Should remdesivir be used for COVID-19?

This clinical evidence summary outlines existing evidence on the use of remdesivir as a potential treatment for patients with COVID-19. The information may be revised as new evidence emerges. The summary is not exhaustive of the subject matter and does not replace clinical judgement. The responsibility for making decisions appropriate to the circumstances of the individual patient remains at all times with the healthcare professional.

Background

Remdesivir is a novel nucleotide analog prodrug (broad spectrum antiviral). It was developed as a treatment for Ebola and Marburg virus infections, although when trialed in patients with Ebola virus it failed to show a survival benefit.[1] Remdesivir has subsequently shown reasonable antiviral activity against more distantly related viruses including MERS-coronavirus; therefore activity against other coronaviruses including SARS-CoV-2 infection is predicted.[2-4] Review articles identified remdesivir as one of several possible treatments for COVID-19.[5-7] Lu (2020) stated that remdesivir "may be the best potential drug for the treatment of [COVID-19]" given the drug had completed the clinical program for Ebola virus infection with relatively complete safety and pharmacokinetics data in humans.[7]

The Health Sciences Authority (HSA) in Singapore has issued a conditional registration for remdesivir to treat adults with COVID-19 who have an oxygen saturation ≤ 94% or who require supplemental oxygen, invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Prescription is restricted to infectious disease physicians and the manufacturer is required to submit further data in the future for HSA analysis.[8] The US Food and Drug Administration (FDA) has issued emergency use authorisation for remdesivir to treat severe COVID-19 in hospitalised adults and children on the basis of initial data from two trials: NCT04280705 and NCT04292899.[9] The European Medicines Agency (EMA) lists remdesivir as an investigational product for COVID-19[10] and has recommended conditions for compassionate use in patients with COVID-19.[11,12] Remdesivir has received exceptional approval in Japan, while other jurisdictions, such as Taiwan and South Korea have approved it for emergency use for patients with SARS-CoV-2 infection.[13, 14, 15]

Clinical evidence

Clinical evidence for remdesivir to treat COVID-19 is limited, with initial results requiring confirmation and publication in peer reviewed journals:

- Preliminary results from a randomised controlled trial (RCT) of 1,063 patients hospitalised with COVID-19 (NCT04280705 or ACTT-1) revealed that the remdesivir group had a 31% faster time to recovery than the placebo group with a median time to recovery of 11 days (95% confidence interval [CI] 9 to 12) versus 15 days (95%CI 13 to 19) respectively (p<0.001). Nearly 89% of the patients had severe disease at enrolment. Remdesivir was administered intravenously as a 200-mg loading dose on day 1, followed by a 100-mg daily maintenance dose on days 2 to 10 or until hospital discharge or death. Kaplan-Meier estimates for mortality at 14 days were not significantly different for remdesivir compared with placebo (7.1% vs 11.9%; hazard ratio [HR]: 0.70; 95% CI 0.47 to 1.04). Mortality rates at 28 days are pending as a large proportion of patients are yet to complete the trial. Changes in viral load were not measured. Serious adverse events (AEs) were reported in 21.1% of the remdesivir group and 27.0% of the placebo group. A subgroup analysis suggested that the recovery rate in Asian patients was lower compared with non-Asian patients; however, results are currently inconclusive as they are likely to be confounded by the small number of Asians in the trial and differences in baseline disease severity and clinical practices at the various clinical trial sites. The authors highlighted the need to start antiviral treatment before a patient requires mechanical ventilation and advised that an antiviral agent alone is unlikely to be sufficient given the high mortality rate in the remdesivir group.[16]
- An RCT (NCT04257656) in 237 adults with severe COVID-19 in China found no difference in the time to clinical improvement (on a six-point scale from death to hospital discharge) between

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remdesivir and placebo, and remdesivir did not result in a significant reduction in SARS-CoV-2 RNA load; however, the study was terminated before reaching the prespecified sample size due to difficulty in recruitment. Adverse events were comparable between groups leading the authors to conclude that remdesivir was adequately tolerated.[17]

- A randomised, open label study of a five-day versus ten-day remdesivir regimen in 397 patients with severe COVID-19 (NCT04292899) found that both regimens achieved similar clinical improvement on the ordinal scale at 14 days (64% of patients in the five-day group and 54% in the ten-day group improved two points in status). No new safety signals were identified although the proportions of patients experiencing serious AEs and discontinuing treatment due to AEs were numerically higher in the ten-day group.[18]
- Published non-comparative studies and case reports have generally described improvement in clinical status in patients after initiation of remdesivir. Efficacy and mortality rates vary although the available data suggest that remdesivir may be more beneficial in patients with less severe disease, who do not require invasive ventilation or treatment in an intensive care unit. Serious AEs such as hypertransaminasemia, acute kidney injury, and multiple organ dysfunction syndrome, among others, were frequently observed.[19-23]

