thebmj

BMJ 2020;369:m1610 doi: 10.1136/bmj.m1610 (Published 22 April 2020)

EDITORIALS

Remdesivir in covid-19

A drug with potential—don't waste time on uncontrolled observations

Robin E Ferner *honorary professor of clinical pharmacology*[1], Jeffrey K Aronson *clinical pharmacologist*[2]

[1]Institute of Clinical Sciences, University of Birmingham, Birmingham, UK; [2]Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

The recent publication of an industry sponsored, open, non-randomised study of remdesivir in a heterogeneous patient population has added to the confusion surrounding the drug treatment of covid-19.[1]

The SARS-CoV-2 virus that causes covid-19 has potential therapeutic targets similar to those of other RNA coronaviruses such as SARS-CoV-1, which causes severe acute respiratory syndrome (SARS), and MERS-CoV, the cause of Middle East respiratory syndrome.

Coronaviruses enter host cells by binding to and fusing with cell membranes. Once inside, they subvert the host cell's machinery to replicate, using the virus's RNA dependent RNA polymerase (RdRp).[2] This non-structural protein is highly conserved among different strains, making it a potentially attractive drug target. The principle of using synthetic analogues of nucleosides and nucleotides to inhibit RdRp has led, for example, to sofosbuvir, a successful treatment for hepatitis C infection.[3]

Remdesivir is a pro drug. Its active analogue enters and accumulates in cells, inhibiting viral RdRp[4] and stopping viral replication. Coronaviruses have a "proofreading" enzyme (exoribonuclease) that corrects errors in the RNA sequence, potentially limiting the effects of analogues,[5 6] but remdesivir is able to evade this proofreading.[4 7] In the laboratory, viral mutation can lead to resistance to remdesivir, but the mutant viruses are less infective.[5]

Animal studies

In animal studies, pretreatment with remdesivir protected rhesus monkeys from MERS-CoV infection and reduced the severity of lung damage when given after exposure to MERS-CoV.[8] It protected African green monkeys when given 24 hours after infection with Nipah virus, a cause of fatal encephalitis,[9] and when given intravenously in a dose of 10 mg/kg for 12 days it prevented rhesus monkeys dying from Ebola disease even when treatment started three days after infection.[7]

A preprint of a randomised, well masked, controlled trial in 12 rhesus monkeys infected with SARS-CoV-2 reported that a course of remdesivir administered from 12 hours after inoculation attenuated respiratory symptoms and lung damage.[10]

However, efficacy in vitro or in animals does not inevitably predict outcomes in humans. When remdesivir was compared with three different antibody treatments in a randomised controlled trial in 681 patients with Ebola, mortality in the 175 treated with remdesivir was 53%, significantly worse than the 35% mortality in 174 patients treated with the most active antibody.[11] Patients in the remdesivir group may have been "somewhat sicker" at baseline, according to the authors.

Use in covid-19

Initial reports of the use of remdesivir in humans with covid-19 were either anecdotal cases or small, uncontrolled case series lacking any information on outcomes.[12 13] Short term outcomes have now been reported for 53 of 61 patients with covid-19 treated in over 20 hospitals on three continents.[1] Patients received at least one dose of a 10 day course of intravenous remdesivir as part of a compassionate use programme organised by the manufacturer, and not as part of a clinical trial. Thirty were being ventilated and four treated with extracorporeal membrane oxygenation (ECMO) at the start of remdesivir treatment. After a median of 18 days, 25/53 patients (47%) had been discharged from hospital and seven (13%) had died. Mortality was 5% among patients who were not ventilated. The overall probability of improvement by 18 days was 68% (95% confidence interval 40% to 80%).

Thirty two (60%) patients in this study had at least one adverse event; 12 (23%) experienced serious adverse events. The most common adverse events were abnormal liver function, diarrhoea, rashes, renal impairment, and hypotension. As the authors stated, "Interpretation of the results of this study is limited by the small size of the cohort, the relatively short duration of follow-up, potential missing data owing to the nature of the program, the lack of information on eight of the patients initially treated, and the lack of a randomized control group."

