Whose Interests do Public Health Officials Represent?

How a dangerous drug exacerbated the pandemic, prevented early intervention, and forced dangerous treatment on Americans

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This is a working document that I am posting because we are in a public health emergency. If anything is inaccurate or if I missed anything, please contact me.
Let’s Examine the case for Remdesivir AND Expedited FDA approvals
To Gilead’s credit it does refer to the underlying NIH version of the studies.

Additional Information About VEKLURY® (remdesivir)

Please refer to the links below for information on clinical trials investigating the use of VEKLURY in COVID-19:

- Gilead Phase 3 Study: [540-9012](#)
- NIAID studies: [NCT04280705; NCT04404579; NCT04492475](#)
- Gilead study in patients with moderate disease: [NCT04292730](#)
- Gilead study in patients with severe disease: [NCT04292899](#)
- INSERM DisCoVeRy Trial: [2020-000926-23; NCT04315948](#)
- WHO Solidarity Trial
- Gilead pediatric study: [NCT04431453](#)

Gilead also supported 2 clinical trials of VEKLURY in China, which were coordinated by the China-Japan Friendship Hospital. These trials were terminated early due to low enrollment.

- China study in patients with mild/moderate disease: [NCT04252664](#)
- China study in patients with severe disease: [NCT04257656](#)

Healthcare providers should visit [ClinicalTrials.gov](https://clinicaltrials.gov) to determine whether a patient may be eligible for enrollment in a clinical trial.

Note to IG’s: Might want to follow up on this. Review slides 21-22. Did they suspend to reduce statistical power?
Linking to NIH studies only has limited value

IG’s: What was the substance of representations made to USG officials?
Hey guys, did you forget anything? 

Ebola Studies.

A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics

Sabue Mulangu, M.D., Lori E. Dodd, Ph.D., Richard T. Davey, Jr., M.D., Olivier Tshian Mbaya, M.D., Michael Proschan, Ph.D., Daniel Mukadi, M.D., Mariano Lusakibanza Manzo, Ph.D., Didier Nzolo, M.D., Antoine Tshomba Olorna, M.D., Augustin Ibanda, B.S., Rosine Ali, M.S., Sinaré Coulibaly, M.D., et al., for the PALM Consortium Study Team

Abstract

**BACKGROUND**

Although several experimental therapeutics for Ebola virus disease (EVD) have been developed, the safety and efficacy of the most promising therapies need to be assessed in the context of a randomized, controlled trial.
Is this December 2019 paper what justified the Golden Wonka FDA Ticket? Well actually no...

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**Table 2. Comparison of Death at 28 Days According to Treatment Group.**

<table>
<thead>
<tr>
<th>Population</th>
<th>ZMapp</th>
<th>Remdesivir</th>
<th>Difference, Remdesivir vs. ZMapp</th>
<th>MAb114</th>
<th>Difference, MAb114 vs. ZMapp</th>
<th>REGN-EB3</th>
<th>ZMapp Subgroup</th>
<th>Difference, REGN-EB3 vs. ZMapp Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of deaths/total no. (%)</td>
<td>no. of deaths/total no. (%)</td>
<td>percentage points (95% CI)</td>
<td>no. of deaths/total no. (%)</td>
<td>percentage points (95% CI)</td>
<td>no. of deaths/total no. (%)</td>
<td>no. of deaths/total no. (%)</td>
<td>percentage points (95% CI)</td>
</tr>
<tr>
<td>Overall</td>
<td>84/169 (49.7)</td>
<td>93/175 (53.1)</td>
<td>3.4 (-7.2 to 14.0)</td>
<td>61/174 (35.1)</td>
<td>-14.6 (-25.2 to -1.7)*</td>
<td>52/155 (33.5)</td>
<td>79/154 (51.3)</td>
<td>-17.8 (-28.9 to -2.9)*</td>
</tr>
<tr>
<td>Patients with high viral load†</td>
<td>60/71 (84.5)</td>
<td>64/75 (85.3)</td>
<td>0.8 (-15.3 to 17.2)</td>
<td>51/73 (69.9)</td>
<td>-14.6 (-33.0 to -0.5)</td>
<td>42/66 (63.6)</td>
<td>56/65 (86.2)</td>
<td>-22.5 (-41.8 to -5.1)</td>
</tr>
<tr>
<td>Patients with low viral load†</td>
<td>24/98 (24.5)</td>
<td>29/100 (29.0)</td>
<td>4.5 (-9.1 to 19.1)</td>
<td>10/101 (9.9)</td>
<td>-14.6 (-32.4 to -2.6)</td>
<td>10/89 (11.2)</td>
<td>23/89 (25.8)</td>
<td>-14.6 (-32.6 to -2.3)</td>
</tr>
</tbody>
</table>

* The result is significant according to the interim stopping boundary of P<0.035 for the MAb114 group and P<0.028 for the REGN-EB3 group.
† Patients with a high viral load had an EBOV nucleoprotein Ct value of 22.0 or less. Patients with a low viral load had an EBOV nucleoprotein Ct value of more than 22.0. The total number is the total number of patients in this category for each group.

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I’m just asking, but how anti-viral is Veklury/Rem really?
Why ask if its really that antiviral? Because CQ seems to be more anti-viral here than Remdesivir.

Pro tip: one would think HCQ would be even MORE effective than CQ.
And there is also this in the Lancet Chinese Remdesivir Study. Is Remdesivir anti-viral?

