Critical reappraisal of remdesivir investigational trials in COVID-19

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Remdesivir investigational trials in COVID-19: a critical reappraisal. REVISED v2

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Abstract: A lot of effort are generally made by the industry during outbreak to promote clinical trials with new drugs. Here we review evidence of the 10 most recent reports on remdesivir. We conclude that it is far too premature to identify remdesivir as a curative or life-saving intervention.

Introduction

Since the first described infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) in December 2019, the coronavirus disease 2019 (COVID-19) has developed into a pandemic, the symptoms of which range from asymptomatic course to pneumonia, acute lung and multi-organ 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 (MERS-CoV), remdesivir appears to be effective *in vitro* in SARS-Cov2 (1). Good outcomes have been reported in cases report (2;3). Many studies are ongoing or already published to demonstrate the efficacy of remdesivir on patient with COVID-19, some showing the lack of difference with control arms (4) , some others reporting efficacy but discussed (5-7). Treating patients early in disease has always been a crucial issue in treating potentially life-threatening infectious diseases. The aim of this review presented below was to evaluate the quality of the published and not yet peer-reviewed trials on remdesivir and to highlight pitfalls to inform readers that a careful analysis of reported data is needed to offer a more accurate interpretation of the results.

Literature search

We look at all scientific paper available as peer and not yet peer reviewed paper in the major literature from data base Pub Med, Web of Knowledge, scholar google and BioRxiv and MedRxiv. The key words were [remdesivir alone or with COVID]. We recover 91 articles in MedRxiv, 81 in BioRxiv and 112 in Pub Med. When we added COVID to remdesivir, PubMed recover 79 articles. On Web of Knowledge remdesivir recover 25 articles. In Scholar Google remdesivir recovered 1480 articles in 2020. Of them we selected 17 papers responding to the aims of this article. When available we look at the following endpoints: time to improvement at D14 and 28, death, and adverse events.

Results and discussion

As today, 10 studies report the use of remdesivir in COVID and are summarized in Table 1. The first is a single case, having received remdesivir on the day 11 of disease, and which on day 12 saw condition improve (stopping oxygenation and oxygen saturation at 96%) (8).

The second is a non-yet peer review paper that reports the first 12 case of COVID in the united states. It is a descriptive paper in which 3 of the 7 hospitalized patients received remdesivir for compassionate use for a duration of 4-10 days (9) . All hospitalized patient had serial SARSCov2 RT PCR testing. When reanalyzed, the mean delay in normalization of nasal RT PCR was 8.6 days in remdesivir patient versus 6.75 days (p=0.85) in untreated patient.

The third reports a series of 5 cases, 3 of which received at least one dose of remdesivir. In two patients, treatment occurred at the time of the disease's worsening. In one of them, the remdesivir was discontinued after 5 days (ALT elevation and rash). In the third patient, the remdesivir was stopped after a single dose due to renal dialysis to avoid the accumulation of cyclodextrin. Therefore, the authors indicate that they cannot draw any conclusions based on their data as to the potential efficacy of remdesivir in the treatment of COVID-19 (3).

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

The fifth study is an uncontrolled, prospective, open observational study of patients having received, as compassionate used, a 10-day remdesivir therapy with a target follow-up period of 28 days. Between 25.01.2020 and 07.03.2020, 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, 8 were excluded of the study which, in an intention to treat analysis should have been considered as failure. Finally, data from 53 patients were analyzed of whom one was already published in the study N°3 (Lescure et al). Of them 40 received the complete 10-day remdesivir therapy, 10 received 5 to 9-day therapy and 3 patients received less than 5 days of remdesivir (7) . On average, COVID-19 symptoms lasted 12 days before remdesivir therapy was initiated. In the median follow-up period of 18 days, 36 of the 53 patients (68%) were able to improve under Remdesivir. An improvement was shown in all patients who were mild receiving no or only low-dose oxygen supplementation (n = 12), or in 5 of the 7 non-invasive ventilated patients. This also raised an ethical comment on the compassionate used of remdesivir in some patients whom were not engaged in short term. Of the 53 patients followed, 10 were treated while they were on ambient air (2) or low flow oxygen (8) Of the 30 invasively ventilated patients, 17 were extubated and 3 of the 4 patients receiving ECMO were able to terminate ECMO; and it is assumed that all these patients were alive at the time of the last follow-up examination. Finally, a total of 7 of the 53 patients died (13%), on average 15 days after the onset of remdesivir therapy; 6 out of 7 patients were invasively ventilated at the start of the study and one non-invasively ventilated (hazard ratio 2.78). But there is a lot of missing data in this study. At time of publication no data were obtained from the 9 patient whom did not improved during the follow-up among whom was a patient on ECMO since the early beginning suggesting a very poor prognosis. Consequently, if mortality was calculated on available data at the end of follow up (Day 28), 7 of 44 (15.9%) patients died. What happened since for the 9 patients still in ICU under mechanical ventilation and or ECMO? Moreover, one patient N°46 was discharge on day 8, but we don't know if he finished remdesivir and what was his outcome. Scientific veracity and credibility of this paper sponsored and written by Gilead employees is questioned as well as the quality of the review by the New England Journal of Medicine (NEJM) , ethical consideration of what is compassionate used and the role of industrial funding in trials bias (10).

