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

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Conflict of interest

None of the authors have conflict of interest allowing to biased analyses in this article

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.

1 Introduction

2 Since the first described infection with the severe acute respiratory syndrome coronavirus 2 (SARS-
3 CoV2) in December 2019, the coronavirus disease 2019 (COVID-19) has developed into a pandemic,
4 the symptoms of which range from asymptomatic course to pneumonia, acute lung and multi-organ
5 failure and death. In order to develop a meaningful therapy strategy, different medications are used
6 "off label". One of these is remdesivir, a precursor of a nucleotide analogue that inhibits viral RNA
7 polymerases. As for Ebola, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV),
8 remdesivir appears to be effective *in vitro* in SARS-Cov2 (1). Good outcomes have been reported in
9 cases report (2;3). Many studies are ongoing or already published to demonstrate the efficacy of
10 remdesivir on patient with COVID-19, some showing the lack of difference with control arms (4) ,
11 some others reporting efficacy but [discussed](#) (5-7). [Treating patients early in disease has always been](#)
12 [a crucial issue in treating potentially life-threatening infectious diseases](#). The aim of this review
13 presented below was to evaluate the quality of the published and not yet peer-reviewed trials on
14 remdesivir and to highlight pitfalls to [inform](#) readers that a careful analysis of reported data is
15 needed to offer a more accurate interpretation of the results.

16 Literature search

17 We look at all scientific paper available as peer and not yet peer reviewed paper in the major
18 literature from data base Pub Med, Web of Knowledge, scholar google and BioRxiv and MedRxiv. The
19 key words were [remdesivir alone or with COVID]. We recover 91 articles in MedRxiv, 81 in BioRxiv
20 and 112 in Pub Med. When we added COVID to remdesivir, PubMed recover 79 articles. On Web of
21 Knowledge remdesivir recover 25 articles. In Scholar Google remdesivir recovered 1480 articles in
22 2020. Of them we selected 17 papers responding to the aims of this article. [When available we look](#)
23 [at the following endpoints: time to improvement at D14 and 28, death, and adverse events](#).

24 Results and discussion

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

28 The second is a non-yet peer review paper that reports the first 12 case of COVID in the united
29 states. It is a descriptive paper in which 3 of the 7 hospitalized patients received remdesivir for
30 compassionate use for a duration of 4-10 days (9) . All hospitalized patient had serial SARS-CoV2 RT
31 PCR testing. When reanalyzed, the mean delay in normalization of nasal RT PCR was 8.6 days in
32 remdesivir patient versus 6.75 days ($p=0.85$) in untreated patient.

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

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

44 The fifth study is an uncontrolled, prospective, open observational study of patients having received,
45 as compassionate used, a 10-day remdesivir therapy with a target follow-up period of 28 days.
46 Between 25.01.2020 and 07.03.2020, 61 patients were included in the study and received at least
47 one dose of remdesivir, some of which may have been part of previous studies. Of those patients, 8
48 were excluded of the study which, in an intention to treat analysis should have been considered as
49 failure. Finally, data from 53 patients were analyzed of whom one was already published in the study
50 N°3 (Lescure et al). Of them 40 received the complete 10-day remdesivir therapy, 10 received 5 to 9-
51 day therapy and 3 patients received less than 5 days of remdesivir (7) . On average, COVID-19
52 symptoms lasted 12 days before remdesivir therapy was initiated. In the median follow-up period of
53 18 days, 36 of the 53 patients (68%) were able to improve under Remdesivir. An improvement was
54 shown in all patients who were mild receiving no or only low-dose oxygen supplementation (n = 12),
55 or in 5 of the 7 non-invasive ventilated patients. This also raised an ethical comment on the
56 compassionate used of remdesivir in some patients whom were not engaged in short term. Of the 53
57 patients followed, 10 were treated while they were on ambient air (2) or low flow oxygen (8) Of the
58 30 invasively ventilated patients, 17 were extubated and 3 of the 4 patients receiving ECMO were
59 able to terminate ECMO; and it is assumed that all these patients were alive at the time of the last
60 follow-up examination. Finally, a total of 7 of the 53 patients died (13%), on average 15 days after the
61 onset of remdesivir therapy; 6 out of 7 patients were invasively ventilated at the start of the study
62 and one non-invasively ventilated (hazard ratio 2.78). But there is a lot of missing data in this study.
63 At time of publication no data were obtained from the 9 patient whom did not improved during the
64 follow-up among whom was a patient on ECMO since the early beginning suggesting a very poor
65 prognosis. Consequently, if mortality was calculated on available data at the end of follow up (Day
66 28), 7 of 44 (15.9%) patients died. What happened since for the 9 patients still in ICU under
67 mechanical ventilation and or ECMO? Moreover, one patient N°46 was discharge on day 8, but we
68 don't know if he finished remdesivir and what was his outcome. [Scientific veracity and credibility of
69 this paper sponsored and written by Gilead employees is questioned as well as the quality of the
70 review by the New England Journal of Medicine \(NEJM\) , ethical consideration of what is
71 compassionate used and the role of industrial funding in trials bias \(10\).](#)