**THE LANCET**

**Summary**

Findings. In one murine model of SARS, remdesivir treatment starting at 2 days after infection, after virus replication and lung airway epithelial damage had already peaked, significantly reduced SARS-CoV-1 lung titres but did not decrease disease severity or mortality. A need for early treatment has been found in non-human primate models of SARS and MERS in which virus replication is very short-lived and lung pathology appears to develop more rapidly than in human infections. Such findings argue for testing of remdesivir earlier in COVID-19.

**Results**

Remdesivir did not result in significant reductions in SARS-CoV-2 RNA loads or detectability in upper respiratory tract or sputum specimens in this study despite showing strong antiviral effects in preclinical models of infection with coronaviruses. In African green monkey kidney Vero E6 cells, remdesivir inhibited SARS-CoV-2 with a 50% effective concentration (EC₅₀) of 0.46 μg/mL and an

**Discussion**

Just how “anti-viral is remdesivir?”
But I digress, back to the **Ebola** study where Remdesivir seems to have done poorly.
But if the fact that the Remdesivir Ebola study was a disaster is still unclear, let’s drill down even further.

Independent Monitoring Board Recommends Early Termination of Ebola Therapeutics Trial in DRC Because of Favorable Results with Two of Four Candidates

August 12, 2019

The Pamoja Tulinde Maisha (PALM [together save lives]) study is a randomized, controlled trial of four investigational products (though Remdesivir is not one of them) for treatment of Ebola virus disease (EVD) in the Democratic Republic of the Congo (DRC). The trial was sponsored by the National Institutes of Health (NIH).
Special Magic: from getting yanked by Data and Safety Monitoring Board (DSMB) to mandated FDA Protocol in less than 1 year!

The trial is monitored by an independent Data and Safety Monitoring Board (DSMB) that meets periodically to review interim safety and efficacy data and to make recommendations to the study team and the sponsors. As a result of their August 9, 2019 review, the DSMB recommended that the study be stopped and that all future patients be randomized to receive either REGN-EB3 or mAb114 in what is being considered an extension phase of the study. This recommendation was based on the fact that an early stopping criterion in the protocol had been met by one of the products, REGN-EB3. The preliminary results in 499 study participants indicated that those individuals receiving REGN-EB3 or mAb114 had a greater chance of survival compared to those participants in the other two arms. The principal investigators of the study, its statistician and its co-sponsors accepted this recommendation, and the ETC staff at the sites were promptly informed. In addition to limiting future patient randomizations to REGN-EB3 and mAb114, patients who were randomized to ZMapp or remdesivir in the last 10 days now have the option, at the discretion of their treating physician, to receive either REGN-EB3 or mAb114.

NIH references the uncapitalized word mystery drug as “remdesivir” only twice in the body of the article making this hard to find.
So what could overcome Remdesivir’s Ebola Experience?
First Case of 2019 Novel Coronavirus in the United States

Michelle L. Holshue, M.P.H., Chas DeBolt, M.P.H., Scott Lindquist, M.D., Kathy H. Lofy, M.D., John Wiesman, Dr.P.H., Hollianne Bruce, M.P.H., Christopher Spitters, M.D., Keith Ericson, P.A.-C., Sara Wilkerson, M.N., Ahmet Tural, M.D., George Diaz, M.D., Amanda Cohn, M.D., et al., for the Washington State 2019-nCoV Case Investigation Team

Summary

An outbreak of novel coronavirus (2019-nCoV) that began in Wuhan, China, has spread rapidly, with cases now confirmed in multiple countries. We report the first case of 2019-nCoV infection confirmed in the United States and describe the identification, diagnosis, clinical course, and management of the

IG's need communications

appropriate urgency?
Again, just how powerful of an anti-viral is Remdesivir?

SPECIMEN TESTING FOR 2019-nCoV

The initial respiratory specimens (nasopharyngeal and oropharyngeal swabs) obtained from this patient on day 4 of his illness were positive for 2019-nCoV (Table 2). The low cycle threshold (Ct) values (18 to 20 in nasopharyngeal specimens and 21 to 22 in oropharyngeal specimens) on illness day 4 suggest high levels of virus in these specimens, despite the patient’s initial mild symptom presentation. Both upper respiratory specimens obtained on illness day 7 remained positive for 2019-nCoV, including persistent high levels in a nasopharyngeal swab specimen (Ct values, 23 to 24). Stool obtained on illness day 7 was also positive for 2019-nCoV (Ct values, 36 to 38). Serum specimens for both collection dates were negative for 2019-nCoV. Nasopharyngeal and oropharyngeal specimens obtained on illness days 11 and 12 showed a trend toward decreasing levels of virus. The oropharyngeal specimen tested negative for 2019-nCoV on illness day 12. The rRT-PCR results for serum obtained on these dates are still pending.

Table 2.

Now for the study you probably did not hear about
Case report study of the first five COVID-19 patients treated with remdesivir in France

Marie Dubert h,1, *, Benoit Viseaux b,1, *, Valentina Isernia a, Lila Bouadma d,6, *, Laurène Deconinck a, Juliette Patrier h,6, *, Paul-Henri Wicky g,6, *, Diane Le Pluert a, Laura Kramer a, Christophe Rioux a, Quentin Le Hingrat b,6, *, Nadhiria Houssein-Fidouh b, Yazdan Yazdanpanah h,6, *, Jade Ghosn h,6, *, Francois-Xavier Lesure h,6, * 

Abstract
A novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) causing a cluster of respiratory infections (coronavirus disease 2019, COVID-19) in Wuhan, China, was identified on 7 January 2020. The epidemic quickly disseminated from Wuhan and as at 12 February 2020, 45,179 cases have been confirmed in 25 countries, including 1,116 deaths. Strengthened surveillance was implemented in France on 10 January 2020 in order to identify imported cases early and prevent secondary transmission. Three categories of risk exposure and follow-up procedure were defined for contacts. Three cases of COVID-19 were confirmed on 24 January, the first cases in Europe. Contact tracing was immediately initiated. Five contacts were evaluated as low risk of exposure and 18 at moderate/high risk. As at 12 February 2020, two cases have been discharged and the third one remains symptomatic with a persistent cough, and no secondary transmission has been identified. Effective collaboration between all parties involved in the surveillance and response to emerging threats is required to detect imported cases early and to implement adequate control measures.