Wang et al reported in the Lancet a Randomized Controlled Trial (RCT) on the efficacy of remdesivir versus placebo in 236 (158:78) patient from 10 hospital in Wuhan (4). The mean age, sex ratio, delay from onset to enrolment, comorbidity, enrolment criteria (O2< 95%), RX confirmed pneumonia, were comparable in the two arms but also to other published study reported in table 1. The endpoint was time to recovery and death at 28 days and 100 % of patient enrolled end the study and were evaluated in both intention to treat (ITT) and per protocol (PP) analysis. Serious adverse event or event leading to stop the drug were reported in 18 and 12 % in remdesivir versus 6 and 5% in placebo demonstrating the poor safety of the drug. Although no significant difference was noted in other treatment between the two groups, in almost all the RCT reporting evaluation of treatment for COVID, patient are also treated with several other drugs such as antibiotics (9), among some have demonstrated antiviral efficacy (11) , corticosteroid, antiviral , and anti-inflammatory among which some anti IL6 seems promising (12) . This may bias the data such as shown in the Hillaker et al study cited above. This questioned the multicentric nature of the randomized controlled studies which is needed by the high number of patients to be enrolled. This is a bias which is difficult to control because it is directly related to the "standard of care" of each center likely to be different in term of equipment, protocols, surveillance, and staff skills. Consequently, the care of patient might not be comparable in between centers and the outcome biased by the expertise of the team in charged.

In the preliminary announcement on efficacy of remdesivir on an RCT involving 1061 patients , the NIH said that preliminary results indicate that patients who received remdesivir had a 31% faster

time to recovery than those who received placebo (11 days/15 days) but that the survival benefit on 1063 patients was insignificant compared to placebo (p=0.059) concluding that remdesivir has an effect but not a wonder effect. In her commentary, Mahase said : ….in time of epidemics… "expedite publication are fine but hinting that results are going to be positive, only benefits the drug companies (6). Fast-flowing, conflicting information on remdesivir in the past few weeks has left people reeling.

Recently the paper was released with preliminary reports in the NEJM but with different results the survival benefits becoming significant in the overall analyzed population (13). This conclusion is over interpreted. In the table 2, as mentioned, the hazard ratio indicates that only mild form of infection benefit from remdesivir but that there is no difference in severe form of COVID-19 with placebo. It is noteworthy to notice that results are given in intention to treat but that one third of enrolled patient in both arms only (33.8 / 35.7%) received the complete protocol, 180/531 and 185/518 for remdesivir and placebo respectively. Of them 288/ 1049 (27.4%) were discharged because they were cured before the end of treatment and were loss of follow up, the remaining still receiving the treatment or having missing treatment data at time to analyses. 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 number of loss of follow up is unacceptable because it might modified the benefits of randomization, those loss 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 arms versus 120 in the placebo, which is significantly different (p<0001). It is likely that those patients had a baseline score of 4 or 5 as they discharge before the end of treatment explaining in part the better outcome in the remdesivir arms. Some have suggested that <5% loss leads to little bias, while >20% poses serious threats to validity (15). Nevertheless, a per-protocol (PP) analysis as recommend in the CONSORT guidelines should be reported for all planned outcomes to allow readers to interpret the effect of an intervention (16).

Goldman et al. compares 5 days to 10 days treatment for remdesivir with no significant mortality nor improvement of clinical status between the two arms. Altogether, any serious adverse event is reported in 27.7% of treated patient among them 4.7% of acute kidney injury. In 7.3% of patient adverse events lead to stop the treatment (17).