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

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

91 time to recovery than those who received placebo (11 days/15 days) but that the survival benefit on
92 1063 patients was insignificant compared to placebo ($p=0.059$) concluding that remdesivir has an
93 effect but not a wonder effect. In her commentary, Mahase said :in time of epidemics... “expedite
94 publication are fine but hinting that results are going to be positive, only benefits the drug companies
95 (6). Fast-flowing, conflicting information on remdesivir in the past few weeks has left people reeling.

96 Recently the paper was released with preliminary reports in the NEJM but with different results the
97 survival benefits becoming significant in the overall analyzed population (13). This conclusion is over
98 interpreted. In the table 2, as mentioned, the hazard ratio indicates that only mild form of infection
99 benefit from remdesivir but that there is no difference in severe form of COVID-19 with placebo. It is
100 noteworthy to notice that results are given in intention to treat but that one third of enrolled patient
101 in both arms only (33.8 / 35.7%) received the complete protocol, 180/531 and 185/518 for
102 remdesivir and placebo respectively. Of them 288/ 1049 (27.4%) were discharged because they were
103 cured before the end of treatment and were loss of follow up, the remaining still receiving the
104 treatment or having missing treatment data at time to analyses. While an analysis according to the
105 ITT principle aims to preserve the original randomization and to avoid potential bias due to exclusion
106 of patients, such a number of loss of follow up is unacceptable because it might modified the
107 benefits of randomization, those loss to follow-up often having a different prognosis than those who
108 complete the study (14). In this study 168 patient were discharged before the end of treatment in
109 the remdesivir arms versus 120 in the placebo, which is significantly different ($p<0001$). It is likely
110 that those patients had a baseline score of 4 or 5 as they discharge before the end of treatment
111 explaining in part the better outcome in the remdesivir arms. Some have suggested that <5% loss
112 leads to little bias, while >20% poses serious threats to validity (15). Nevertheless, a per-protocol (PP)
113 analysis as recommend in the CONSORT guidelines should be reported for all planned outcomes to
114 allow readers to interpret the effect of an intervention (16).

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

119 Antinori et al. report the compassionate use of remdesivir in two small cohort of patient those in ICU
120 (18 patients) and those in infectious disease ward (17 patients) (18). While no control was provided
121 for comparison, the global case fatality rate reported at 28 day was 25.7% (9/35) but 20 of 35 (57%)
122 still needed oxygen or invasive ventilation. As discussed above conclusions are speculative when half
123 of the patient are still under care at time of publication. Most paper, because of the understandable
124 need of quickness give data on a small proportion of included patient. Complement information on
125 outcome of the remaining patient are needed as it is likely that those patients had more chance to
126 died rather than survive the case fatality in ICU been link to the length of stay (19).

127 The last study was conceived, designed and analyzed by Gilead and compared interim data from two
128 ongoing study, one phase 3 randomized open label study reported above (17) and a real world
129 experience retrospective, longitudinal cohort study (20) . Patient receiving remdesivir were
130 compared to those not receiving remdesivir. Recovery ratio at Day 14 was reported to be 232/312
131 (74.4%) in the remdesivir cohort and 483/818 (59%) in the non-remdesivir cohort. The nature of the
132 study including bias due to uncontrolled associated therapy, retrospective collection of a part of data
133 the lack of disease characteristics notably comorbidity , and the fact that conception of the study was
134 set up by the provider of the drug need a very careful interpretation of data (21).

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

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

154

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207

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	HCO	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