Received: 18 May 2020 | Revised: 24 October 2020 | Accepted: 16 November 2020

DOI: 10.1111/bcp.14677

REVIEW ARTICLE

Clinical studies assessing the efficacy, effectiveness and safety of remdesivir in management of COVID-19: A scoping review

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Aims: Remdesivir is 1 of the repurposed drugs under investigation to treat patients with COVID-19. Clinicians and decision-makers need a summary of the most recent evidence. This scoping review maps the evidence on the efficacy, effectiveness and safety of remdesivir for patients with COVID-19, up to 14 September 2020.

Methods: Our scoping review searched Pubmed, Embase (Ovid), Scopus and 17 primary trial registries for empirical publications or active registered clinical trials for data on the efficacy, effectiveness, or safety of remdesivir for COVID-19 or SARS-CoV-2. We conducted a narrative synthesis of the included publications.

Results: Seventeen empirical studies and 23 clinical trial registrations (n = 40) accumulated 46 508 participants. We found 4 published randomized–controlled trials accumulating 2293 patients. Two trials reported shorter median recovery time and better clinical status among patients who received remdesivir compared with the control groups. Observational studies report an association between remdesivir treatment and decreased mortality, as well as increased survival. The most common adverse reaction was hepatic impairment, although the trials reported a similar proportion of adverse events in the intervention and control groups.

Conclusion: Remdesivir might shorten the time to clinical improvement among hospitalized adults with severe COVID-19. Trial data report a similar proportion of adverse events in treated and control groups. The results of the 23 registered active trials, including more than 30 000 participants, will shed light on the efficacy and safety of the antiviral. The findings of the remaining clinical trials expected to report results in 2020 will allow a quantitative synthesis of available evidence.

KEYWORDS

COVID 19, GS 5734, remdesivir, scoping review, severe acute respiratory syndrome coronavirus 2

1 | INTRODUCTION

On 12 March 2020, the World Health Organization (WHO) classified the emergent disease caused by the virus SARS-CoV-2 (COVID-19) as a pandemic.[1] Worldwide, the number of critically ill patients is growing exponentially but no effective drugs or vaccines are yet available to treat or prevent COVID-19.[2,3] Oxygen supplementation and supportive care are not always effective.[4] There is an urgent need to discover drugs that could reduce mortality and expedite recovery, alleviating the burden on severely strained health systems. Exploring whether existing drugs are effective and safe to treat COVID-19 is a time-efficient approach to drug discovery.[5,6]

Remdesivir (formerly GS-5734) is a monophosphoramidate prodrug with broad-spectrum antiviral activity against paramyxoviruses (e.g. Nipah virus), filoviruses (e.g. Ebola), and coronaviruses, including human coronaviruses (hCoV-OC43 and hCoV-229E),

SARS-CoV and MERS-CoV.[7,8] Remdesivir is intracellularly metabolized into an adenosine analogue that combines with nascent viral RNA chains producing pre-mature termination of RNA transcription.[9]

Several clinical studies report compassionate use of remdesivir to treat patients with COVID-19.[10–12] Beigel *et al.*[13] described the preliminary results of the first stage of the Adaptative COVID-19 Treatment Trial (ACTT-1), which compared a 10-day course of remdesivir against placebo in 1063 adults with evidence of SARS-CoV-2 pneumonia. The authors reported a median recovery time of 11 days in the treated group and of 15 days in the control group (rate ratio for recovery 1.32, 95% confidence interval [CI] 1.12 to 1.55), and similar proportions of adverse events in the intervention and control groups.

On 1 May 2020, the Food and Drug Administration issued an Emergency Use Authorization for intravenous remdesivir in treatment of adults and children with confirmed or suspected COVID-19. The authorization allowed patients requiring mechanical ventilation, supplemental oxygen, or extracorporeal membrane oxygenation, or with oxygen saturation ≤94% on room air to receive the drug.[14] On 7 May, the government of Japan approved remdesivir for treatment of patients with COVID-19.[15] On 25 June, the European Medicines Agency granted a conditional market authorization for the drug to treat patients from age 12 years with COVID-19 pneumonia who require supplemental oxygen.[16]

