MINI-REVIEW

Critical reappraisal of remdesivir investigational trials in COVID-19

P. Brouqui, A. Giraud-Gatineau and D. Raoult
Aix-Marseille Université, IRD, MEPHI, IHU-Méditerranée Infection, Marseille, France

Abstract

During disease outbreaks, the pharmaceutical industry generally puts a lot of effort into promoting clinical trials studying their new drugs. We review evidence of the ten most recent reports on remdesivir. We conclude that it is far too premature to identify remdesivir as a curative or life-saving intervention during the COVID-19 pandemic.

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Corresponding author: P. Brouqui, IHU-Méditerranée Infection, 19-21, Boulevard Jean Moulin, 13005 Marseille, France.
E-mail: philippe.brouqui@univ-amu.fr

Introduction

Since the first described infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, coronavirus disease 2019 (COVID-19) has developed into a pandemic, the symptoms of which range from asymptomatic course to pneumonia, acute lung and/or multiorgan failure and death. In order to develop a meaningful therapy strategy, different medications are used off label. One of these is remdesivir, a precursor of a nucleotide analogue that inhibits viral RNA polymerases. As for Ebola, SARS-CoV and Middle East respiratory syndrome coronavirus, remdesivir appears to be effective *in vitro* in SARS-CoV-2 [1]. Good outcomes have been reported in case reports [2,3]. Many studies are ongoing or have already been published that study the efficacy of remdesivir in COVID-19, some showing a lack of difference with control arms [4] and others reporting efficacy [5–7].

Treating patients early in a disease course has always been crucial in treating potentially life-threatening infectious diseases. We therefore evaluated the quality of both published and not yet peer-reviewed trials on remdesivir and highlight pitfalls. A careful analysis of reported data is needed to offer the most accurate interpretation of results.

Literature search

We looked at all the scientific papers available, both peer reviewed and not, in the major literature from the databases PubMed, Web of Knowledge and Google Scholar, as well as the preprint websites bioRxiv and medRxiv. The keywords were remdesivir alone or with COVID-19. We recovered 91 articles in medRxiv, 81 in bioRxiv and 112 in PubMed. When we added the keyword COVID-19 to remdesivir, PubMed recovered 79 articles or papers, Web of Knowledge 25 and Google Scholar 1480. Of these, we selected 17 that addressed the aims of this article. When available, we assessed the following endpoints: time to improvement at days 14 and 28, death and adverse events (AEs).

Results and discussion

Ten studies have reported the use of remdesivir in COVID-19; they are summarized in Table 1. We turn to each in turn. The first describes a single case. The patient received remdesivir on day 11 of disease; day 12 saw her condition improve. She was able to be withdrawn from oxygenation, and oxygen saturation was 96% [8].

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The second study, which has not yet been peer reviewed, reports the first 12 cases of COVID-19 in the United States. It is a descriptive paper. Three of seven hospitalized patients received remdesivir for compassionate use for a duration of 4 to 10 days [9]. All hospitalized patients underwent serial SARS-CoV-2 real-time reverse transcriptase PCR (RT-PCR) testing. When reanalysed, the mean delay in normalization of nasal RT-PCR results was 8.6 days in patients who received remdesivir versus 6.75 days (p 0.85) in untreated patients.

The third study reports a series of five patients, three of whom received at least one dose of remdesivir. In two patients, treatment occurred at the time of the disease's worsening. In one of them, remdesivir was discontinued after 5 days because of alanine aminotransferase elevation and rash. In the third patient, remdesivir was stopped after a single dose because the patient had to undergo renal dialysis to avoid the accumulation of cyclodextrin. Therefore, the authors indicate that they cannot draw any conclusions on the basis of their data regarding the potential efficacy of remdesivir in treating COVID-19 [3].

The fourth study analyses remdesivir provided to a single patient on day 13 of disease [2]. At the time of remdesivir administration, the patient was in the intensive care unit (ICU) and intubated. He was treated with hydroxychloroquine 400 mg per day and azithromycin for 7 days. Forty-eight hours after remdesivir initiation, the patient's condition improved. The patient was extubated 60 hours after treatment and was able to breathe ambient air 24 hours later.