Keywords: coronavirus, COVID-19, SARS-CoV-2, 2019-nCov, Surveillance, contact tracing, containment, France

Why so long? early influential studies must have had incredible results to ramrod FDA approval, right? Well actually.....

Opposite of urgency
Well, this study had five patients. Patient 1’s remdesivir was stopped after Day 4 because of ALT elevation (liver failure)

Case 1

A 31-year-old Chinese male originating from Wuhan and reporting flu-like symptoms for 6 days was diagnosed with COVID-19 on January 24, 5 days after arriving in Paris. He was immediately hospitalized with mild lymphopenia (1.00 × 10^9/l) and thrombocytopenia (1.46 × 10^9/l); there were no abnormalities on chest X-ray. RT-qPCR on nasopharyngeal samples was positive, with a SARS-CoV-2 viral load (VL) of 10.5 log_{10} copies/ml. On day 10 of illness, he was transferred to the intensive care unit (ICU) due to worsening oxygen saturation (PO_2 = 58 mmHg; low-flow nasal cannula 4 l/min) and bilateral ground-glass and alveolar opacities on chest computed tomography (CT) scan with no increase in VL. Remdesivir was started on January 29, 2020 (day 11 of illness) and was stopped on day 15, due to alanine aminotransferase (ALT) elevation (195 IU/l versus 46 IU/l before remdesivir administration) and the presence of a maculopapular rash. A rapid decline in VL from a cycle threshold (Ct) value of 27.6 to undetectability was observed on day 2 of remdesivir infusion. The skin and liver abnormalities improved within 3 days after discontinuing treatment. The patient was discharged on February 12.
Case 2

An 80-year-old tourist originating from Hubei Province, with a past medical history of thyroid cancer, presented on January 25 with fever and diarrhoea of 4-day duration. A chest X-ray showed bilateral alveolar opacities, but he did not fulfil the COVID-19 case definition at that time. Airborne and contact precautions were observed and the diagnosis of COVID-19 was eventually made 3 days later. On January 26, acute respiratory failure with multiple organ failure triggered his admission to the ICU. Broad-spectrum antibiotic therapy was started and adapted for co-infection with a susceptible *Acinetobacter baumannii* (diagnosed by multiplex PCR and confirmed by tracheal aspirate culture) and *Aspergillus flavus* (tracheal aspirate culture). Remdesivir was started on January 29, but was discontinued on January 31, as the patient needed renal replacement therapy. The nasopharyngeal VL decreased from a Ct value of 21.0 before infusion to 28.9 on day 2 of infusion. A CT scan performed on January 31 showed bilateral alveolar condensations, ground-glass opacities, and pulmonary cysts. On February 5, because of the disease severity and the persistence of viral detection, remdesivir was re-initiated. Multiple organ failure persisted without any other co-infection identified. He died on February 14.
OK, **how did Patient 3 do?** Discontinued. ALT elevation...liver failure again? This shows it took 5 days for ALT to return to normal after Remdesivir was stopped. This seems hard on liver.

Case 3

A 39-year-old male airport worker, who was obese (body mass index = 33 kg/m²) and had obstructive sleep apnoea syndrome, was diagnosed with severe COVID-19 and admitted to the ICU on February 26. He had had a cough and fever since February 21. He presented acute respiratory failure (PaO₂ = 74 mmHg; high-flow nasal cannula 40 l/min, 40%) and basal interstitial syndrome on chest X-ray. Remdesivir was started on February 27. Viral RNA levels increased slightly from a Ct value of 32.5 to 28.8 during the first 4 days of infusion, and started to decline on day 5 until undetectability. On March 1, he was referred to the infectious diseases ward, and he was weaned off oxygen on day 13 of illness. His VL was below the RT-qPCR limit of detection on day 14. Remdesivir was discontinued after eight administrations because of ALT elevation (116 IU/l versus 43 IU/l before remdesivir administration) and a maculopapular rash. These symptoms resolved 5 days after remdesivir discontinuation and the patient was discharged on day 20 of illness.
Patient 4: I don’t know what happened here. Did patient get better with or without the remdesivir?