Real-time dissemination of reliable information is key to guiding front-line clinicians managing patients, epidemiologists, epidemic modellers and decision-makers working to control the COVID-19 pandemic and to address public panic.[17] Two systematic reviews have explored the efficacy, effectiveness and safety of remdesivir for patients with COVID-19.[18,19] This, however, is the first scoping review assessing the efficacy, effectiveness and safety of remdesivir in management of COVID-19. Compared with systematic reviews, scoping reviews typically address broader research questions, seeking to examine the extent, range and nature of the research activity on a research area.[2] This approach allows identification of research gaps in the existing literature, which is critical to inform ongoing research in a rapidly evolving landscape such as COVID-19 research.[3] Our scoping review aimed to map the extent and nature of the evidence on the efficacy, effectiveness, and safety of remdesivir for patients with COVID-19, up to 14 September 2020.

2 | METHODS

Our scoping review follows the methods proposed by Arksey and O'Malley[20] and Levac[21]: (i) define the research question; (ii) search for and identify the relevant studies; (iii) chart the data; and (iv) summarize and report the results. Our review answered the question: what is the extent and nature of the evidence on the efficacy, effectiveness, and safety of remdesivir for treating patients with COVID-19? The protocol for our study is available in Supporting information 1.

2.1 | Inclusion and exclusion criteria

Our inclusion criteria were as follows: (i) empirical publications (case series, observational and experimental studies) or active randomized controlled trial registrations; (ii) the objective of the study was to investigate efficacy, effectiveness or safety of remdesivir; (iii) the disease was COVID-19; and (iv) the language was English, Spanish, French, Italian or Portuguese. We excluded publications that did not fulfil all inclusion criteria, such as single case reports.

2.2 | Search strategy

We searched in Pubmed, Embase (Ovid), and Scopus, using Boolean operators, truncators, and search terms according to each database. Since the first reports of COVID-19 appeared by the end of 2019,[22] we restricted our search to 2019 and 2020. An experienced health sciences librarian at McGill University reviewed, adjusted, and approved the search strategy. We ran the original search on 4 September 2020, and, through daily email alerts evaluated by 2 reviewers (J.P. and C.L.), we last updated it on 14 September 2020. Appendix 1 shows our search strategy.

We searched for clinical trials registered in 17 primary registries from the WHO Registry Network[23]: Clinical Trials from US National Library of Medicine; Australian New Zealand Clinical Trials Registry (ANZCTR); Brazilian Clinical Trials Registry (ReBec); Chinese Clinical Trial Registry (ChiCTR); Clinical Research Information Service (CRiS, Republic of Korea); Cuban Public Registry of Clinical Trials (RPCEC); EU Clinical Trials Register (EU-CTR); German Clinical Trials Register (DRKS); Iranian Registry of Clinical Trials (IRCT); ISRCTN; Japan Primary Registries Network (JPRN); Lebanese Clinical Trials Registry (LBCTR); Thai Clinical Trials Registry (TCTR); The Netherlands National Trial Register (NTR); Pan African Clinical Trial Registry (PACTR); Peruvian Clinical Trial Registry (REPEC); and Sri Lanka Clinical Trials Registry (SLCTR). These trial registries meet criteria for quality and validity, content, unique identification, accessibility, technical capacity and administration, as well as the criteria of the International Committee of Medical Journal Editors.[24]

2.3 | Study selection and data extraction

Two independent reviewers (C.L. and J.P.) performed the initial title and abstract screening using the open-source systematic review application Rayyan.[25] They resolved discrepancies by discussion and consensus. They retrieved the full-text format of the included documents, removed duplicates using Endnote X8.2, and performed the final selection of studies using an eligibility format based on the inclusion criteria.

Charting the included studies is a "technique for synthesizing and interpreting qualitative data by sifting, categorizing, and sorting material according to key issues and themes."[20] Through regular meetings, we developed and adjusted the data charting form based on

the variables that would answer our research question. We piloted the form with 5% of the studies and registries. The data extraction form is available in Supporting information 2.

