Remdesivir against coronavirus, hope or hype?

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By Professor Peter C. Gøtzsche
Institute for Scientific Freedom
Copenhagen

On 22 May 2020, preliminary data from a placebo-controlled randomised trial of remdesivir in 1063 patients hospitalized with Covid-19 with lower respiratory tract involvement was published in the *New England Journal of Medicine (NEJM)*.[1]

There was a lot of enthusiasm and governments in many countries immediately declared that they would make remdesivir available.

I shall discuss here what the trial report showed and didn't show or didn't tell the readers about, and how it was inappropriately hyped by two co-authors on the trial report, Jens Lundgren and Thomas Benfield, professors of infectious diseases in Denmark who have constantly been in the TV news offering their guidance to the Danish population during the coronavirus epidemic.

The primary outcome was time to recovery defined by discharge from the hospital or hospitalization for infection-control purposes only. For an epidemic that has caused panic in the whole world because of the many deaths it has caused, it is very odd that the primary outcome is not mortality.

Furthermore, it is highly subjective to decide when a patient is well enough to go home, and placebo-controlled trials are rarely sufficiently blinded, as the active drug has conspicuous side effects. One would therefore expect the results obtained with this outcome to be biased. The trial reported a median recovery time of 11 days (95% confidence interval (CI) 9 to 12) on drug and 15 days on placebo (95% CI 13 to 19) ($p < 0.001$).

The Tamiflu "miracle" should make us cautious

It would not make much sense to use an expensive drug in order to reduce the hospital stay for a couple of days, if this is the only effect the drug has. We were totally fooled by the Swiss drug giant Roche that claimed that oseltamivir (Tamiflu) for influenza could reduce reduce hospital admissions by 61%, secondary complications by 67%, and lower respiratory tract infections requiring antibiotics by 55%.[2] These claims were based on unpublished data and when all the data came to light, it turned out they were false.

The only thing Tamiflu does is to reduce the time to first alleviation of symptoms by 17 hours,[3] and this trivial effect might even be non-existent. The trials were not effectively blinded because the drug has conspicuous side effects, and it is highly subjective to tell when an influenza stops.

The FDA asked Roche to stop claiming that Tamiflu reduces the severity and incidence of secondary infections while the European Medicines Agency accepted this claim.[2]

We have wasted and still waste billions of any currency on this ineffective drug and a similar one, zanamivir (Relenza, from GlaxoSmithKline).

Are we going to do the same with remdesivir? We will need to look at its effect on mortality to arrive at an informed guess.

The effect of remdesivir on mortality

The *NEJM* trial was stopped early for benefit. Not a mortality benefit, but a benefit on hospital stay. While the trial was ongoing, the data and safety monitoring board recommended that a preliminary primary analysis report and mortality data be provided to trial team members from the National Institute of Allergy and Infectious Diseases, which decided to make the preliminary results public: "Given the strength of the results about remdesivir, these findings were deemed to be of immediate importance for the care of

patients still participating in the trial as well as for those outside the trial who might benefit from treatment with remdesivir."[1]

I am not convinced that this rush was needed. Most importantly, the trial did not find a statistically significant effect on mortality. Furthermore, it was shown in a 2010 meta-analysis that trials reported as having stopped early for benefit exaggerated the effect by 39% compared to trials of the same intervention that had not stopped early.[4]

The Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI 0.47 to 1.04). This difference is not statistically significant. Furthermore, "Other outcomes included mortality at 14 and 28 days after enrolment," and we have no data yet on mortality after 28 days. There will likely be more deaths, "given the large number of patients that had yet to complete day 29 visits."[1]

There were 32 vs 54 deaths among the 538 vs 521 enrolled patients. The investigators mention in the Discussion a placebo-controlled trial of remdesivir from China, with 158 vs 79 patients, which was also stopped prematurely, in this case because of lack of patients.[5] But the only thing the *NEJM* authors mention is time to clinical improvement, which was 21 days (95% CI 13 to 28) vs 23 days (95% CI 15 to 28), a difference of two days, which was not statistically significant.