All in here patients like these should arguably receive early treatment, just not Veklury.
Case 5

A 70-year-old male with a past medical history of chronic obstructive pulmonary disease was diagnosed with COVID-19 on March 1. He had had a cough and fever since February 23 while taking non-steroidal anti-inflammatory drugs for renal lithiasis. He was admitted to the ICU on March 2 with acute respiratory distress syndrome. Remdesivir was started on March 4 (day 11 of illness) and discontinued on March 6 because of acute kidney injury (creatinine level up to 396 μmol/l) needing renal replacement therapy. The VL in nasopharyngeal samples decreased significantly from Ct 26 to undetectability on day 2 of remdesivir infusion. However, the SARS-CoV-2 VL was detectable in bronchoalveolar lavage on March 10. Cefotaxime was initiated because of a *Haemophilus influenzae* respiratory co-infection. Nevertheless, he developed multiple organ failure and refractory acute respiratory distress syndrome despite prone positioning and adapted mechanical ventilation. Dexamethasone and lopinavir/ritonavir were started on March 12. He died on March 24 (day 31 of illness).
Discussion

Of this case series of five COVID-19 patients requiring ICU treatment for respiratory distress and treated with remdesivir, three (patients 1, 3, and 4) had a favourable outcome despite the initial respiratory severity. They were weaned off oxygen between day 14 and day 19 of illness and were discharged between day 20 and day 26 of illness. Patients 2 and 5 died in the ICU on day 25 and day 31 of illness with multi-organ failure. While on remdesivir treatment, we observed a decrease in nasopharyngeal VL in all but patient 2, for whom the treatment was re-introduced after an early interruption, without any additional decrease in VL in the upper or lower respiratory tract. For patient 5, viral replication was still ongoing in the lower respiratory tract despite a concomitant undetectable VL in the nasopharyngeal area, highlighting the discrepancies between viral replication in the upper and lower respiratory tract among the most severe patients. Plasma samples were only positive for SARS-CoV-2 for patient 2.

As described in previous case reports (Grein et al., 2020, Kujawski et al., 2020), four of the five patients experienced major side effects while on remdesivir treatment: two suffered acute renal injury and two had a maculopapular rash with cytolitic hepatitis. Both kidney failure events could have been related either to remdesivir or to the SARS-CoV-2 infection. None of these patients received immunomodulatory drugs. Grein et al. (2020) described 53 COVID-19 patients treated with remdesivir, among whom 30 were on mechanical ventilation. After a median follow-up of 18
Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

Yeming Wang, MD † • Dingyu Zhang, MD † • Prof Guanhua Du, PhD † • Prof Ronghui Du, MD † • Prof Jianping Zhao, MD † • Prof Yang Jin, MD † • et al. Show all authors • Show footnotes

Published: April 29, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)31022-9 • Check for updates
Sad but there are indications that Chinese research methods seem more reliable than US research under NIAID. IG’s Is this why Chinese studies were suspended and not started? 

Findings
Between Feb 6, 2020, and March 12, 2020, 237 patients were enrolled and randomly assigned to a treatment group (158 to remdesivir and 79 to placebo); one patient in the placebo group who withdrew after randomisation was not included in the ITT population. Remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1.23 [95% CI 0.87–1.75]). Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (hazard ratio 1.52 [0.95–2.43]). Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early.

Interpretation
In this study of adult patients admitted to hospital for severe COVID-19, remdesivir was not associated with statistically significant clinical benefits. However, the numerical reduction in time to clinical improvement in those treated earlier requires confirmation in larger studies.

Funding
Chinese Academy of Medical Sciences Emergency Project of COVID-19, National Key Research and Development Program of China, the Beijing Science and Technology Project.
Compassionate Use of Remdesivir for Patients with Severe Covid-19

Jonathan Grein, M.D., Norio Ohmagari, M.D., Ph.D., Daniel Shin, M.D., George Diaz, M.D., Erika Asperges, M.D., Antonella Castagna, M.D., Torsten Feldt, M.D., Gary Green, M.D., Margaret L. Green, M.D., M.P.H., François-Xavier Lescuré, M.D., Ph.D., Emanuele Nicasiri, M.D., Rentaro Oda, M.D., et al.

Abstract

29 References  694 Citing Articles  Letters

Metrics

June 11, 2020

DOI: 10.1056/NEJMoa2007016
Chinese Translation 中文翻译

Related Articles

NEJM again
Best Results From Gilead Study. Have these ever been replicated?

RESULTS
Of the 61 patients who received at least one dose of remdesivir, data from 8 could not be analyzed (including 7 patients with no post-treatment data and 1 with a dosing error). Of the 53 patients whose data were analyzed, 22 were in the United States, 22 in Europe or Canada, and 9 in Japan. At baseline, 30 patients (57%) were receiving mechanical ventilation and 4 (8%) were receiving extracorporeal membrane oxygenation. During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged, and 7 patients (13%) died; mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation.

CONCLUSIONS
In this cohort of patients hospitalized for severe Covid-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy. (Funded by Gilead Sciences.)

IG: Theoretically can hide bad outcomes here

Really? Independent peer review warranted
largely because clinical improvement enabled discharge from the hospital. The effectiveness of a shorter duration of therapy (e.g., 5 days, as compared with 10 days), which would allow the treatment of more patients during the pandemic, is being assessed in ongoing randomized trials of this therapy.

No new safety signals were detected during short-term remdesivir therapy in this compassionate-use cohort. Nonclinical toxicology studies have shown renal abnormalities, but no clear evidence of nephrotoxicity due to remdesivir therapy was observed. As reported in studies in healthy volunteers and patients infected with Ebola virus, mild-to-moderate elevations in ALT, AST, or both were observed in this cohort of patients with severe Covid-19.\textsuperscript{18,19} However, considering the frequency of liver dysfunction in patients with Covid-19, attribution of hepatotoxicity to either remdesivir or the underlying disease is challenging.\textsuperscript{29} Nevertheless, the safety and side-effect profile of remdesivir in patients with Covid-19 require proper assessment in placebo-controlled trials.
Supported by Gilead Sciences.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

This article was published on April 10, 2020, at NEJM.org.