We extracted the following data from eligible studies: authors; type of study (case series, observational, experimental); aim; sample size; inclusion criteria; remdesivir scheme; primary outcome; main findings; and reported adverse events. In the case of the clinical trial registries, we extracted the trial identifier, recruitment status, trial design, country, sample size, intervention and control details, primary outcome, date registered or start date, and anticipated end date.

2.4 | Synthesis and presentation of results

We generated a narrative synthesis of the main results and created tables to display an overview of the included studies. In this article, we adhered to the PRISMA extension for reporting scoping reviews (PRISMA-ScR)[26] (Appendix 2).

2.5 | Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[27]

3 | RESULTS

We included 17 empirical studies. which accumulated 8696 patients and 23 clinical trial registrations, which will accumulate at least 37 812 participants. (Figure 1 and Appendix 3). Among the empirical studies, we found 2 completed randomized–controlled trials (RCTs),[28,29] a preliminary report of an RCT,[13] an RCT that was prematurely stopped,[30] 2 analyses based on RCT data,[31,32] 6 case series,[33–38] a pharmacovigilance analysis,[39] a cohort study[40] and cohort description,[41] a retrospective comparison study,[42] and a prospective open-label study.[4]

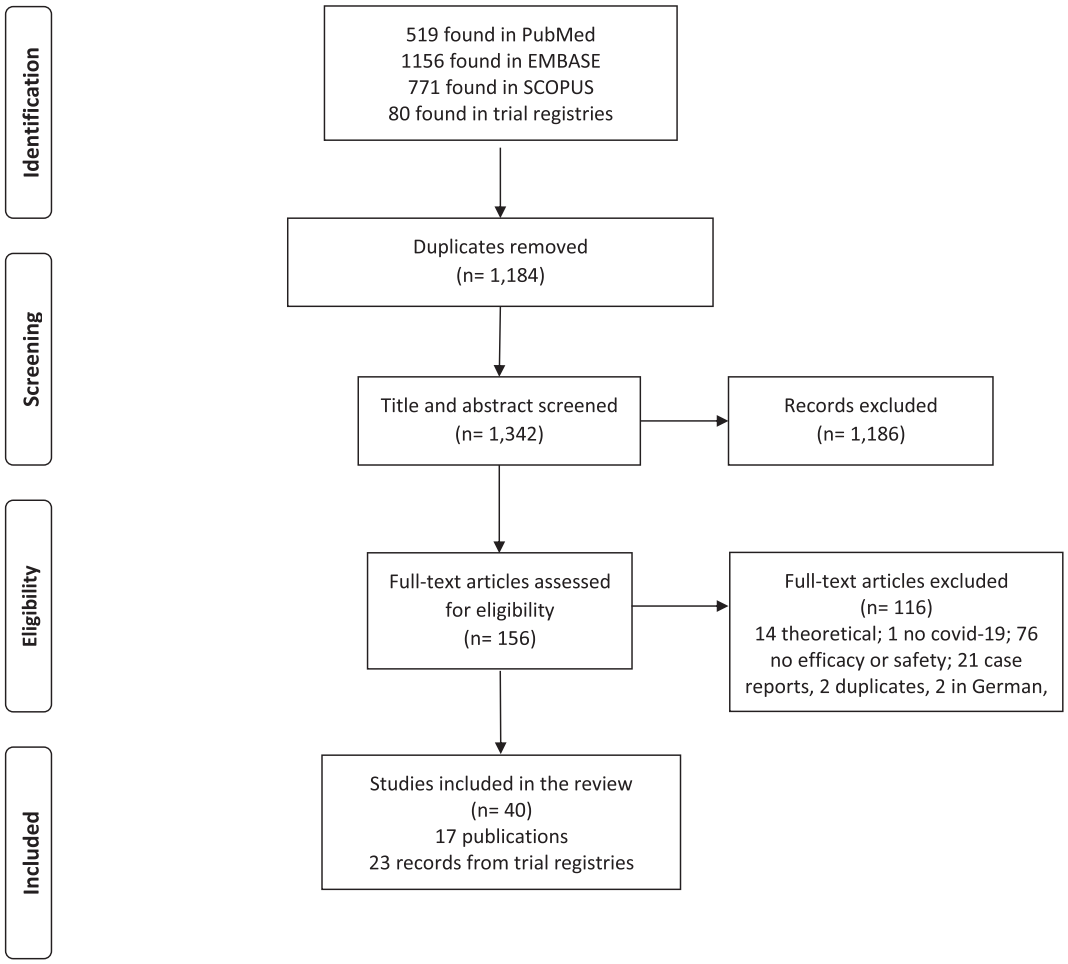

FIGURE 1 Flow diagram of the scoping review

TABLE 1 Characteristics of the trials included in our study

Authors	Type of study	Patients randomized	Inclusion criteria	Intervention	Control	Randomization	Primary outcome	Main findings	Reported adverse events
Olender *et al.*[31]	Comparison of interim data from a phase 3, randomized, open-label study, with a retrospective cohort study	1130	Hospitalized patients with SARS-CoV-2 confirmed infection, SaO2 < 95% on room air or requiring supplemental oxygen, with pulmonary infiltrates	200-mg loading dose on d 1, followed by 100 mg daily for up to 4 or 9 additional d (plus standard care)	Standard-of-care treatment according to local clinical practice	NA	Proportion of patients with recovery on d 14 based on a 7-point clinical status ordinal scale	Compared with 59.0% in the control group, 74.4% of patients in the remdesivir group had recovered by d 14 (aOR 2.03: 95% CI 1.34–3.08, $P < .001$). Compared with 12.5% in the control group, 7.6% of patients in the remdesivir group died by d 14 (aOR 0.38, 95% CI: 0.22–0.68, $P = .001$).	Not reported
Beigel *et al.*[13]	Double-blind, randomized, placebo-controlled trial	1063	Adults with SARS-CoV-2 infection, SaO2 < 95% on room air or requiring supplemental oxygen, with pulmonary infiltrates	200-mg loading dose on d 1, followed by 100 mg daily for up to 9 additional d	Matching placebo	1:1, stratified by study site and disease severity at enrolment	Time to recovery (discharge from the hospital or hospitalization for infection control)	Median recovery time was 11 d (95% CI 9–12) for patients in the remdesivir group, compared to 15 d (95% CI, 13–19) for patients in the placebo group (RRR 1.32; 95% CI, 1.12–1.55; $P < .001$).	114/541 (21.1%) patients in the remdesivir group and 141/522 (27.0%) in the control group had serious adverse events.
