and protected all infected animals against this lethal infection [15]. Besides, in a mouse model of SARS-CoV infection, prophylactic and early therapeutic dosing of remdesivir effectively decreased the viral load in the lungs and improved pulmonary function [20].

According to the previous rhesus monkey model of Ebola virus infection, an intravenous (i.v.) 10 mg/kg dose of remdesivir could lead to a lasting level of active triphosphate form in peripheral blood mononuclear cells (PBMCs), >10  $\mu M$ , for at least 24 h [15], and such data may be valuable in the same animal species with SARS-CoV-2 infection. Although in the animal study the plasma half-life of remdesivir was short (0.39 h), remdesivir was rapidly distributed into PBMCs, converted into its active form within 2 h post-infusion, and had an intracellular half-life of 14 h. In the absence of any human pharmacokinetic information, such data from rhesus monkeys indicate that parenteral daily dosing of remdesivir may achieve sustained intracellular concentrations of nucleotide triphosphate, which are above its  $EC_{90}$  for SARS-CoV-2. These in vitro and animal data provide preliminary evidence supporting the clinical potential of remdesivir for human infections caused by contemporary and emerging coronaviruses, including SARS-CoV-2.

Early clinical experience of remdesivir therapy in a female nurse from Scotland with Ebola meningoencephalitis, which was supported by the detection of Ebola virus RNA in plasma and cerebrospinal fluid, its first use for Ebola virus infection in humans, was reported in 2016 [22]. She was successfully treated with high-dose corticosteroids and 14 days of remdesivir therapy (once-daily infusion of 150 mg over 2 h for 2 days, and then daily 225 mg for another 12 days). No serious clinical or biochemical events occurred except a transient rise of serum amylase level.

In a recently published, randomised controlled clinical trial of four experimental therapeutics for Ebola virus disease, a total of 175 patients ever received remdesivir [23]. Although remdesivir therapy was not favoured due to the high mortality rate of 53.1% (93/175), no detailed clinical or biochemical side effects associated with remdesivir therapy was ever described; the safety profile of

remdesivir was not challenged. One patient on remdesivir therapy developed hypotension and cardiac arrest after discontinuation of the loading dose; however, the authors explained that such an adverse event cannot be excluded to be related to underlying Ebola virus disease, a potentially fatal infectious disease.

## 5. Preliminary data on the clinical efficacy of remdesivir in COVID-19 pneumonia and ongoing clinical trials

The first case of COVID-19 in Washington, USA, was compassionately treated with i.v. remdesivir for the progression of pneumonia on Day 7 of hospitalisation [24]. Interestingly, the patient's condition improved and no obvious adverse effects were observed. Of note, real-time reverse transcription PCR testing for SARS-CoV-2 in nasopharyngeal and oropharyngeal swabs remained positive at 4 days after the administration of remdesivir, but the authors noted a trend in the decline of viral load in nasopharyngeal swabs [cycle threshold values: illness Day 7 (the day of remdesivir administration), 23–24; Day 11, 33–34; and Day 12, 37–40]. The oropharyngeal swab tested negative for SARS-CoV-2 one day later. Of course, it is too early to conclude the direct antiviral effect of remdesivir on enhanced clearing of viral loads in the respiratory tract, but it indeed suggests a promising therapeutic effect of remdesivir.

There are two phase 3, randomised, double-blind, placebo-controlled multicentre clinical trials currently ongoing in China. These trials have been submitted to ClinicalTrials.gov on 31 January 2020 and are designed to evaluate the efficacy and safety of parenteral remdesivir in hospitalised adults with mild-to-moderate and severe COVID-19, i.e. NCT04252664 (<https://clinicaltrials.gov/ct2/show/NCT04252664>) and NCT04257656 (<https://clinicaltrials.gov/ct2/show/NCT04257656>), respectively. The number of cases planned to be enrolled is 308 and 452, respectively. A 10-day regimen of remdesivir treatment is as follows: 200 mg loading dose on Day 1, followed by 100 mg once-daily maintenance doses for 9 days in both studies. The former regimen of remdesivir therapy was used in the randomised clinical trial of Ebola virus disease [23].

## 6. Conclusions

With an effective reduction of pulmonary viral load in a murine model of SARS-CoV infection, potent antiviral activity against SARS-CoV-2, acceptable safety profile of parenteral remdesivir therapy in two case reports, and a randomised trial of Ebola virus disease, the clinical use of remdesivir in the cases of COVID-19 is highly anticipated. Two randomised clinical trials of parenteral remdesivir therapy in the treatment of COVID-19 in China may open the window for effective antiviral therapy for such an epidemic infectious disease.

