Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Viewpoint | Published 04 May 2020 | doi:10.4414/smw.2020.20265
Cite this as: Swiss Med Wkly. 2020;150:w20265

Five reasons why data on compassionate use of remdesivir deserved publication (and are worth reading)

Lapadula Giuseppe

"San Gerardo" Hospital, ASST Monza, University of Milano-Bicocca, Italy

With the spread of the SARS-CoV-2 pandemic and the exponential increase in deaths worldwide, the demand for new clinical evidence on the treatment of the infection has become increasingly pressing. Several molecules are candidates for possible treatment of COVID-19 and they are often used in patients despite the absence of hard clinical evidence. Among the various candidates, remdesivir, a drug originally proposed by the American company Gilead as a treatment for Ebola, is one of those considered "most promising", based on evidence of efficacy from in vitro data and animal models [1, 2]. Although pre-clinical data are still scarce and results from clinical trials currently underway are awaited, the drug has been and is still used in many patients for the treatment of forms of COVID-19 of differing severity, as part of compassionate use or expanded access programmes. Despite these premises, the recent publication in a prestigious journal of the first case-series of COVID-19 patients treated with remdesivir under a compassionate use programme has been welcomed with considerable scepticism, if not open hostility [3].

A tour of social networks, which during this pandemic have become one of the most used and fastest source of opinions from the scientific community, reveals opinions against the article ranging from futility (data would be useless without a control arm and should not have been published) to more or less veiled accusations of an attempt to confuse reality to favour the subsequent stages of commercial development of the drug. As I share only in part most of the criticisms (declaration of conflict of interest: I am among the co-authors of the article, although my contribution in drafting the final version of the paper was negligible – or neglected), I tried to briefly list the five reasons why I believe, instead, not only that the editorial choice to publish the paper was right, but also that the article deserves to be read in its entirety (although keeping in mind the obvious and never hidden limitations that a descriptive study, without control arm, has).

1. Something is better than nothing.

Although nobody questioned the legitimacy of using remdesivir in compassionate use programmes, particularly in patients with life-threatening conditions where no other comparable treatment options are available, some seem to believe that the data from these programmes should not be made public or published in medical journals, because they are not easy to interpret owing to the lack of a control arm. This argument is very hard for me to understand. How can we find it acceptable to use a drug in humans on the basis of scarce in vitro evidence and without any single published evidence of its clinical efficacy, and then reject the idea that the first available clinical information should be publicly available? It is out of my scope (and it would be pleonastic) to explain why all clinical data on experimental drugs should be reported, but I just want to mention the fact that the publication of these results adds valuable information (safety, point estimates of mortality and clinical improvement) in a field where such information is lacking. In addition, it makes the data widely available to the scientific community and reusable in future research. Hopefully, it is also the base for demanding the company to share publicly the whole dataset (unfortunately, I had not myself the chance to see the raw data), according to journal policy [4].

2. Scientific papers are not primarily meant for the public, but for the healthcare and research professionals.

Although I share the fear that, under the pressure of a frightened public opinion, mainstream journals, people on social media or even government representatives can overinterpret the real meaning of the data on remdesivir efficacy, this is not a good argument against the publication of "difficult-to-interpret" results. the risk of misinterpretation is around the corner for every article, if we think that academic articles are rarely read in their entirety by health professionals themselves. Nonetheless, explaining research to the public is a step distinct from the decision to publish it. By the way, if the concern is that publication of inconclusive results can influence decisions of clinicians beyond their real value, we should also worry about the fact that "pathogenic models", with eye-catching figures, have been incorporated as such into the decision processes of many colleagues dealing with COVID-19, without waiting for data to confirm them [5].

3. Research is not just a matter of randomisation or comparison with a control arm.

Correspondence:
Dr Giuseppe Lapadula, MD, Azienda Socio Sanitaria Territoriale di Monza, Via Ruggero Leoncavallo 54, IT-Monza, MB 20900, giusppe.lapadula[at]unimib.it