We thank Sarah Tse, Deborah Ajayi, and Gretchen Schmelz of BioScience Communications for creating earlier versions of the figures. Writing and editorial assistance with earlier versions of the manuscript were provided by David McNeel and Sandra Chen, both of Gilead Sciences. The names of those who assisted in the care of the patients in this program are listed in the Supplementary Appendix. We express our solidarity with those who are or have been ill with Covid-19, their families, and the health care workers on the front lines of this pandemic.

Author Affiliations

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RESULTS

A total of 1062 patients underwent randomization (with 541 assigned to remdesivir and 521 to placebo). Those who received remdesivir had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), as compared with 15 days (95% CI, 13 to 18) among those who received placebo (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; P<0.001, by a log-rank test). In an analysis that used a proportional-odds model with an eight-category ordinal scale, the patients who received remdesivir were found to be more likely than those who received placebo to have clinical improvement at day 15 (odds ratio, 1.5; 95% CI, 1.2 to 1.9, after adjustment for actual disease severity). The Kaplan–Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Serious adverse events were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%).

CONCLUSIONS

Our data show that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. (Fundied by the National Institute of Allergy and Infectious Diseases and others; ACTT-1 ClinicalTrials.gov number, NCT04280705.)

Why would you prevent “off patent” solutions from preventing or shedding the virus early so that you can use this IV drug later to reduce hospital stays when it doesn’t save anyone?
The trial was sponsored and primarily funded by the NIAID, National Institutes of Health (NIH), Bethesda, MD. This trial has been funded in part with federal funds from the NIAID and the National Cancer Institute, NIH, under contract HHSN261200800001E 75N910D00024, task order number 75N91019F00130/75N91020F00010, and by the Department of Defense, Defense Health Program. This trial has been supported in part by the NIAID of the NIH under award numbers UM1AI148684, UM1AI148576, UM1AI148573, UM1AI148575, UM1AI148452, UM1AI148685, UM1AI148450, and UM1AI148689. The trial has also been funded in part by the governments of Denmark, Japan, Mexico, and Singapore. The trial site in South Korea received funding from the Seoul National University Hospital. Support for the London International Coordinating Centre was also provided by the United Kingdom Medical Research Council (MRC_UU_12023/23).

Wouldn’t you rather put these two in charge of the above study than NIAID?
Dr. Chu reports receiving consulting fees from Merck and GlaxoSmithKline, grant support from Sanofi Pasteur, and research supplies from Cepheid, Elune, and Genentech; Dr. Luetkemeyer, receiving grant support, paid to the University of California, San Francisco, from Gilead; Dr. Paredes, receiving grant support and advisory fees from Gilead Sciences, Merck Sharp and Dohme, and ViIV Healthcare; Dr. Touloumi, receiving grant support from Gilead Sciences Europe; Dr. Benfield, receiving grant support from Pfizer, Novo Nordisk Foundation, Simonsen Foundation, and Lundbeck Foundation, grant support and advisory board fees from GlaxoSmithKline, grant support and lecture fees from Pfizer, teaching fees from Boehringer Ingelheim, grant support and teaching fees from Gilead, and teaching fees and advisory board fees from Merck Sharp and Dohme; Dr. Fäkkenheuer, receiving grant support, advisory board fees, and travel support from Gilead Sciences and Janssen and grant support and advisory board fees from Merck Sharp and Dohme and ViIV Healthcare; Dr. Kortepečer, receiving consulting fees and serving on a board for Integrum Scientific; Dr. Pett, receiving grant support from Gilead Sciences and ViIV Healthcare; and Dr. Osinusi, being employed by Gilead Sciences. No other potential conflict of interest relevant to this article was reported.

Does this pass for objective science today?
Original Title has been alleged to be “Remdesivir with IV Administration Alone is Unlikely to Achieve Adequate Efficacy and Pulmonary Delivery should be Investigated in COVID-19 Patients” by Duxin Sun, PhD

Original Publish Date: April 13, 2020

IG: Was this turned down by NEJM and why? Who made decision to make the title innocuous?
Abstract

Remdesivir is one of the most promising drugs to treat COVID-19 based on the following facts: remdesivir has a broad-spectrum antiviral mechanism of action; it demonstrated in vitro activity against SARS-CoV-2 and in vivo efficacy in animal models against the similar coronavirus MERS-CoV; its safety profile has been tested in Ebola patients and in compassionate use in COVID-19 patients. Currently, remdesivir is being investigated in ten randomized controlled trials against COVID-19. The dose regimen of remdesivir is an IV loading dose of 200 mg on day 1 followed by daily IV maintenance doses of 100 mg for 5–9 days. Based on our data analysis, however, remdesivir with IV administration alone is unlikely to achieve excellent clinical efficacy. This analysis is based on the following observations: plasma exposures of remdesivir and its active metabolite are unlikely to be correlated with its clinical efficacy; remdesivir and its active metabolites are unlikely to be adequate in the lung to kill the SARS-CoV-2 virus. Even if remdesivir demonstrates benefits in the current randomized controlled trials, its efficacy may be limited. We suggest that a combination of an IV and pulmonary delivery dose regimen should be studied immediately to realize a potentially more effective antiviral therapy against COVID-19.

Even in a hospital through an IV its not a good platform!

Ouch!