Correspondence to: R E Ferner r.e.ferner@bham.ac.uk

The existence of a compassionate use programme for remdesivir does not mean that its benefits outweigh its potential harms. That balance is still unknown. Compassionate use of remdesivir is reminiscent of the early compassionate use of penicillin for acute infective endocarditis[14] but with important differences. The mortality from covid-19 is low compared with the mortality from acute infective endocarditis and differs across countries. Also, the criteria for mechanical ventilation are partly subjective. An open, uncontrolled trial cannot determine whether a treatment is beneficial overall.

Better evidence, faster

The mechanism of action of remdesivir makes it potentially useful in the treatment of covid-19. We shall find out for certain only if patients are recruited to well powered, adequately masked, randomised controlled trials. At least 23 studies of remdesivir are currently listed on various trial registers, intending to study 23 500 patients, but fewer than a quarter are double blind, and some are uncontrolled observational studies. The use of standard protocols prepared in expectation of future urgent needs would help. So too would wider adoption of adaptive trial protocols, such as platform trials,[15] which allow the evaluation of several treatments at once and permit interim analyses after which treatments may be discarded or introduced.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare that JKA is a member of the Centre for Evidence-Based Medicine in Oxford, which jointly runs the EvidenceLive Conference with the BMJ and the overdiagnosis conference with some international partners, which are based on a non-profit model. He is an associate editor of *BMJ Evidence Based Medicine* and was until recently vice president publications for the British Pharmacological Society. REF was until recently a member of the Birmingham, Sandwell and Solihull Area prescribing committee, is a series editor of *The BMJ*'s Therapeutic Series, and has an honorary position at University College London.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med* 2020. [Epub ahead of print.] . 10.1056/NEJMoa2007016 32275812
2 Amirian ES, Levy JK. Current knowledge about the antivirals remdesivir (GS-5734) and GS-441524 as therapeutic options for coronaviruses. *One Health* 2020;9:100128. 10.1016/j.onehlt.2020.100128 32258351
3 Xie Y, Ogah CA, Jiang X, Li J, Shen J. Nucleoside inhibitors of hepatitis C virus NS5B polymerase: a systematic review. *Curr Drug Targets* 2016;17:1560-76. 10.2174/1389450117666151209123751 26648061
4 Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Götte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. *J Biol Chem* 2020;295:4773-9; [Epub ahead of print.]. 10.1074/jbc.AC120.013056 32094225
5 Agostini ML, Andres EL, Sims AC, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *mBio* 2018;9:e00221-18. 10.1128/mBio.00221-18 29511076
6 Pruijssers AJ, Denison MR. Nucleoside analogues for the treatment of coronavirus infections. *Curr Opin Virol* 2019;35:57-62. 10.1016/j.coviro.2019.04.002 31125806
7 Warren TK, Jordan R, Lo MK, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature* 2016;531:381-5. 10.1038/nature17180 26934220
8 de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci USA* 2020;117:6771-6. 10.1073/pnas.1922083117 32054787
9 Lo MK, Feldmann F, Gary JM, et al. Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge. *Sci Transl Med* 2019;11:eaau9242. 10.1126/scitranslmed.aau9242 31142680
10 Williamson BN, Feldmann F, Schwarz B, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. biorXiv 2020.04.15.043166. [Preprint.] 10.1101/2020.04.15.043166
11 Mulangu S, Dodd LE, Davey RTJr, et alPALM Writing GroupPALM Consortium Study Team. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med* 2019;381:2293-303. 10.1056/NEJMoa1910993 31774950
12 Holshue ML, DeBolt C, Lindquist S, et alWashington State 2019-nCoV Case Investigation Team. First case of 2019 novel coronavirus in the United States. *N Engl J Med* 2020;382:929-36. 10.1056/NEJMoa2001191 32004427
13 Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region — case series. *N Engl J Med* 2020. 10.1056/NEJMoa2004500 32227758
14 Dolphin A, Cruickshank R. Penicillin therapy in acute bacterial endocarditis. *BMJ* 1945;1:897-901. 10.1136/bmj.1.4408.897 20786144
15 Park JJH, Siden E, Zoratti MJ, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. *Trials* 2019;20:572. 10.1186/s13063-019-3664-1 31533793