COVID-19 STRATEGIC COMMENTARY

IS REMDESIVIR IT? – 3 MAY 2020

By Professor Frank Gannon

I have a friend who is a cynic. We were talking about the positive mentions by Dr Anthony Fauci about remdesivir from Gilead as the treatment of choice of COVID-19. He said that every time he hears the word "breakthrough" he thinks, "share price". A check on the past six months shows that Gilead's share price was hovering around US$65 until it jumped to approximately US$80 at the end of February, soon after COVID-19 was recognised as a pandemic in need of a treatment. There is no reason to make any link between Dr Fauci, (or President Trump who also name-checked remdesivir at an early stage) and Gilead. The market did that for us. The world was delighted to hear from a well-placed and respected researcher/clinician that there was a possible cure on its way. Even cynics have to hope that there is a breakthrough. Human nature wants some good news when all seems gloomy. Many hope that remdesivir will be the magic bullet. In an upcoming commentary, I will look at what the literature is presenting as alternative candidates. Not all of them got the White House promotion, followed rapidly by FDA approval to remove any barriers to widespread use. So, this commentary is about remdesivir as it is the story of the week.

What is remdesivir?

Remdesivir is not new. It seems like a treatment looking for the right disease. It comes from Gilead, a company that grew to be a major pharmaceutical, based in particular on its successful treatment of Hepatitis C. The parallel research at Gilead on nucleoside analogues that can block RNA viruses (including Coronaviruses) resulted in the selection of remdesivir. The initial aim was to treat the deadly Marburg Virus or Ebola Virus (both are RNA viruses but are not Coronaviruses). The steps to showing a drug has potency starts *in vitro* with studies to show that it interferes with the designed target (1) or the virus in a cellular context. In this case, the target is the RNA dependent RNA polymerase and remdesivir is an analogue of an essential substrate that blocks the normal replication of the virus. It may also have a function as a competitor for ATP (2). Then the drug moves to use in animal experiments, usually culminating in the treatment of non-human primates. Remdesivir was successful in all of those tests (3,4). When there was an outbreak of Ebola Virus in the Democratic Republic of the Congo, remdesivir was one of the treatments tried on 400 patients. The outcome was disappointing, despite all of the pre-clinical positive results. It was marginally better than no treatment, but not as effective as an antibody used in the different treatment regimes. (3). This is a warning that the extrapolation to humans may turn out to be fraught.

Remdesivir vs COVID-19

The drug was not back on the shelf for long as it was tested for use when there was a MERS outbreak (5). That challenge to the world faded, and now we have COVID-19, and remdesivir has put its cape on to slay the latest enemy. Looking at the published literature, (my preference over press releases) this week, I found 70 publications in PubMed (the repository for medical publications) when using Coronovirus remdesivir as search words. In the list of publications, several reviews and commentaries look at the potential of different drug treatments, and some are instructive in terms of the known effects in different systems (6-11). The WHO identified remdesivir as one of the top prospects for the treatment of COVID-19 and included it as one option for its SOLIDARITY Trial, which encourages

clinicians worldwide to report their results of the compassionate use of four different shortlisted treatments (11).

The global efforts soon yielded some outcome reports. One cluster has published (12) its data based on the compassionate use of the drug provided by Gilead concluding that: "*clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy".* There was an almost instant editorial from the British Medical Journal that is well-worth reading entitled, "A drug with potential—don't waste time on uncontrolled observations" (13). The title says it all. The authors noted that: "*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".* While we wait for such trials with some hopeful expectations, new reports seep into the system. Some of these are prior to standard detailed examination by peer review in journals. Almost puncturing the hopes for remdesivir was a report that was leaked about a trial that had been initiated by Gilead in China. It was said to be "inconclusive". The data did not support an impact by the remdesivir treatment. Gilead helpfully clarified that it was not able to conclude the trial to achieve statistical significance because of an inability to recruit the required number in the Wuhan district. Hence, it was "inconclusive" in a formal sense. The clinical trial websites confirm this (14). The results have now been published by Lancet (15) again with an editorial (16), essential reading, highlighting the need for correctly powered studies.

Currently "inconclusive"

Then there was a report picked up from Chicago, where a researcher was enthusiastic about the results that were being observed and shared them with an online journal. Optimism spiked, followed by silence and "no comments" as the protocols for the reporting of clinical trials were respected. Soon after there was the Dr Fauci statement. Details are never in a press release or a press conference, so we have to rely on those that have got some access to more detail (for example, the informed contributors of the *Issues in Science and Technology journal*). Maybe it was based on adequately powered preliminary data. Maybe it could be described as currently "inconclusive". What it (and the Ebola trial) tells us is that remdesivir requires injection and that the timing of the treatment may be important. Some earlier commentaries have pointed out that a drug to block replication would be expected to be most effective if given before the virus had multiplied. The tests appear to be performed on those people already in a hospital setting; so, it will not be similar to taking a pill at home at the first sign of a fever. The positive data reported show a reduction in the time before a patient's release from hospital, from a mean of 15 days to 11. That is good news in terms of making limited bed facilities available. It is less clear if the clinical objective parameters are also improved; many hospitals try to limit the occupancy by a patient for different reasons, so a letter permitting exit may not be a strong endpoint. Were all patients in Intensive Care Units, or were they under observation? Happily, these questions and information (including, for example, the age profile of those that responded) will be available for the experts to parse when the study is submitted to peer review and all of the data are accessible. This would allow more definitive conclusions to be drawn and the benefits of remsedivir appraised.