Spinner *et al.*[29]	Three-arm randomized, open-label trial	596	Hospitalized patients with RT-PCR confirmed SARS-CoV-2 infection and moderate	Intravenous remdesivir 200 mg on d 1 followed by 100 mg/d. Arm 1: 10-d course of remdesivir;	Standard care	1:1:1, not stratified	Clinical status on d 11 (7-point ordinal scale)	The odds of a better clinical status distribution was higher among patients in the 5-d remdesivir	The most frequent adverse events were nausea (10 *vs* 3%), hypokalaemia (6 *vs* 2%), and headache (5 *vs*

(Continues)

TABLE 1 (Continued)

Authors	Type of study	Patients randomized	Inclusion criteria	Intervention	Control	Randomization	Primary outcome	Main findings	Reported adverse events
			pneumonia (room air SaO2 > 94% and pulmonary infiltrates)	Arm 2: 5-d course of remdesivir				group compared to those receiving standard care (OR 1.65; 95% CI, 1.09–2.48; P = .02). The clinical status distribution between the 10-d remdesivir and standard care groups was not significantly different on d 11 (P =0.18).	3%) among patients in the remdesivir compared to the standard care group.
Goldman *et al.*[28]	Randomized, open-label, phase 3 trial	397	Hospitalized patients with confirmed SARS-CoV-2 infection, at least 12 years old, SaO2 < 95% on ambient air, and pneumonia	200-mg loading dose on d 1, followed by 100 mg daily for 4 additional d	200 mg loading dose on d 1, followed by 100 mg daily for 9 additional d	1:1, not stratified	Clinical status on d 14 (7-point ordinal scale)	At d 14, the distribution in clinical status among patients in the 10-d group was similar to that among patients in the 5-d group (p = .14).	Common adverse events were similar in both groups (70% in 5-d and 74% in 10-d); included nausea (9%), worsening respiratory failure (8%), elevated alanine aminotransferase level (7%), and constipation (7%).
Wang *et al.*[30]	Randomized, double-blind, placebo-controlled, multicentre trial	237	Hospitalized patients with confirmed SARS-CoV-2 infection, >17 years old, interval from symptom onset to enrolment <13 d, room air SaO2 < 95% or a ratio of arterial oxygen to	200-mg loading dose on d 1, followed by 100 mg daily for 9 additional d	Placebo infusion	2:1, stratified according to the level of respiratory support	Time to clinical improvement up to d 28 (6-point ordinal scale)	There was no statistically significant difference in time to clinical improvement between arms (HR 1.23, 95% CI 0.87–1.75). Among treated patients with symptom duration <11 d,	There were 102/155 (66%) adverse events reported in remdesivir patients and 50/78 (64%) reported in placebo patients.