The fifth study is an uncontrolled prospective open observational study of patients having received as compassionate use a 10-day regimen of remdesivir with a target follow-up period of 28 days. Between 25 January and 7 March 2020, a total of 61 patients were included in the study and received at least one dose of remdesivir, some of which may have been part of previous studies. Of those patients, eight were excluded, which in an intention-to-treat (ITT) analysis should have been considered as a failure. Finally, data from 53 patients were analysed, with data of one patient previously published by Lescure et al. [3]. Of these, 40 received the complete 10-day remdesivir therapy, ten received 5- to 9-day therapy and three patients received <5 days of therapy [7]. On average, COVID-19 symptoms lasted 12 days before remdesivir therapy was initiated. At a median follow-up of 18 days, the disease of 36 (68%) of 53 patients improved while receiving remdesivir. An improvement was shown in all 12 patients with mild disease who received no or only low-dose oxygen supplementation and in five of seven noninvasively ventilated patients.

This also raises an ethical question regarding the compassionate provision of remdesivir to some patients who were not engaged in the short term. Of the 53 patients followed, ten were treated while they were receiving ambient air [2] or low-flow oxygen [8]. Of the 30 invasively ventilated patients, 17 were extubated and three of the four patients receiving extracorporeal membrane oxygenation (ECMO) were able to terminate ECMO; it is assumed that all these patients were alive at the time of the last follow-up examination. Finally, a total of seven (13%) of the 53 patients died, on average 15 days after the onset of remdesivir therapy; six of seven patients were invasively ventilated at the start of the study and one was noninvasively ventilated (hazard ratio, 2.78). But there is a lot of missing information in this study. At time of publication, no data had been obtained from the nine patients who did not improve during follow-up, among whom was a patient who had received ECMO from the very beginning of admission, suggesting a poor prognosis. Consequently, we calculated on the basis of the available data that at the end of follow-up (day 28), seven (15.9%) of 44 patients died. What happened to the nine patients still in the ICU receiving mechanical ventilation and/or ECMO? Moreover, one patient (patient 46) was discharged on day 8, but we never learned whether he finished the course of remdesivir or what his outcome was. Further, the scientific veracity and credibility of this paper, which was sponsored and written by Gilead employees, has been questioned, as was the quality of its review by the *New England Journal of Medicine*. Further, ethical considerations must be debated regarding what compassionate use is and what role industrial funding plays in trial bias [10].

Wang et al. [4] reported in the *Lancet* a randomized controlled trial (RCT) on the efficacy of remdesivir versus placebo in 236 patients (158 receiving remdesivir and 78 placebo) from ten hospitals in Wuhan, China. The mean age, sex ratio, delay from onset to enrollment, comorbidity, enrollment criteria (O_2 <95%) and presence of X-ray–confirmed pneumonia were comparable in the two arms, but also to that of other published studies reported in Table 1. The endpoint was time to recovery and death at 28 days; 100% of patient remained enrolled at the end the study and were evaluated in both ITT and per-protocol (PP) analyses. Serious AEs or events leading to stopping the study drug were reported in 18 (12%) in the remdesivir cohort versus six (5%) in the placebo group, demonstrating the drug's poor safety. Although no significant difference was noted in terms of other treatment in the two groups, in almost all the RCTs reporting evaluation of treatment for COVID-19, patients were also treated with several other drugs, such as antibiotics [9], some of which have demonstrated antiviral efficacy [11], as well as corticosteroids, antivirals and anti-inflammatory drugs, among which anti–interleukin 6 seems promising [12]. This may bias the data, as in the Hillaker et al. study [2]. This also may call into question the multicentric nature of the RCTs, which is needed to obtain a high enough number of enrolled patients to perform statistical