Good news is needed from the completed study. Amelioration of symptoms is, of course, important and could equate to lives saved. However, it does not seem, as yet, to be a cure. Maybe there will not be one for this virus; anti-viral agents in general, are not great drugs. With the global need and the engagement of researchers in private and public settings, now is the time to get a better outcome. Remdesivir may not be it, but it could point in the direction that will answer our need for a solution.

References

1.Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro.
Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G.Wang M, et al. Cell Res. 2020 Mar;30(3):269-271. doi: 10.1038/s41422-020-0282-0. Epub 2020 Feb 4. Cell Res. 2020. PMID: 32020029

2. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus.
Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Götte M.Gordon CJ, et al. J Biol Chem. 2020 Apr 10;295(15):4773-4779. doi: 10.1074/jbc.AC120.013056. Epub 2020 Feb 24.J Biol Chem. 2020. PMID: 32094225

3. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection.
de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, Scott D, Cihlar T, Feldmann H.de Wit E, et al. Proc Natl Acad Sci U S A. 2020 Mar 24;117(12):6771-6776. doi: 10.1073/pnas.1922083117. Epub 2020 Feb 13. Proc Natl Acad Sci U S A. 2020. PMID: 32054787
4. 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(7594): 381- 385.

5. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV.
Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, Montgomery SA, Hogg A, Babusis D, Clarke MO, Spahn JE, Bauer L, Sellers S, Porter D, Feng JY, Cihlar T, Jordan R, Denison MR, Baric RS.Sheahan TP, et al. Nat Commun. 2020 Jan 10;11(1):222. doi: 10.1038/s41467-019-13940-6. Nat Commun. 2020. PMID: 31924756

6. Compounds with Therapeutic Potential against Novel Respiratory 2019 Coronavirus.
Martinez MA.Martinez MA. Antimicrob Agents Chemother. 2020 Apr 21;64(5):e00399-20. doi: 10.1128/AAC.00399-20. Print 2020 Apr 21.

7. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence.
Cao YC, Deng QX, Dai SX.Cao YC, et al. Travel Med Infect Dis. 2020 Apr 2:101647. doi: 10.1016/j.tmaid.2020.101647. Online ahead of print.Travel Med Infect Dis. 2020. PMID: 32247927

8. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review.
Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB.Sanders JM, et al. JAMA. 2020 Apr 13. doi: 10.1001/jama.2020.6019. Online ahead of print.JAMA. 2020. PMID: 32282022

9. Arguments in favour of remdesivir for treating SARS-CoV-2 infections.
Ko WC, Rolain JM, Lee NY, Chen PL, Huang CT, Lee PI, Hsueh PR.Ko WC, et al. Int J Antimicrob Agents. 2020 Apr;55(4):105933. doi: 10.1016/j.ijantimicag.2020.105933. Epub 2020 Mar 6. Int J Antimicrob Agents. 2020. PMID: 32147516

10. Controversial treatments: An updated understanding of the coronavirus disease 2019.

Zhang C, Huang S, Zheng F, Dai Y.Zhang C, et al. J Med Virol. 2020 Mar 26. doi: 10.1002/jmv.25788. Online ahead of print.J Med Virol. 2020. PMID: 32219882 Review.

11. Race to find COVID-19 treatments accelerates.
Kupferschmidt K, Cohen J.Kupferschmidt K, et al. Science. 2020 Mar 27;367(6485):1412-1413. doi: 10.1126/science.367.6485.1412.Science. 2020. PMID: 32217705

12. Compassionate Use of Remdesivir for Patients with Severe Covid-19.
Grein J, et al. N Engl J Med. 2020 Apr 10: NEJMoa2007016. doi: 10.1056/NEJMoa2007016. Online ahead of print.N Engl J Med. 2020. PMID: 32275812 Free PMC article.

13. Remdesivir in covid-19. : Editorial A drug with potential—don't waste time on uncontrolled observations Ferner RE, Aronson JK.Ferner RE, et al. BMJ. 2020 Apr 22;369:m1610. doi: 10.1136/bmj.m1610.BMJ. 2020. PMID: 32321732

14. Clin trials NCT04252664 (https://clinicaltrials.gov/ct2/show/NCT04252664) and NCT04257656 (https://clinicaltrials.gov/ct2/show/NCT04257656),

15. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial Yeming Wang, MD et al Lancet Open AccessPublished:April 29, 2020DOI:https://doi.org/10.1016/S0140-6736(20)31022-9
16. Remdesivir for COVID-19: Challenges of underpowered studies John David Norris Lancet April 29, 2020 DOI https://doi.org/10.1016/S0140-6736(20)31023-0