I believe it constitutes biased reporting not to mention the mortality results from the Chinese trial: "28-day mortality was similar between the two groups (22 [14%] died in the remdesivir group vs 10 (13%) in the placebo group; difference 1·1% [95% CI -8·1 to 10·3])." The authors also failed to mention that, "Viral load decreased over time similarly in both groups." I wonder how an antiviral can work if it does not decrease viral load? Viral load was not measured in the *NEJM* trial.

We don't know if remdesivir reduces mortality. It will be interesting to see the 28-day results and the results of other trials.

There are other drugs than remdesivir and the following ones are not under patent.[6] A combination of three drugs, interferon beta-1b, lopinavir–ritonavir, and ribavirin, was compared with lopinavir–ritonavir in 86 vs 49 patients in an open trial published 8 May 2020.[7] The combination group had a significantly shorter median time to negative nasopharyngeal swab (7 vs 12 days, p = 0.001), time to complete symptom alleviation (4 vs 8 days, p < 0.0001), and duration of hospital stay (9 vs 15 days, p = 0.02). These patients were not very ill, as no one died.

The hype: remdesivir touted as a "miracle" drug

When an overall result is not statistically significant, it is a clear violation of good scientific practice to fish for subgroup results that tell a better story. But this is what the two Danish professors did.

Jens Lundgren: "When I saw these data … it is totally insane … we need to start early against corona … if the drug remdesivir is given at the right time … to the group that needs oxygen … when the patients start getting pneumonia but before they are transferred to intensive care … it can reduce corona mortality by about 80 per cent."[8,9]

Thomas Benfield: "This is fantastic news. So far, the medical discovery of the year, in all fields … remdesivir should reach everyone … the results are totally unbelievable."[8,10]

In contrast to the two Danish key opinion leaders, Anthony Fauci, top advisor on health for President Donald Trump and director for the National Institute of Allergy and Infectious Diseases, has stated that remdesivir is not a miracle cure against the coronavirus.[8]

So, how could a non-significant effect on mortality be hyped so much that it became a miraculous 80% reduction in mortality?

The protocol was unduly complicated. Something as simple as whether the patients returned home alive, and after how many days, was described this way:[1]

"The primary outcome measure was the time to recovery, defined as the first day, during the 28 days after enrollment, on which a patient satisfied categories 1, 2, or 3 on the eight-category ordinal scale. The categories are as follows:

1, not hospitalized, no limitations of activities;

2, not hospitalized, limitation of activities, home oxygen requirement, or both;

3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons);

4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19–related or other medical conditions);

5, hospitalized, requiring any supplemental oxygen;

6, hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices;

7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and

8, death."

The investigators changed the protocol's primary outcome after 72 patients had been enrolled, but this is not important for an evaluation of the trial. What is important is that the trial statisticians tested if the primary outcome was different in the various patient categories, those who did not need oxygen, those who needed oxygen, those who needed noninvasive ventilation, and those who needed invasive mechanical ventilation or extracorporeal membrane oxygenation (the most severely ill patients). There was no difference, which makes it even worse that the two Danish professors embarked on a fishing expedition in the data focusing on only 23 deaths in subgroup 5 out of a total of 86 deaths:[1]

Table 2. Outcomes Overall and According to Score on the Ordinal Scale in the Intention-to-Treat Population.*

	Overall*		Ordinal Score at Baseline							
			4		5		6		7	
	Remdesivir (N=538)	Placebo (N=521)	Remdesivir (N=67)	Placebo (N=60)	Remdesivir (N=222)	Placebo (N=199)	Remdesivir (N=98)	Placebo (N=99)	Remdesivir (N=125)	Placebo (N=147)
Recovery										
No. of recoveries	334	273	61	47	177	128	47	43	45	51
Median time to recovery (95% CI) — days	11 (9–12)	15 (13–19)	5 (4–6)	6 (4–8)	7 (6–8)	9 (7–11)	16 (NE– 10)	22 (NE– 12)	NE–NE	28 (NE– 22)
Rate ratio (95% CI)†	1.32 (1.12–1.55 [P<0.001])		1.38 (0.94–2.03)		1.47 (1.17–1.84)		1.20 (0.79–1.81)		0.95 (0.64–1.42)	
Mortality										
Hazard ratio (95% CI)	0.70 (0.47–1.04)		0.46 (0.04–5.08)		0.22 (0.08–0.58)		1.12 (0.53–2.38)		1.06 (0.59–1.92)	
No. of deaths by day 14	32	54	1	1	4	19	13	13	13	19
Kaplan–Meier estimate — % (95% CI)	7.1 (5.0–9.9)	11.9 (9.2–15.4)	1.5 (0.2–10.1)	2.5 (0.4–16.5)	2.4 (0.9–6.4)	10.9 (7.1–16.7)	15.2 (9.0–25.0)	14.7 (8.7–24.3)	11.3 (6.7–18.8)	14.1 (9.2–21.2)

The seemingly "better effect" in subgroup 5 in a trial that did not find an effect should be dismissed, as it is likely just a chance finding.