TABLE 1. Summary of ten studies reporting treatment with remdesivir

Study	Study type	Sample size	Mean age (years)	Sex ratio (M:F)	Mean time to treatment (days)	Comorbidity	Inclusion criterion O_2 sat <95%	Inclusion criterion pneumonia	Supplementary ATB	Other treatment	Median time to improvement or recovery (days)	ITT and PP analysis	Death/patients analysed (%)/total days 14–18[a]	Death/patient analysed (%)/total day 28	Stop due to AE[b]
Holshue [8]	Case report	1	35	M	11	No	Yes	Yes	1/1	NA	Improve at day 1 of remdesivir	NA	0/1	0	0
Kujawski [9]	Case series	12	53	2	11	6/12	3/3	Yes	3/3 AZT (1)	Yes	PCR negative at mean 6.5 days	NA	0/12	NA	NA
Lescure [3]	Case series	3	31/48/80	M	15/23/26	30%	1/3	3/3	1/3	NA	NA	NA	0/3	NA	30%
Hillaker [2]	Case report	1	40	M	13	Yes	Yes	Yes	Azithromycin	HCQ	Discharged	NA	0/1	NA	0
Grein [5]	Compassionate	53	64	1.87	12 (9–15)	68%	43/53	NA	NA	NA	NA	NA	7/53 (13%)/53	7/44 (15.9%)/53	32/53 (60%)
Wang [4]	RCT, remdesivir:placebo	158:78	66:64	1.28:1.88	≤12	71%:71%	Yes	Yes	142 (90%):73 (94%)	102 (65%):53 (68%)	21:23 (NS)	ITT and PP	15/153 (10%)/153:7/78 (9%)/78	22/150 (15%)/150:10/77 (13%)/77	12%:5%
Biegel	RCT, remdesivir:placebo	538:531	58.6:59.2	1.86:1.74	9 (6–12)	39.2%:38.2%	No	NA	NA	NA	11:15	ITT	32:538 (5.9%)/180:54/521 (10.3%)	NA	21.1%:27%
Goldman [17]	RCT, remdesivir 5 days:remdesivir 10 days	200:197	61:62	1.00:1.04	1.47	27%:27%	Yes	Yes	NA	NA	10:11 (NS)	ITT	16/200 (8%):21/197 (10,6%)	NA	4%:10%
Antinori [18]	Compassionate	35	63	2.8	13	51.4%	Yes	Yes	NA	HCQ	NA	NA	NA	9/35 (25.7%)	22.8%
Olender [20]	Congregate of RCT and retrospective study, remdesivir/no remdesivir	312:818	NA	NA	NA	NA	Yes	Yes	NA	NA	232/312 (74.4%)[c] 483/818 (59%)	NA	NA	24/312 (7.6%) 102/818 (12.5%)	NA

AE, adverse event; HCQ, hydroxychloroquine; ITT, intention to treat; NS, not significant; O_2 sat, oxygen saturation; PP, per protocol; RCT, randomized controlled trial.
[a]Total patients treated for PP analysis.
[b]Serious AEs leading to stopping treatment.
[c]Improvement at day 14 (at least two patients).

analysis. This is a bias which is difficult to control because it is directly related to the standard of care of each centre, which is likely to be different in terms of equipment, protocols, surveillance and staff skills. Consequently, patient care might not be comparable between centres, and the outcome might be biased by the expertise of the team in charge.

In a preliminary announcement regarding the efficacy of remdesivir in a RCT involving 1061 patients, the US National Institutes of Health said that preliminary results indicated that patients who received remdesivir had a 31% faster time to recovery than those who received placebo (11 days vs. 15 days), but that the survival benefit on 1063 patients was insignificant compared to placebo (p 0.059), thus concluding that remdesivir had an effect, but it was not a wonder drug. In a commentary, Mahase [6] noted that during epidemics, expedited publications are acceptable, but hinting at positive results will only benefit drug companies. Fast-flowing, conflicting information on remdesivir in the past few weeks has left people reeling.

