Should remdesivir be used for COVID-19?

This write-up summarises a rapid evidence review of remdesivir as a potential treatment for patients with COVID-19. The information may be revised as new evidence emerges.

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 US Food and Drug Administration (FDA) has recently authorised remdesivir for emergency use to treat suspected or laboratory confirmed COVID-19 in adults and children hospitalised with severe disease.[8] This emergency use authorisation is different to an FDA approval and was made on the basis of initial data from two trials: NCT04280705 and NCT04292899.[8] The European Medicines Agency (EMA) lists remdesivir as an investigational product for COVID-19[9] and has recommended conditions for compassionate use in patients with COVID-19 requiring invasive ventilation who are not eligible for inclusion in clinical trials.[10, 11] Separately, remdesivir is available under an expanded access protocol for treatment of SARS-CoV-2 infection.[12, 13] A news article reports that remdesivir is likely to be approved in Japan in May for the treatment of patients with COVID-19.[14]

Clinical evidence

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

- An interim analysis of a double blind randomised controlled trial (RCT) of 1,063 patients hospitalised with COVID-19 revealed that the remdesivir group had a 31% faster time to recovery than the placebo group (median time to recovery of 11 days versus 15 days respectively; p<0.001). A non-significant trend towards survival benefit was observed for remdesivir with a mortality rate of 8.0% compared with 11.6% for placebo (p=0.059). These are preliminary results from NCT04280705 and not yet published in a peer reviewed journal.[15]
- A double blind 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 remdesivir and placebo; however, the study was terminated before reaching the prespecified sample size due to difficulty in recruitment as the outbreak was brought under control in China. Adverse events (AEs) were comparable between groups leading the authors to conclude that remdesivir was adequately tolerated.[16]
- A press release from the manufacturer of remdesivir reported initial results from an open label study of a five-day regimen versus a ten-day regimen in 397 patients with severe COVID-19 (NCT04292899). According to the statement, both treatment courses achieved similar clinical improvement with an odds ratio of 0.75 (95% confidence interval: 0.51 – 1.12) and no new safety signals were identified. The study has been expanded to recruit a total of 6,000 patients and a second similar trial will compare the two regimens in patients with moderate COVID-19.[17]
- Clinical improvement after use of remdesivir was observed in 36 of 53 (68%) patients hospitalised with COVID-19 in an open label and uncontrolled study with short duration.[18] At baseline, 30 patients (57%) were receiving mechanical ventilation and 17 (57%) were extubated over the course of the study. Seven patients (13%) died with a higher mortality rate in those

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receiving invasive ventilation. Serious AEs were reported in 23% of the cohort. Eight patients were excluded from analysis due to missing data.

- Two case reports describe patients hospitalised with COVID-19 who experience improvement in clinical status after the initiation of remdesivir.[19, 20]

A number of other ongoing trials are listed on the US National Library of Medicine's register (Table 1).

Table 1: Ongoing or planned studies for remdesivir in patients with COVID-19

Study identifier	Study Design	Intervention	Comparator	Date of primary completion
NCT04257656 [21, 16] [Terminated]	DB, SC*, phIII, RCT	Remdesivir	Placebo	May 2020
NCT04252664 [22] [Suspended]	DB, SC*, phIII, RCT	Remdesivir	Placebo	April 2020
NCT04292899 [23, 17]	MC†, OL, phIII, RCT	Remdesivir (5 day regimen), remdesivir (10 day regimen)	Standard of care	Part A completed Part B extension completion not stated
NCT04292730 [24, 17]	MC†, OL, phIII, RCT	Remdesivir (5 day regimen), remdesivir (10 day regimen)	Standard of care	Part A May 2020 Part B extension completion not stated
NCT04280705 [25, 15]	DB, MC†, phII, RCT	Remdesivir	Placebo	April 2020
NCT04315948 [26]	MC, OL, phIII, RCT	Remdesivir, lopinavir/ritonavir, lopinavir/ritonavir + interferon β-1A	Standard of care	March 2023
NCT04314817 [27]	SC‡, observational	Any drug used	-	January 2023
NCT04321616 [28]	MC, OL, phII/III, RCT	Remdesivir, hydroxychloroquine	Standard of care	August 2020
NCT04365725 [29]	MC‡, observational, retrospective	Remdesivir	-	May 2020
NCT04330690 [30]	MC[C], OL, phII, RCT	Remdesivir, lopinavir/ritonavir, hydroxychloroquine	Standard supportive care	March 2022
NCT04365764 [31]	MC, case control observational	Remdesivir, hydroxychloroquine, azithromycin, baricitinib, tocilizumab, sarilumab, lopinavir/ritonavir, oseltamivir and others	-	May 2020
NCT04359901 [32]	SC**, OL, phII, RCT	Sarilumab	Standard of care including remdesivir	April 2022
NCT04356417 [33]	MC‡, observational cohort	Remdesivir, hydroxychloroquine, lopinavir/ritonavir ± interferon β-1A, methylprednisolone and others including antihypertensives	-	June 2020
NCT04349410 [34]	phII/III, randomised trial	Remdesivir, hydroxychloroquine, azithromycin, doxycycline, primaquine, clindamycin, methylprednisolone, tocilizumab, interferon, losartan, convalescent serum	-	October 2020

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

In addition, the World Health Organization (WHO) has begun conducting a large, global trial (SOLIDARITY)[35] on the four most promising therapies identified to date to treat COVID-19, including remdesivir. Over 70 countries are currently included in the trial, with more countries likely to be included over time. The date of primary completion is March 2021, with findings reported by December 2021.

Recommendations from professional bodies

WHO has yet to recommend any specific antiviral medicine to prevent or treat COVID-19.[36]

Locally, the Singapore National Centre for Infectious Diseases (NCID) notes there are no proven or licensed therapies for any coronavirus infection. However, in interim treatment guidelines for COVID-19, NCID suggests using remdesivir under a trial setting if possible and 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.[37]

COVID-19 treatment guidelines from the National Institutes of Health (NIH) including the Centers for Disease Control and Prevention (CDC) in the USA identify remdesivir as an investigational therapeutic. Although, the CDC states that "there are insufficient clinical data to recommend either for or against using remdesivir".[38]

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.[39]

The seventh edition of the China National Health Commission (NHC) clinical guidance for COVID-19 diagnosis and treatment does not specifically refer to remdesivir.[40]

Conclusion

Interim RCT results showing a swifter recovery for patients who receive remdesivir compared with placebo must be weighed against the first published RCT in China that found no significant difference in time to clinical improvement. A limitation of the Chinese trial was its reduced power to detect a significant result as it was halted prematurely. Formal peer reviewed publications of the latest trial results may provide further clarity of the role of remdesivir in the clinical management of patients with COVID-19.

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