(Continues)

TABLE 1 (Continued)

Authors	Type of study	Patients randomized	Inclusion criteria	Intervention	Control	Randomization	Primary outcome	Main findings	Reported adverse events
			inspired oxygen < 301 mm, and pneumonia					there was a numerical reduction in time to clinical improvement (HR 1.52, 0.95–2.43).	
Shih *et al.*[32]	Re-analysis of Wang paper	NA	NA	NA	NA	NA	Time to recovery (reaching the clinical status with point = 2 or 1 in the 6-category scale)	On d 28, the response rate for the remdisivir group with baseline status = 3 (moderately severe category) was 85%, and for the placebo group, the response rate was 70% (OR = 2.38, *P* = .0012). The response rate was 43% for the remdesivir group compared to 33% for the placebo group on d 14 (OR = 1.53, *P* = .0022).	NA

SaO2 = oxygen saturation; NA = not applicable; aOR = adjusted odds ratio; CI = confidence interval; RRR = rate ratio for recovery; RT-PCR = reverse transcription polymerase chain reaction; OR = odds ratio; HR = hazard ratio

3.1 | Clinical trials exploring the efficacy and safety of remdesivir for COVID-19

On 29 April Wang *et al.*[30] published the first randomized trial exploring the efficacy of remdesivir for COVID-19 with 237 hospitalized patients. Compared with placebo, remdesivir was not statistically significantly associated with clinical improvement (hazard ratio [HR] 1.23, 95% CI 0.87 to 1.75), and did not significantly improve mortality or time to clearance of SARS-CoV-2. Among patients with symptom duration of <10 days, there was a suggestion that time to clinical improvement was faster in the treatment than control group; however, the difference was not statistically significant (HR 1.52, 95% CI 0.95 to 2.43). Patient enrolment was prematurely stopped due to the decline in COVID-19 cases, thus reducing the statistical power from 80 to 58%. The researchers reported adverse events in 66% of the patients in the intervention group and 64% in the patients of the control group.

Shih *et al.*[32] reanalysed the data from Wang *et al.*[30] using a "more powerful and clinically meaningful method," focusing their analysis on patients whose condition was not critically severe. The authors reported a response rate of 85% among those in the intervention group who were in the moderately severe category at baseline, and 70% for the placebo group on day 28 (odds ratio [OR] = 2.38, $P = .0012$). They suggested that remdesivir should be provided to hospitalized patients as early as possible.

Goldman *et al.*[28] reported the results of an RCT evaluating the efficacy and safety of 2 schemes of remdesivir treatments (5-day *vs* 10-day course) in 397 patients with severe COVID-19. The researchers reported that at day 14, patients in the 10-day group had a distribution in clinical status similar to that among patients in the 5-day group ($P = .14$), and a similar proportion of adverse events in both groups. They could not determine the magnitude of benefit or harm due to lack of a placebo control group.

Olender *et al.*[31] reported their study comparing interim data from a phase 3 RCT with a retrospective cohort study. The intervention group, based on the RCT data, received either a 5- or 10-day course of remdesivir and the control group, based on the cohort data, received standard care according to local clinical practice. Including data from 1130 patients, the authors reported an association between remdesivir treatment and significantly greater recovery at day 14 of follow-up, and 62% reduced odds of death *vs* standard care for COVID-19.