Will we see a repetition of the "miracle" drugs for AIDS and influenza?

The first placebo-controlled trial of the first AIDS drug, zidovudine, earlier called azidothymidine, was also published in *New England Journal of Medicine*, in 1987.[11] Many of us felt at the time that the results were too good to be true, which they also were. Only one of 145 patients on the drug died, compared to 19 of 137 on placebo, a reduction in mortality of 95%. If true, this was truly a miracle drug.

It became a miracle drug for Burroughs Wellcome. The drug was synthesised at the Michigan Cancer Foundation in 1964, and it cost very little to develop it, but the company nevertheless charged $10,000 per year for one patient,[12] an enormous amount of money in 1987.

Those of us who worked with AIDS patients as clinicians back then were enraged by Burroughs Wellcome's extortion and abuse of a monopoly situation. We decided to do our own trial, and I became the co-ordinator of a trial sponsored by the Nordic Medical Research councils that started in early 1988 and compared three doses of zidovudine, 400 mg, 800 mg and 1200 mg. We bought the drug and the corresponding placebos from Burroughs Wellcome that protested that the lowest dose was unethical. I

responded that we doctors took care of the ethics, not the drug companies, and we kept the three doses and found very similar death rates.[13]

We suspected fraud was involved with the 1987 *NEJM* trial, particularly when we later found out that the trial was published at precisely the "right" moment when the difference in death rates was largest. When more deaths accrued, and other trials were published, the miracle was gone. The big Concorde trial, published in Lancet in 1994, was particularly revealing:[14] 1749 HIV-infected patients were randomised to zidovudine or placebo (418 of the 872 patients on placebo started zidovudine at some time during the trial, but there was a large difference in drug use, 81% vs 16% of the time before onset of AIDS-related complex or AIDS). There was no difference in mortality. The 3-year estimated survival probabilities were 92% (95% CI 90-94%) vs 94% (92-95%) (p = 0.13).

An additional issue was that the virus developed resistance to the drug. This would also be expected for drugs against coronaviruses.

Financial ties to Gilead were not declared

When Benfield was interviewed about the trial for the *Journal of the Danish Medical Association*, he declared as a conflict of interest that he was an investigator in the *NEJM* remdesivir trial.[15] It was far more than this. There are no declarations in the *New England Journal of Medicine*; one has to look them up on the journal's homepage. The disclosure forms for the authors take up 122 pages; it took two minutes to download them, and the pdf was not searchable. But searches can be done directly on the *NEJM* website. I searched on "Gilead" to find out if any of the authors had financial conflicts of interest in relation to the company that stands to make a fortune on remdesivir.

Benfield had received grants and personal fees from Gilead; "unrestricted grants" from Pfizer, Novo Nordisk Foundation, Simonsen Foundation and GSK; personal fees from GSK, Pfizer, Boehringer Ingelheim and MSD; and grants from the Lundbeck Foundation.

This is a bit more than just being an investigator in a trial sponsored by public funds and governments.[1] Industry is very careful about how it spends shareholders' money, and if it gives away some, it's not a sudden outburst of altruism but because it expects more in return than it spends. The industry buys loyalty with their "unrestricted grants," which are therefore a form of corruption.[12]

Benfield has been on TV almost every day for many weeks. He is the key opinion leader in Denmark in relation to the coronavirus epidemic, but I have never seen him declare any of his many conflicts of interest in relation to Gilead or other drug companies.

Six other authors also declared having received grants or personal fees from Gilead, and one was even an employee of Gilead.

Nothing material has changed since I published my book about organised crime in the drug industry in 2013.[12] Doctors still think they can have the cake and eat it and get away with not declaring their conflicts of interest when they give advice to whole nations about serious issues or expensive drugs with little known effects.