IG’s: if its true that this study was delayed, barred form publishing at another journal, this may be part of the scheme. Need communications and discussions and titling, drafts, etc.
Anaphylactic reactions during AND after?! Motive for cardiac study that came out of nowhere are required telemetry on a totally safe drug? Liver Problems even in healthy patients

Warnings and precautions

- **Hypersensitivity, including infusion-related and anaphylactic reactions**: Hypersensitivity, including infusion-related and anaphylactic reactions, has been observed during and following administration of VEKLURY. Monitor patients under close medical supervision for hypersensitivity reactions during and following administration of VEKLURY. Symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. Slower infusion rates (maximum infusion time ≥120 minutes) can potentially prevent these reactions. If a severe infusion-related hypersensitivity reaction occurs, immediately discontinue VEKLURY and initiate appropriate treatment (see Contraindications).

- **Increased risk of transaminase elevations**: Transaminase elevations have been observed in healthy volunteers and in patients with COVID-19 who received VEKLURY; these elevations have also been reported as a clinical feature of COVID-19. Perform hepatic laboratory testing in all patients (see Dosage and administration). Consider discontinuing VEKLURY if ALT levels increase to ≥10× ULN. Discontinue VEKLURY if ALT elevation is accompanied by signs or symptoms of liver inflammation.

- **Risk of reduced antiviral activity when coadministered with chloroquine or hydroxychloroquine**: Coadministration of VEKLURY with chloroquine phosphate or hydroxychloroquine sulfate is not recommended due to antagonism observed in cell culture, which may lead to a decrease in antiviral activity of VEKLURY.
Remdesivir for 5 or 10 Days in Patients with Severe Covid-19

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Affiliations + expand

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Abstract

Background: Remdesivir is an RNA polymerase inhibitor with potent antiviral activity in vitro and efficacy in animal models of coronavirus disease 2019 (Covid-19).
So 10 days doesn’t work better than 5 days which begs the question: Is 5 days of treatment efficacious?

Methods: We conducted a randomized, open-label, phase 3 trial involving hospitalized patients with confirmed SARS-CoV-2 infection, oxygen saturation of 94% or less while they were breathing ambient air, and radiologic evidence of pneumonia. Patients were randomly assigned in a 1:1 ratio to receive intravenous remdesivir for either 5 days or 10 days. All patients received 200 mg of remdesivir on day 1 and 100 mg once daily on subsequent days. The primary end point was clinical status on day 14, assessed on a 7-point ordinal scale.

Results: In total, 397 patients underwent randomization and began treatment (200 patients for 5 days and 197 for 10 days). The median duration of treatment was 5 days (interquartile range, 5 to 5) in the 5-day group and 9 days (interquartile range, 5 to 10) in the 10-day group. At baseline, patients randomly assigned to the 10-day group had significantly worse clinical status than those assigned to the 5-day group (P = 0.02). By day 14, a clinical improvement of 2 points or more on the ordinal scale occurred in 64% of patients in the 5-day group and in 54% in the 10-day group. After adjustment for baseline clinical status, patients in the 10-day group had a distribution in clinical status at day 14 that was similar to that among patients in the 5-day group (P = 0.14). The most common adverse events were nausea (9% of patients), worsening respiratory failure (8%), elevated alanine aminotransferase level (7%), and constipation (7%).

Conclusions: In patients with severe Covid-19 not requiring mechanical ventilation, our trial did not show a significant difference between a 5-day course and a 10-day course of remdesivir. With no placebo control, however, the magnitude of benefit cannot be determined. (Funded by Gilead Sciences; GS-US-540-5773 ClinicalTrials.gov number, NCT04292899.)
10 days not better than 5 days

Original Investigation

August 21, 2020

Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19
A Randomized Clinical Trial

Christoph D. Spinner, MD; Robert L. Gottlieb, MD, PhD; Gerard J. Criner, MD; et al

Author Affiliations | Article Information

COVID-19 Resource Center
**Funding/Support:** This study was sponsored by Gilead Sciences.

**Role of the Funder/Sponsor:** The sponsor, in consultation with the Food and Drug Administration and investigators, designed and conducted the study. Collection of data and management of trial sites were conducted by a contract research organization (PPD) with sponsor oversight. An independent data monitoring committee reviewed trial data. All authors contributed to interpretation of the data, including sponsor coauthors. A preliminary draft of the manuscript was prepared by a writer employed by Gilead. All authors reviewed the final version of the manuscript for approval and concurred with the decision to submit the manuscript for publication.
Conflicts of Interest Disclosures: Dr. Spinner reported receipt of personal fees from AbbVie and grants and personal fees from Janssen-Cilag, Merck Sharp & Dohme, and ViV HealthCare/GlaxoSmithKline. Dr. Gottlieb reported receipt of nonfinancial support from Gilead. Sciences outside the current work: Dr. Arribas López reported receipt of honoraria from Gilead for participating in an advisory board, and his institution has received grants from Gilead for an unrelated project; he also reported receipt of grants and personal fees from ViV and personal fees from Janssen, Merck Sharp & Dohme, Teva, and Aelix. Dr. Soriano Viladomiu reported receipt of honoraria as speaker or advisor from Pfizer, Merck Sharp & Dohme, Angelini, Menarini, and Shionogi. Dr. Ogbuagu reported receipt of advisory board honoraria from Gilead and ViV and speakers fees from Gilead. Dr. Chai reported receipt of grant support from and advisorship/consultancy for Pfizer, Gilead, Astellas, and Merck Sharp & Dohme. Dr. Bernasconi reported that his institution has received fees for his participation in advisory boards and travel grants from Gilead, Merck Sharp & Dohme, ViV, Pfizer, AbbVie, and Sandoz. Dr. Bhagani reported receipt of research support and honoraria for lectures and advisory boards from Gilead Sciences and grants and personal fees from AbbVie, Merck Sharp & Dohme, Roche, and ViV. Dr. Sanyal reported being employed at Sanyal Bio; receiving royalties from Elsevier and UpToDate; holding stock in Exhalenz, Akarna, Genfit, Hemoshear, Durect, and Tzoaama; receiving grants from Galextin and Bristol-Myers; consulting for Conatus, Gilead, Pfizer, Boehringer Ingelheim, Merck, Hemoshear, Lilly, Novo Nordisk, Ardelyx, Terns, ENYO, Birdrock, Albireo, Sanofi, Janssen, Takeda, Zydus, AMRA, Poxel, Servier, Second Genome, and General Electric; receiving grants and consulting for Mallinckrodt, Salix, Novartis, and Nimbus; being principal investigator of an ongoing trial for Genfit; receiving grants and being principal investigator of an ongoing trial for Immuron; receiving grants, consulting for, and being principal investigator of ongoing trials for Echosens-Sandill and Sequana; providing advice but receiving no personal remuneration for Intercept, Galextin, Fractyl, Durect, Indalo, Allergan, Chemomab, Affimmune, Teva, BASF, Perspectum, and B8bio; and being the inventor for a patent held jointly by OWL and Virginia Commonwealth University. Dr. Huh reported that his institution received grants from Gilead, GlaxoSmithKline/ViV, Janssen, Bristol-Meyers Squibb, Proteus, Lilly, and the National Institute of Allergy and Infectious Diseases and that he received consulting fees from Gilead, ViV, Janssen, and Theratechnologies. Dr. Marty reported receipt of grants from Ansun, Chimerix, Gilead, and Merck and personal fees from AlloVir, Janssen, Kyorin, Merck, ReViral, and Symbio. Drs. Sen Gupta, Hyland, Osinusi, Cao, Blair, Wang, Gagar, and Brainard are employees of and own stock in Gilead Sciences. No other disclosures were reported.
Liver injury in remdesivir-treated COVID-19 patients