Particularly when dealing with new pathogenic entities, severe conditions or rapidly evolving fields, case series can influence clinical practice as much as properly conducted trials. This is a fact. Case series have contributed to the advancement of medicine in many ways, encompassing the discovery of new conditions and the description of their course [6], the recognition of previously unreported side-effects [7] or even the validation of effective treatments [8]. Is there any randomised controlled trial demonstrating the efficacy of extracorporeal membrane oxygenation (ECMO) for acute respiratory distress syndrome (ARDS) [9]? Nonetheless, as of today, a dozen patients with COVID-19 are being treated or have been treated with ECMO in the intensive care unit of my hospital and I am eager to see the results of these treatments being published. We are all familiar with the metaphor of the "pyramid of scientific evidence", with randomised controlled trials and systematic reviews on its top. But how can a top sustain itself without the basement? Finally, the epidemic of HIV/AIDS in the late eighties and nineties have taught us that waiting for randomised control trials results is not always feasible, advisable or ethically acceptable. This does not mean, in any way, that randomised trials cannot or should not be conducted during a public emergency such as the SARS-CoV-2 pandemic, but it means that we should expect also comparisons between observational data and historical cohorts. How this historical cohort should be constructed and how we should watch over the way data are obtained and used, is, in my opinion, one of the most important topics of the future.

4. Publication of data from a compassionate use programme DOES NOT undermine properly conducted randomised controlled trial data.

Randomised controlled trials of remdesivir are currently underway and there is no evidence from this or any other observational study that could cause them to be halted or modified. Conversely, given the difficulties of enrolment experienced in the Chinese trials that ultimately led to their discontinuation, publication of the results of compassionate use was timely and needful. Nonetheless, the presented data are incomplete, as they report the outcome of a minority of patients enrolled in the compassionate use programme (just about 60 out of a few hundreds, I guess) and reported no data on virological outcome, which, at least theoretically, should have been collected. It is advisable that Gilead will continue to share updates on this cohort of patients.

5. The case series includes patients very different from those enrolled in randomised controlled trials.

Something that has not been underlined enough is that 65% of the patients in the study were mechanically ventilated. To the best of my knowledge, there are no randomised controlled trials on remdesivir including patients in this condition. One of the Chinese trials that were halted was supposed to include patients with "severe COVID-19" (ClinicalTrials.gov identifier: NCT04257656). However, the definition of "severe" was very broad (SaO2/SPO2 <94% on room air or Pa02/Fi02 ratio <300 mg Hg). Everybody who has dealt with COVID-19 knows that this condition is pretty common in those with pneumonia and does not identify those with severe disease (with ARDS or pre-ARDS). Similarly, studies currently underway are either focused on patients without hypoxaemia (NCT04292730), who barely require hospitalisation or medical follow-up, in my experience, or specifically exclude patients requiring mechanical ventilation (NCT04292899). Hence, information regarding the role of remdesivir in patients in the intensive care unit is very unlikely to come from randomised controlled trials in the short term (and maybe never will).

In summary, I do not think that any new evidence should be regarded with suspicion or criticism, in this phase. I understand that the fear of the unknown is so alien to the scientific way of thinking that we may be tempted to turn it into something else we know better, such as the fear of "pure science contamination" or even of scientific misconduct. Nonetheless, if the best evidence we have does not meet our ideal standards and this leads us to ignore the only data we have, maybe it is our standards that should be revised, at least temporarily. We should get used to thinking that we have to do what we know or we think useful and, in the meantime, practice science and medicine with reasonable prudence but without the illusion of omniscience and omnipotence, perched in a ivory tower.

Disclosure statement

No financial support and no other potential conflict of interest relevant to this article was reported.

References

1 Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269–71 . http://dx.doi.org/10.1038/s41422-020-0282-0. PubMed.

2 Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020;11(1):222 . http://dx.doi.org/10.1038/s41467-019-13940-6. PubMed.

3 Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med. 2020; . http://dx.doi.org/10.1056/NEJMoa2007016. PubMed.

4 Drazen JM. Data Sharing and the Journal. N Engl J Med. 2016;374(19): . http://dx.doi.org/10.1056/NEJMe1601087. PubMed.

5 Hasan K, et al. COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal. J Heart Lung Transplant. 2020. [Epub ahead of print].

6 Gottlieb MS. Discovering AIDS. Epidemiology. 1998;9(4):365–7 . http://dx.doi.org/10.1097/00001648-199807000-00001. PubMed.

7 McBride WG. Thalidomide and congenital abnormalities. Lancet. 1961;278(7216):1358. doi: http://dx.doi.org/10.1016/S0140-6736(61)90927-8.

8 Riou B, Barriot P, Rimailho A, Baud FJ. Treatment of severe chloroquine poisoning. N Engl J Med. 1988;318(1):1–6 . http://dx.doi.org/10.1056/NEJM198801073180101. PubMed.

9 Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JF, Jr, Weaver LK, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med. 1994;149(2 Pt 1):295–305 . http://dx.doi.org/10.1164/ajrccm.149.2.8306022. PubMed.