Spinner *et al.*[29] published the first trial exploring the efficacy of 5 or 10 days of remdesivir treatment against standard care on the clinical status of adults with moderate pneumonia (oxygen saturation >94% on room air). The authors found a statistically significant difference among patients randomized to a 5-day course of the antiviral compared with standard care, but concluded that "the difference was of uncertain clinical importance." Additionally, patients in the 10-day group did not show a significant difference compared with standard care at day 11 of treatment. Nausea, hypokalaemia and headache were more frequent in the treated group compared with standard care. Table 1 shows the characteristics of the trials included in our study.

3.2 | Trial registries

At the time of reporting, there are 13 trials registered in the USA, 7 in Europe, and 1 each in Iran, UK and Japan. The trials include 37 812 participants. One registered trial (ISRCTN83971151) did not specify the sample size but is planning to recruit "several thousand" participants. The biggest trial (NCT04501978) is a multicentre trial in US sites, planning to recruit 10 000 participants. Eleven trials will include more than 1 country, with 1 trial (ISRCTN83971151) including 23 countries.

Five trials will evaluate remdesivir exclusively, and 11 will include additional arms evaluating **chloroquine**, **hydroxychloroquine**, **lopinavir** plus **ritonavir**, and/or **interferon**. One trial, however, recently discontinued the additional arms (NCT04315948). Other drugs being tested, typically in combination with remdesivir, include **merimepodib**, **tocilizumab**, **baricitinib**, **cenicriviroc**, **icatibant**, **razuprotafib**, **apremilast**, **LY3819253**, **methylprednisolone**, **losartan**, convalescent serum, **azithromycin**, **doxycycline**, **clindamycin**, and **primaquine** ($n = 6$). One study will explore inhaled remdesivir (NCT04539262).

Nine trials explicitly stated an arm would include remdesivir and standard care. The remaining trials did not specify patients would receive standard care. Regarding the control group, 9 trials will use standard care for COVID-19, 4 trials will use a placebo drug (either aerosolized, intravenous or tablet form), 1 trial will use standard care and placebo, and for the remaining 9 studies, the comparator arm is another drug.

For the primary outcome, 10 trials will evaluate patient mortality, 7 studies will use scale-based clinical status of participants, and 5 trials will use other primary outcomes. Although the dose details are not available for all registrations, 8 studies will use a loading dose of 200 mg of intravenous remdesivir on day 1, followed by 100 mg daily on days 2–10.

Five trials (NCT04410354, NCT04321616, NCT04349410, NCT04409262, NCT04539262) are expected to end in 2020, while 3, 2, 3 and 1 trials are expected to finish each year in 2021, 2022, 2023 and 2029, respectively. The end date is not available for the remaining trials ($n = 9$). Nineteen trials are ongoing and 4 are not yet recruiting participants. Table 2 shows the characteristics of the registered trials included in our study.

3.3 | Observational studies and case series exploring the effectiveness and safety of remdesivir for COVID-19

Rivera[40] *et al.* conducted a cohort study to explore the association between COVID-19 treatment including remdesivir and 30-day all-cause mortality in adults with cancer. Treatment with remdesivir was