Rosa Zampino, Ferruccio Mele, Letizia Lucia Florio, Lorenzo Bertolino, Roberto Andini, Maria Galdo, Rosanna De Rosa, Antonio Corcione & Emanuele Durante-Mangoni

Hepatology International 14, 881–883(2020) | Cite this article

1699 accesses | 2 citations | 20 altmetric | Metrics

Novel Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) infection results predominantly in pulmonary involvement (Coronavirus disease 2019, COVID-19), but a direct, SARS-CoV-2-induced liver damage has also been described [1, 2]. Thus, it is important to monitor liver function and evaluate hepatic safety of drugs administered to COVID-19 patients. Remdesivir (RDV), a nucleotide analogue RNA polymerase inhibitor, originally developed and tested for Ebola virus disease, showed in vitro efficacy against SARS-CoV-2 [3], and experience on its efficacy and safety for COVID-19 is accumulating [4, 5]. However, hepatic safety of RDV in COVID-19 has not been the focus of detailed investigation. Here, we describe patterns of liver toxicity in 5 COVID-19 patients treated with RDV in the intensive care unit (ICU) of Monaldi Hospital, Naples, Italy, during March and April 2020. Overall, our Hospital cared for 32 critically ill COVID-19 patients.
What does the WHO say?

Repurposed antiviral drugs for COVID-19 – interim WHO SOLIDARITY trial results

WHO Solidarity trial consortium*

* A complete list of SOLIDARITY Trial investigators is provided in the Supplementary Appendix.

International Steering Committee *National PI; †National Coordinator; #Executive Group; § Discovery add-on study.
RESULTS
In 405 hospitals in 30 countries 11,266 adults were randomized, with 2750 allocated Remdesivir, 954 Hydroxychloroquine, 1411 Lopinavir, 651 Interferon plus Lopinavir, 1412 only Interferon, and 4088 no study drug. Compliance was 94-96% midway through treatment, with 2-6% crossover. 1253 deaths were reported (at median day 8, IQR 4-14). Kaplan-Meier 28-day mortality was 12% (39% if already ventilated at randomization, 10% otherwise). Death rate ratios (with 95% CIs and numbers dead/randomized, each drug vs its control) were: Remdesivir RR=0.95 (0.81-1.11, p=0.50; 301/2743 active vs 303/2708 control), Hydroxychloroquine RR=1.19 (0.89-1.59, p=0.23; 104/947 vs 84/906), Lopinavir RR=1.00 (0.79-1.25, p=0.97; 148/1399 vs 146/1372) and Interferon RR=1.16 (0.96-1.39, p=0.11; 243/2050 vs 216/2050). No study drug definitely reduced mortality (in unventilated patients or any other subgroup of entry characteristics), initiation of ventilation or hospitalisation duration.

CONCLUSIONS
These Remdesivir, Hydroxychloroquine, Lopinavir and Interferon regimens appeared to have little or no effect on hospitalized COVID-19, as indicated by overall mortality, initiation of ventilation and duration of hospital stay. The mortality findings contain most of the randomized evidence on Remdesivir and Interferon, and are consistent with meta-analyses of mortality in all major trials. (Funding: WHO. Registration: ISRCTN83971151, NCT04315948)

HCQ studies have tendency to be framed so that they are LATE and without zinc, Was this to protect Remdesivir?