Table 1: Registered international RCTs for remdesivir in patients with COVID-19

Study identifier	Study Design	Intervention	Comparator	Date of primary completion
NCT04257656 [24, 17] [Terminated]	DB, SC*, phIII, RCT	Remdesivir	Placebo	May 2020
NCT04252664 [25] [Suspended]	DB, SC*, phIII, RCT	Remdesivir	Placebo	April 2020
NCT04292899 [26, 18]	MC†, OL, phIII, RCT	Remdesivir (5 day regimen)	Remdesivir (10 day regimen)	Part A completed
NCT04292730 [27, 18]	MC†, OL, phIII, RCT	Remdesivir (5 day regimen)	Remdesivir (10 day regimen)	Part A May 2020
NCT04280705 [28, 16]	DB, MC†, phII, RCT	Remdesivir	Placebo	April 2020
NCT04315948 [29]	MC, OL, phIII, RCT	Remdesivir, lopinavir/ritonavir, lopinavir/ritonavir + interferon β-1A	Standard of care	March 2023
NCT04321616 [30]	MC, OL, phII/III, RCT	Remdesivir, hydroxychloroquine	Standard of care	August 2020
NCT04330690 [31]	MC[C], OL, phII, RCT	Remdesivir, lopinavir/ritonavir, hydroxychloroquine	Standard supportive care	March 2022
NCT04349410 [32]	phII/III, randomised trial	Remdesivir, hydroxychloroquine, azithromycin, doxycycline, primaquine, clindamycin, methylprednisolone, tocilizumab, interferon, losartan, convalescent serum	-	October 2020
NCT04410354 [33]	DB, MC,** phII, RCT	Merimepodib + remdesivir	Remdesivir + placebo	July 2020
NCT04409262 [34]	DB, MC,** phIII, RCT	Remdesivir + tocilizumab	Remdesivir + placebo	July 2020
NCT04401579 [35]	DB, MC,† phIII, RCT	Baricitinib + remdesivir	Remdesivir + placebo	August 2023
EudraCT 2020-000982-18 [36]	OL, MC,[N] phIII, RCT	Remdesivir, hydroxychloroquine	Standard of care	Not stated
EudraCT 2020-001784-88 [37]	OL, MC,[F] phIII, RCT	Remdesivir, hydroxychloroquine	Standard of care	Not stated
EudraCT 2020-001366-11 [38]	OL, MC,[S, Ir, I, P] phIV, RCT	Remdesivir, chloroquine, hydroxychloroquine, lopinavir/ritonavir, interferon β-1A	Standard of care	Not stated
EudraCT 2020-000936-23 [39]	OL, MC, [‡, Au] phIII, RCT	Lopinavir/ritonavir, interferon β-1A, remdesivir, hydroxychloroquine	-	Not stated

Abbreviations: DB, double blind; MC, multicenter; OL, open label, phII, phase II; phIII, phase III; RCT, randomised controlled trial; SC, single centre. * China; ** USA † Study has sites in Singapore; ‡ France; [C] Canada; [I] Italy; [Cr] Croatia; [N] Norway; [F] Finland; [S] Spain; [Ir] Ireland; [P] Portugal; [Au] Austria

The World Health Organization (WHO) has begun conducting a large, global trial (SOLIDARITY)[40] on the most promising therapies identified to date to treat COVID-19, including remdesivir. Over 100 countries are currently included in the trial. The date of primary completion is March 2021, with findings expected to be reported by December 2021.

Recommendations from professional bodies

WHO recommends remdesivir (among other drugs) should not be administered as treatment or prophylaxis for COVID-19 outside of clinical trials.[41]

Locally, the Singapore National Centre for Infectious Diseases (NCID) has issued interim treatment guidelines for COVID-19, which recommend remdesivir be used for hospitalised patients with severe COVID-19 (oxygen saturation less than 94% on room air, requiring supplemental oxygen, mechanical ventilation or ECMO). Approval by an Infectious Diseases (ID) physician and request for use through NCID via the Infectious Diseases consultant-on-call is required. NCID recommends an initial treatment duration of 5 days which might be extended to 10 days in patients with more severe illness with ID approval. The NCID notes that timing of antiviral initiation may be important as administration after the peak viral titer is unlikely to reduce lung damage despite reducing viral loads.[42]

COVID-19 treatment guidelines from the National Institutes of Health (NIH) in the USA recommend remdesivir for the treatment of COVID-19 in hospitalised patients with severe disease requiring supplemental oxygen. Remdesivir is not recommended for the treatment of mild or moderate COVID-19 outside of a clinical trial.[43]

In guidelines for COVID-19 clinical management, the Italian National Institute for Infectious Diseases recommends remdesivir be administered to patients in critical condition and those with respiratory symptoms who are clinically unstable.[44]

The seventh edition of the China National Health Commission (NHC) Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment does not specifically refer to remdesivir.[45]

Conclusion

Preliminary RCT results showing a swifter recovery for patients with severe COVID-19 who received remdesivir compared with placebo must be weighed against the first published RCT in China that found no significant difference in time to clinical improvement or reduction in viral load. A limitation was the reduced power of the trial in China to detect a significant result as it was halted prematurely. Further mature clinical trial results are needed to build the evidence base for remdesivir. This will enable several outstanding issues to be addressed such as the impact of remdesivir on viral load, the patients who are most likely to benefit from treatment, and the efficacy and safety of remdesivir relative to other candidate therapeutics for COVID-19.

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