Antinori et al. report the compassionate use of remdesivir in two small cohort of patient those in ICU (18 patients) and those in infectious disease ward (17 patients) (18). While no control was provided for comparison, the global case fatality rate reported at 28 day was 25.7% (9/35) but 20 of 35 (57%) still needed oxygen or invasive ventilation. As discussed above conclusions are speculative when half of the patient are still under care at time of publication. Most paper, because of the understandable need of quickness give data on a small proportion of included patient. Complement information on outcome of the remaining patient are needed as it is likely that those patients had more chance to died rather than survive the case fatality in ICU been link to the length of stay (19).

The last study was conceived, designed and analyzed by Gilead and compared interim data from two ongoing study, one phase 3 randomized open label study reported above (17) and a real world experience retrospective, longitudinal cohort study (20) . Patient receiving remdesivir were compared to those not receiving remdesivir. Recovery ratio at Day 14 was reported to be 232/312 (74.4%) in the remdesivir cohort and 483/818 (59%) in the non-remdesivir cohort. The nature of the study including bias due to uncontrolled associated therapy, retrospective collection of a part of data the lack of disease characteristics notably comorbidity , and the fact that conception of the study was set up by the provider of the drug need a very careful interpretation of data (21).

Still few studies have been reported on evaluation the new drug remdesivir. In many aspects, data from a case report or series without controls mean little to nothing in the context of evaluating efficacy of an experimental drug. On the other hand, RCTs takes time and rarely bring usable information during time of outbreak. Three RCTs have data available, but two share the same aims and give contradictory data. Only one is methodologically adequate with both IPP and PP analysis on a cohort of patient having completed the study demonstrating the absence of difference between drugs and standard of care.

As today no study convincingly supports the use of remdesivir in severe patients. It is interesting however to notice that "a weak recommendation for the use of remdesivir" was suggested in severe case (22) and was followed by the EMA's human medicine committee recommendation to grant a conditional marketing authorization for patient with COVID-19 who require supplemental oxygen. In fact, it is likely that, such as for influenza, the major key for COVID-19 outcome is the early treatment of patient at the time of diagnosis. However serious adverse reactions, some leading to interruption of treatment, and the IV route of remdesivir, would probably limit its use in this indication. We wanted here to aware physician in charge of COVID patient that recommendation in COVID treatment should not only rely on this drug for which convincing data on efficacy are weak, adverse events not negligible, the IV route will limits its indication in mild disease and it will not be affordable for everybody in the world . As a consequence, other option should be evoked, less toxic, more efficient, cheap and affordable for everybody.

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Table 1: Summary of 10 studies reporting treatment with remdesivir. AE*: serious adverse events leading to stop the treatment. ** Improvement at Day 14 (at least 2 pts), (NS) = not significant. $ total patient treated for PP analysis. Remd = remdesivir

References	Study type	Sample size	Mean age (Y)	sex ratio (M/F)	Mean delay onset to treatment (days)	Comorbidity	Inclusion criteria O2 Sat <95%	Inclusion criteria RX pneumonia	Supplementary ATB	Other treatment	Median time to Improvement / recovery (day)	ITT & PP analysis	Death/patient analyzed (%)/ total$ D14-18	Death/patient analyzed (%)/ total D28	AE*
Holshueet et al.	case report	1	35	male	11	no	yes	yes	1/1	NA	improve at day 1 of remdesivir	NA	0/1	0	0
Kujawski et al.	case series	12	53	2	11	6/12	3/3	yes	3/3 AZT (1)	yes	PCR negative at mean 6.5 day	NA	0/12	NA	NA
Lescure et al.	case series	3	31/48/80	males	15/23/26	30%	1/3	3/3	1/3	NA	NA	NA	0/3	NA	30%
Hillaketer et al	case report	1	40	male	13	yes	yes	yes	Azithromycin	HCQ	discharged	NA	0/1	NA	0
Grien et al.	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 et al.	RCT / Remd: placebo	158: 78	66: 64	1.28: 1.88	<=12 D	71%: 71%	yes	yes	142(90%): 73(94%)	102(65%): 53(68%)	21:23 (NS)	ITT &PP	15/153(10%)/153: 7/78(9%)/78	22/150(15%)/150: 10/77(13%)/77	12%: 5%
Biegel et al.	RCT / Remd: 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 et al.	RCT / Remd 5 days: Remd 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 et al.	Compassionate	35	63	2.8	13	51.4%	yes	yes	NA	hydroxychloroquine	NA	NA	NA	9/35(25.7%)	22.8%
Olender S et al.	Congregate of RCT and retrospective study Remd/no Remd	312:818	NA	NA	NA	NA	yes	yes	NA	NA	232/312(74.4%)** 483/818 (59%)	NA	NA	24/312 (7.6%) 102/818 (12.5%)	NA