WHO says no efficacy

No Efficacy
There are 4 trials of Remdesivir vs the same management without it: Solidarity (604 deaths in about 5000 randomized), ACTT-1 (136 deaths in about 1000) and two smaller trials (41 deaths). Figure 4 gives mortality results from each trial, subdivided by initial respiratory support. (These like-vs-like comparisons allow for the proportion already on high-flow oxygen or ventilation at entry into ACTT-1 having been, by chance, somewhat lower with Remdesivir than with placebo.) Combining data appropriately from all 4 trials, the Remdesivir vs control death rate ratio (RR) is 0.91 (95% CI 0.79-1.05).
This is why no-one can say Remdesivir saves lives

<table>
<thead>
<tr>
<th>Trial name, and initial respiratory support</th>
<th>Deaths reported / Patients randomized in ITT analyses (28-day risk, K-M%)</th>
<th>Remdesivir deaths: Observed-Expected (O.E)</th>
<th>Ratio of death rates (RR), &amp; 99% CI (or 95% CI, for total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solidarity: no O₂</td>
<td>11/661 (2.0)</td>
<td>-0.6</td>
<td>0.90 [0.31-2.59]</td>
</tr>
<tr>
<td>Solidarity: low/hi-flow O₂</td>
<td>192/1828 (12.2)</td>
<td>-16.9</td>
<td>0.85 [0.66-1.09]</td>
</tr>
<tr>
<td>Solidarity ventilation</td>
<td>78/254 (43.0)</td>
<td>7.6</td>
<td>1.20 [0.80-1.80]</td>
</tr>
<tr>
<td>ACTT: no O₂</td>
<td>3/75 (4.1)</td>
<td>-0.3</td>
<td>0.82 [0.10-6.61]</td>
</tr>
<tr>
<td>ACTT: low-flow O₂</td>
<td>9/232 (4.0)</td>
<td>-8.0</td>
<td>0.30 [0.11-0.81]</td>
</tr>
<tr>
<td>ACTT: hi-flow O₂ or non-invasive ventilation</td>
<td>19/95 (21.2)</td>
<td>9.6</td>
<td>1.02 [0.44-2.34]</td>
</tr>
<tr>
<td>ACTT: invasive ventilation</td>
<td>29/131 (21.9)</td>
<td>14.3</td>
<td>1.13 [0.57-2.23]</td>
</tr>
<tr>
<td>Wuhan: low-flow O₂</td>
<td>11/129 (8.5)</td>
<td>-0.8</td>
<td>0.81 [0.21-3.07]</td>
</tr>
<tr>
<td>Wuhan: hi-flow O₂ or ventilation</td>
<td>11/29 (37.9)</td>
<td>1.8</td>
<td>1.40 [0.20-9.52]</td>
</tr>
<tr>
<td>SIMPLE: no O₂</td>
<td>5/384 (1.3)</td>
<td>-0.9</td>
<td>0.64 [0.10-3.94]</td>
</tr>
<tr>
<td><strong>Subtotals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower risk groups (with no ventilation)</td>
<td>231/3309 (7.0)</td>
<td>-27.8</td>
<td>0.80 [0.63-1.01]</td>
</tr>
<tr>
<td>Higher risk groups</td>
<td>165/509 (30.6)</td>
<td>10.1</td>
<td>1.16 [0.85-1.60]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>387/3818 (10.1)</strong></td>
<td><strong>-17.5</strong></td>
<td><strong>0.91 [0.79-1.05]</strong></td>
</tr>
</tbody>
</table>

- 95% or >95% confidence interval (CI), K-M Kaplan-Meier.
The ‘very, very bad look’ of remdesivir, the first FDA-approved COVID-19 drug

By Jon Cohen, Kai Kupferschmidt | Oct. 28, 2020, 7:05 PM

October was a good month for Gilead Sciences, the giant manufacturer of antivirals headquartered in Foster City, California. On 8 October, the company inked an agreement to supply the European Union with its drug remdesivir as a treatment for COVID-19—a deal potentially worth more than $1 billion. Two weeks later, on 22 October, the U.S. Food and Drug Administration (FDA) approved remdesivir for use against the pandemic coronavirus SARS-CoV-2 in the United States—the first drug to receive that status. The EU and U.S. decisions pave the way for Gilead's drug into two major markets, both with soaring COVID-19 cases.

But both decisions baffled scientists who have closely watched the clinical trials of remdesivir unfold over the past 6 months—and who have many questions about remdesivir’s worth. At best, one large, well-designed study found remdesivir modestly reduced the time to recover from COVID-19 in hospitalized patients with severe illness. A few smaller studies found no impact of treatment on the disease whatsoever. Then, on 15 October—in this month's decidedly unfavorable news for Gilead—the fourth and largest controlled study delivered what some believed was a coup de grâce: The World Health Organization's (WHO's) Solidarity trial showed that remdesivir does not reduce mortality or the time COVID-19 patients take to recover.

Science has learned that both FDA's decision and the EU deal came about under unusual circumstances that gave the company important advantages. FDA never consulted a group of outside experts that it has at the ready to review such drugs. Instead, the FDA released a statement the day before the approval that said remdesivir 'proves to be safe and effective' and the EU did not ask for an independent expert panel to evaluate the drug.
How was this dangerous drug given to the President of the United States?
FDA prevents early treatment and makes remdesivir/Veklury drug of choice
How does Veklury interact with other drugs? They don’t know.
Good News: Kids and Pregnant Women are safe from having to be given this drug. (parody)

Fauci: “Nursing babies?! Beats Me. Your guess is as good as mine” (parody)
IG: Because HCQ and Ivermectin prevent or cure so early, did the capability of these off-patent drugs pose a conflict and threat to Remdesivir (and vaccines) because they made hospitalization unnecessary?

Is it just “all about the Benjamins?” HCQ and Ivermectin eliminate need for hospitalization and expensive drugs and vaccines.