Recently a paper was released with preliminary reports in the *New England Journal of Medicine,* but with different results: the survival benefits became significant in the overall analysed population [13]. However, we think this conclusion is too rosy. In their table 2, as mentionned, the hazard ratio indicates that only a mild infection will benefit from remdesivir but that there is no difference in severe forms of COVID-19 compared to placebo. Interestingly, results are given in ITT, but one third of enrolled patients in each arm (33.8% and 35.7%) only received the complete protocol, 180 of 531 and 185 of 518 for remdesivir and placebo respectively. Of them, 288 (27.4%) of 1049 were discharged because they were cured before the end of treatment and were then lost to follow-up. The remaining patients were still receiving treatment or had missing treatment data at the time of data analysis. While an analysis according to the ITT principle aims to preserve the original randomization and to avoid potential bias due to exclusion of patients, such a high number lost to follow-up is unacceptable because it might modify the benefits of randomization, with those lost to follow-up often having a different prognosis than those who complete the study [14]. In this study, 168 patient were discharged before the end of treatment in the remdesivir arm versus 120 in the placebo arm, which is significantly different ($p < 0001$). It is likely that these patients had a baseline score of 4 or 5 because they were discharged before the end of treatment, which would in part explain the better outcome in the remdesivir arm. Some have suggested that a <5% loss in sample size leads to little bias, but >20% poses serious threats to validity [15]. Nevertheless, a PP analysis, as recommend by the CONSORT (Consolidated Standards of Reporting Trials) guidelines, should be reported for all planned outcomes to allow readers to interpret the effect of an intervention [16].

Goldman et al. [17] studied 5 to 10 days' treatment with remdesivir and found no significant mortality or improvement of clinical status between patients in the two arms. All together, any serious AE was reported in 27.7% of treated patients, among them 4.7% with acute kidney injury. In 7.3% of patients, AEs led to withdrawal of treatment.

Antinori et al. [18] reported the compassionate use of remdesivir in two small cohorts of patients: those in the ICU (18 patients) and those in an infectious disease ward (17 patients). While no control was provided for comparison, the overall case-fatality rate reported at day 28 was 25.7% (9/35), but 20 (57%) of 35 still needed oxygen or invasive ventilation. As discussed above, conclusions can only be speculative when half of the patients are still receiving care at the time of publication. Most papers and articles, because of the understandable urgent need for more clinically relevant information, provide data on just a small portion of the included patients. Complementary information on the outcomes of the remaining patients is needed; it is likely that these patients were more likely to die than survive, as the case-fatality rate in the ICU has been linked to length of stay [19].

The final study we considered was conceived, designed and analysed by Gilead and compared interim data from two ongoing studies: one phase 3 randomized open-label study, reported above [17], and a real-world retrospective longitudinal cohort study [20]. Patients receiving remdesivir were compared to those not receiving remdesivir. Recovery at day 14 was reported to be 232 (74.4%) of 312 in the remdesivir cohort and 483 (59%) of 818 in the cohort without remdesivir. The nature of the study—including bias due to uncontrolled associated therapy, retrospective collection of a part of the data, a lack of description of disease characteristics (notably comorbidity) and the fact that conception of the study was set up by the provider of the drug—requires a very careful interpretation of data [21].

Still, few studies have been reported evaluating the new drug remdesivir. On the one hand, in many aspects, data from a case report or series without controls mean little in the context of evaluating the efficacy of an experimental drug. On the other hand, RCTs take time and are only rarely going to be able to deliver clinically usable information during the course of the outbreak. Three RCTs have data available, but two share the same aims and provide contradictory data. Only one is methodologically adequate, with both ITT and PP analyses on a cohort of patients having completed the study demonstrating no difference between drugs and standard of care.

As of this writing, no study has convincingly supported the use of remdesivir in patients with severe COVID-19. It is interesting, however, to notice that 'a weak recommendation for the use of remdesivir' was suggested in severe cases [22] and was followed by

the European Medicines Agency's human medicine committee recommendation to grant a conditional marketing authorization for patients with COVID-19 who require supplemental oxygen. In fact, it is likely that, as it is for influenza, the key to the best COVID-19 outcome is early treatment of patients at the time of diagnosis. However, serious AEs, some leading to interruption of treatment, and the drug's intravenous route of delivery would likely limit its use in this indication.

We wanted to ask physicians in charge of treating COVID-19 patients to ensure that their recommendations regarding COVID-19 treatment not rely on remdesivir, for which convincing data on efficacy are weak, AEs are not negligible and the cost is relatively high, especially in underresourced settings; further, the intravenous route will limit its indication in mild disease. As a consequence, instead of remdesivir, other option should be considered—one less toxic, more efficient, cheaper and more affordable for everybody.

Conflicts of interest

None declared.

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