**Funding:** None.

**Competing interests:** None declared.

**Ethical approval:** Not required.

## References

- [1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382:727–33. doi:10.1056/NEJMoa2001017.
- [2] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020 Jan 29 [Epub ahead of print]. doi:10.1056/NEJMoa2001316.
- [3] Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020;395:514–23. doi:10.1016/S0140-6736(20)30154-9.
- [4] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506. doi:10.1016/S0140-6736(20)30183-5.
- [5] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13. doi:10.1016/S0140-6736(20)30211-7.
- [6] Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. *Int J Antimicrob Agents* 2020 Feb 17:105924. doi:10.1016/j.ijantimicag.2020.105924.
- [7] Lee PI, Hsueh PR. Emerging threats from zoonotic coronaviruses—from SARS and MERS to 2019-nCoV. *J Microbiol Immunol Infect* 2020 Feb 4 [Epub ahead of print]. doi:10.1016/j.jmii.2020.02.001.
- [8] Gorbalenya A.E., Baker S.C., Baric R.S., de Groot R.J., Drosten C., Gulyaeva A.A., et al. Severe acute respiratory syndrome-related coronavirus: the species and its viruses—a statement of the Coronavirus Study Group. *bioRxiv preprint* doi:10.1101/2020.02.07.937862.
- [9] Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. *J Med Virol* 2020;92:418–23. doi:10.1002/jmv.25681.
- [10] Colson P, Rolain JM, Raoult D. Chloroquine for the 2019 novel coronavirus. *Int J Antimicrob Agents* 2020 Feb 15:105923. doi:10.1016/j.ijantimicag.2020.105923.
- [11] Liu W, Morse JS, Lalonde T, Xu S. Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV. *Chembiochem* 2020;21:730–8. doi:10.1002/cbic.202000047.
- [12] Li G, Cleraq ED. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Dis* 2020 Feb 19. doi:10.1038/d41573-020-00016-0.
- [13] Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L, et al. Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo[2,1-f] triazin-4-amino adenine c-nucleoside (GS-5734) for the treatment of Ebola and emerging viruses. *J Med Chem* 2017;60:1648–61. doi:10.1021/acs.jmedchem.6b01594.
- [14] Pedersen NC, Perron M, Bannasch M, Montgomery E, Murakami E, Liepnieks M, et al. Efficacy and safety of the nucleoside analog GS-441524 for treatment of cats with naturally occurring feline infectious peritonitis. *J Feline Med Surg* 2019;21:271–81. doi:10.1177/1098612X19825701.
- [15] Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature* 2016;531:381–5. doi:10.1038/nature17180.
- [16] Tchesnokov EP, Feng JY, Porter DP, Götte M. Mechanism of inhibition of Ebola virus RNA-dependent RNA polymerase by remdesivir. *Viruses* 2019;11 pii: E326. doi:10.3390/v11040326.
- [17] Agostini ML, Andres E, Sims AC, Graham RL, Sheahan TP, Lu X, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *mBio* 2018;9 pii: e00221-18. doi:10.1128/mBio.00221-18.
- [18] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020 Feb 4. doi:10.1038/s41422-020-0282-0.
- [19] Lo MK, Jordan R, Arvey A, Sudhamsu J, Shrivastava-Ranjan P, Hotard AL, et al. GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. *Sci Rep* 2017;7:43395. doi:10.1038/srep43395.
- [20] Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med* 2017;9 pii: eal3653. doi:10.1126/scitranslmed.aal3653.
- [21] Brown AJ, Won JJ, Graham RL, Dinno KH 3rd, Sims AC, Feng JY, et al. Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. *Antiviral Res* 2019;169:104541.
- [22] Jacobs M, Rodger A, Bell DJ, Bhagani S, Cropley I, Filipe A, et al. Late Ebola virus relapse causing meningoencephalitis: a case report. *Lancet* 2016;338:498–503. doi:10.1016/S0140-6736(16)30386-5.
- [23] Mulangu S, Dodd LE, Davey RT Jr, Tshiani Mbaya O, Proschan M, Mukadi D, et al. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med* 2019;381:2293–303. doi:10.1056/NEJMoa1910993.
- [24] Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med* 2020 Jan 31 [Epub ahead of print]. doi:10.1056/NEJMoa2001191.