Lundgren and Benfield violated not only scientific standards but also EU requirements for advertising:

"No person shall issue an advertisement relating to a relevant medicinal product unless that advertisement encourages the rational use of that product by presenting it objectively and without exaggerating its properties."[16]

Conclusions

We don't know what the true value of remdesivir is, and there might be better and much cheaper options for treating coronavirus. We also don't know what the price will be for remdesivir, but we do know that Gilead is anything but modest. The company had more than $22 billion of revenue in 2019,[6] and Gilead also sells sofosbuvir (Sovaldi) for hepatitis C at a price so obscene that it has been heavily criticised by

governments all over the world. In 2013, Gilead sold Sovaldi at $84,000 in the United States for a 12-week course of treatment.[17]

Governments should introduce compulsory licensing, which will allow others to produce remdesivir without the consent of Gilead, the patent owner.[18] Under the Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS), countries are free to determine the grounds for granting compulsory licences, and to determine what constitutes a national emergency.[19] Governments should also have done this for Sovaldi, long ago.

References

1 Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. N Engl J Med 2020; May 20. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2007764.

2 Gøtzsche PC. Vaccines: truth, lies and controversy. Copenhagen: People's Press; 2020.

3 Jefferson T, Jones M, Doshi P, et al. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ 2014;348:g2545.

4 Bassler D, Briel M, Montori VM, et al. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. JAMA 2010;303:1180–7.

5 Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569-78.

6 Lerner S. Despite the hype, Gilead's remdesivir will do nothing to end the coronavirus pandemic. The Intercept 2020; May 26. https://theintercept.com/2020/05/26/coronavirus-gileand-remdesivir-treatment/.

7 Hung IFN, Lung KC, Tso EYK, et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet 2020;395:1695-1704.

8 Stie HHB, Gliese S. Studie: Medicin reducerer coronadødsfald med 80 procent. TV2 News 2020; May 23. https://nyheder.tv2.dk/samfund/2020-05-23-studie-medicin-reducerer-coronadodsfald-med-80-procent.

9 Boier P. Professorer begejstrede for nyt studie: 'For første gang kan vi behandle coronavirus.' DR 2020; May 23. https://www.dr.dk/nyheder/indland/professorer-begejstrede-nyt-studie-foerste-gang-kan-vi-behandle-coronavirus.

10 Stie HHB. Remdesivir skal 'ud til alle' - resultaterne er 'utrolige', siger professor. TV2 News 2020; May 23. https://nyheder.tv2.dk/samfund/2020-05-23-remdesivir-skal-ud-til-alle-resultaterne-er-utrolige-siger-professor.

11 Fischl MA, Richman DD, Grieco MH, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. N Engl J Med 1987;317:185-91.

12 Gøtzsche PC. Deadly medicines and organised crime: How big pharma has corrupted health care. London: Radcliffe Publishing; 2013.

13 Nordic Medical Research Councils' HIV Therapy Group. Double-blind dose-response study of zidovudine in AIDS and advanced HIV infection. BMJ 1992;304:13-7.

14 Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. Concorde Coordinating Committee. Lancet 1994;343:871-81.

15 Lange P. Videnskab, medicinsk nyhed. Ugeskr Læger 2020; May 25. https://ugeskriftet.dk/videnskab/klinisk-betydende-effekt-af-remdesivir-pa-forlobet-af-indlaeggelseskraevende-infektion-med.

16 Medawar C, Hardon A. Medicines out of Control? Antidepressants and the conspiracy of goodwill. Netherlands: Aksant Academic Publishers; 2004.

17 Rowland C. Taxpayers paid to develop remdesivir but will have no say when Gilead sets price David Paul Morris/Bloomberg. 2010 May 27. https://liber.post-gazette.com/news/health/2020/05/27/Taxpayers-funded-development-remdesivir-Gilead-drug-pricing-coronavirus/stories/202005270100

18 Gøtzsche PC. Patients not patents: Drug research and development as a public enterprise. Eur J Clin Invest 2018;48:e12875.

19 Compulsory licensing of pharmaceuticals and TRIPS. https://www.wto.org/english/tratop_e/trips_e/public_health_faq_e.htm.