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LETTER TO THE EDITOR

Quality of adverse event reporting in clinical trials of remdesivir in patients with COVID-19

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Remdesivir appears to be promising in the treatment of novel coronavirus disease 2019 (COVID-19). However, the evaluation of the effectiveness of remdesivir should be done in parallel with the analysis of its adverse events since only little is known about its safety. In fact, the reporting of a case of symmetrical drug–related intertriginous and flexural exanthema related to the administration of remdesivir in a patient with COVID-19 by Heck et al. [1] indicates a risk signal on the use of this newly approved agent. The medical community is heavily relying on the clinical trials to inform the possible harms of remdesivir. We undertake the evaluation of the quality of adverse event (AE) reporting in clinical trials [2–5] of remdesivir in patients with COVID-19 based on adherence to the recommendations from the extension of the Consolidated Standards of Reporting Trials (CONSORT) statement for better reporting of harms [6]. However, there are multiple items of interest within a single CONSORT harms recommendation, and thus scoring the multiple items within a single recommendation would be difficult and misleading. Therefore, we employed the validated methods by Hadi et al. [7] to split each single CONSORT harms recommendation into two or three items resulting in a 19-item checklist. Each item of the 19-item checklist was scored individually and weighted with equal importance in line with CONSORT recommendations. Each item carries a score of '1' if it was adequately reported or '0' if it was not adequately reported or not reported at all. The total harm reporting score was calculated by summing up all the individual scores, where the total harm reporting score could range from 0 (worst possible score) to 19 (best possible score). Based on the total harm reporting score, we classified the quality of reporting of the adverse event into 'high' (score of 15-19), moderate (score of 10-14), low (score of 5-9), and very low (score 0-4).

The adequacy of the three clinical trials of remdesivir in COVID-19 fulfilling each of the CONSORT harms recommendations is presented in Table 1. The trial by Wang et al. [2] had a total harm reporting score of 10. Both the trials by Beigel et al. [3] and Goldman et al. [4] had a total harm reporting score of 9. Whereas the trial by Spinner et al. [5] had a total harm reporting score of 8. None of the clinical trials provided information on AEs in the introduction section (CONSORT recommendation 2). While all the clinical trials used a validated scale to measure the severity of AEs, none of the clinical trials defined AEs (CONSORT recommendations 3). Only one of the clinical trials each described how AE-related data were collected (Beigel et al. [3]; CONSORT recommendation 4 (4a)) and described AEs leading to withdrawals (Wang et al. [2]; CONSORT recommendation 6 (6b)). All of the clinical trials provided denominators for AEs (CONSORT recommendation 7 (7a)), but none described any subgroup analyses and exploratory analyses for harms, nor presented a balanced discussion on both safety and efficacy of the drug (CONSORT recommendations 9 and 10).

Based on our evaluation of the total harm reporting score, only one of the clinical trials (Wang et al. [2]) of remdesivir in COVID-19 had moderate quality of adverse event (AE) reporting, while the remaining clinical trials of remdesivir in COVID-19 [3–5] had low quality of adverse event (AE) reporting. In addition to the potential for symmetrical drug–related intertriginous and flexural exanthema as reported in the case report by Heck et al. [1], the potential of remdesivir to cause acute hepatotoxicity which was not detected in the clinical trials was also recently discovered in a case report [8]. We urge that future

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Table 1 Adequacy of the four clinical trials of remdesivir in COVID-19 fulfilling each of the CONSORT harms recommendations

Recommendations of 2004 CONSORT harms extension	Quality of reporting criteria	Wang et al [2]	Beigel et al [3]	Goldman et al [4]	Spinner et al [5]
1. If the study collected data on harms and benefits, the title of abstract should state so	AEs mentioned in the title or the abstract	1	1	1	1
2. If the trial addresses both harms and benefits, the introduction should state so	Information on AEs mentioned in introduction	0	0	0	0
3. List addressed adverse events with definitions for each (with attention, when relevant, to grading, expected vs unexpected events, reference to standardised and validated definitions, and description of new definitions)	3a. If article mentioned use of validated instrument to report AE severity	1	1	1	1
	3b. If article mentioned definition of AE	0	0	0	0
4. Clarify how harms-related information was collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms-related monitoring and stopping rules, if pertinent)	4a. Description of how harms data were collected (e.g., diaries, phone interviews, face-to-face interviews)	0	1	0	0
	4b. Description of when AE data were collected	0	1	1	0
	4c. Whether or not AEs were attributed to trial drug (e.g. how AEs were attributed to drugs)	0	0	0	0
5. Describe plans for presenting and analysing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures and any statistical analyses)	5. Description of methods for presenting and/or analysing AEs	1	1	1	1
6. Describe for each arm the participant withdrawals that are due to harms and the experience with the allocated treatment	6a. If the article reported number of withdrawals caused by AEs in each arm	1	0	1	1
	6b. Description of AEs leading to withdrawals	1	0	0	0
	6c. Description of AEs leading to death	1	1	0	1
7. Provide the denominators for analyses on harms	7a. If the article provided denominators for AEs	1	1	1	1
	7b. If the article provided definitions used for analysis set (ITT, per protocol, safety data available, unclear)	1	0	1	0
8. Present the absolute risk of each adverse event (specifying type, grade, and seriousness per arm), and present appropriate metrics for recurrent events, continuous variables, and scale variables, whenever pertinent	8a. Results presented separately for each arm	1	1	1	1
	8b. Separate reporting of severe AEs (grade > 2 or serious AEs)	1	1	1	1
	8c. Provided both number of AEs and number of patients with AEs	0	0	0	0
9. Describe any subgroup analyses and exploratory analyses for harms	-	0	0	0	0
10. Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalisability, and other sources of information on harms	10a. If the discussion was balanced with regard to efficacy and AEs	0	0	0	0
	10b. Limitations of the study specifically in relation to AEs discussed	0	0	0	0
		10	9	9	8

and ongoing clinical trials on remdesivir in COVID-19 should follow the ten CONSORT harm recommendations in terms of reporting adverse events for a better understanding of the safety of remdesivir in its use in COVID-19 patients. This is of utmost importance such that the potential clinical benefits of remdesivir are not negated by the development of adverse events in susceptible patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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