TABLE 2 Characteristics of the trial registrations included in our study

Registration number	Trial design	Countries	Sample size	Interventions	Control	Primary outcome	First posted	Completion date*	Status
NCT04345419	Phase 3, single blind RCT	Egypt	120	Remdesivir. Additional arm testing chloroquine or hydroxychloroquine.	NA	Patient improvement or mortality	14-Apr-20	Dec-29	Recruiting
NCT04539262	Phase 1, blinded RCT	NR	282	Remdesivir (inhaled daily, varied doses).	aerosolized placebo	Average change in SARS-Cov-2 viral load (time-weighted)	4-Sep-20	Dec-20	Not yet recruiting
NCT04410354	Phase 2, blinded RCT	USA	40	Remdesivir and merimepodib *vs* remdesivir and matching placebo.	NA	Participants not hospitalized (or hospitalized but not in respiratory failure)	1-Jun-20	Aug-20	Recruiting
NCT04409262	Phase 3, blinded RCT	USA, Brazil, Russian Federation	450	Remdesivir (IV, d 1–10) and tocilizumab *vs* remdesivir and matching placebo (IV).	NA	Clinical status on d 28 (7-point ordinal scale)	1-Jun-20	Dec-20	Recruiting
NCT04501952	Phase 3, blinded RCT	NR	1230	Remdesivir (d 1: 200 mg, d 2 and 3: 100 mg).	IV placebo (d 1–3)	Patient hospitalization or all-cause mortality by d 14	6-Aug-20	Jan-21	Not yet recruiting
NCT04401579; jRCT2031200035	Phase 3, blinded RCT	USA, Denmark, Japan, Republic of Korea, Mexico, Singapore, Spain, UK	1034	Remdesivir (d 1: 200 mg d 2–10: 100 mg) alone or in combination with baricitinib.	NA	Time to recovery	26-May-20	Aug-23	Active, not recruiting
NCT04492475; jRCT2031200092	Phase 3, adaptive, blinded RCT	USA, Japan, Republic or Korea, Mexico, Singapore	1038	Remdesivir (d 1: 200 mg, d 2–10: 100 mg) with placebo *vs* remdesivir with interferon β-1a.	NA	Time to recovery	30-Jul-20	Nov-23	Recruiting
NCT04330690	Adaptive phase 2, open-label RCT	Canada	2900	SC and remdesivir (d 1: 200 mg, d 2–10: 100 mg). Additional arms include hydroxychloroquine and lopinavir/ritonavir.	NA	All-cause mortality	1-Apr-20	18-Mar-22	Recruiting

(Continues)

TABLE 2 (Continued)

Registration number	Trial design	Countries	Sample size	Interventions	Control	Primary outcome	First posted	Completion date*	Status
NCT04321616	Phase 2/3, open-label RCT	Norway	700	Remdesivir (d 1: 200 mg, d 2–10: 100 mg). An additional arm includes hydroxychloroquine.	SC	All cause in-hospital mortality	25-Mar-20	Nov-20	Recruiting
NCT04315948	Phase 3, open-label RCT	Austria, Belgium, France, Luxembourg	3100	SC and remdesivir (d 1: 200 mg, d 2–10: 100 mg). Additional arms included chloroquine or hydroxychloroquine, lopinavir + ritonavir, and interferon (discontinued in May/June 2020).	SC	Clinical severity on a 7-point ordinal scale	20-Mar-20	Mar-23	Recruiting
NCT04488081	Phase 2, adaptive, open-label, platform RCT	USA	1500	SC and remdesivir (d 1: 200 mg, d 2–10: 100 mg or d 2–5: 100 mg) alone or with 1 of cenicriviroc, icatibant, razuprotafib or apremilast.	NA	Time to change to at least ordinal level 4 (sustained for at least 48 hours)	27-Jul-20	01-Nov-22	Recruiting
NCT04501978	Phase 3, adaptive, blinded RCT	USA	10 000	SC (which includes remdesivir) and LY3819253.	SC and placebo	Oxygen requirements (7-point ordinal scale)	6-Aug-20	Jul-21	Recruiting
NCT04349410	Phase 2/3, randomized, factorial, single-blind RCT	USA	500	Remdesivir (d 1: 200 mg, d 2–10: 100 mg). Additional arms include: tocilizumab, methylprednisolone, interferon-α2B, losartan, convalescent serum, OR hydroxychloroquine with azithromycin, with doxycycline, with clindamycin, or	NA	Improvement in Fleming method for tissue and vascular differentiation and metabolism	16-Apr-20	11-Nov-20	Enrolling by invitation

(Continues)

TABLE 2 (Continued)

Registration number	Trial design	Countries	Sample size	Interventions	Control	Primary outcome	First posted	Completion date*	Status
				with clindamycin and primaquine.					
2020–001784-88	Phase III, open label RCT	Finland	582	Remdesivir (100 mg).	SC	All cause in-hospital mortality	17-Apr-20	NR	Ongoing
2020–000982-18	Phase III open-label, RCT	Norway and Sweden	1218	Remdesivir (100 mg). An additional arm includes hydroxychloroquine.	SC	All cause in-hospital mortality	26-Mar-20	NR	Ongoing
2020–001366-11	Phase 3/4, open-label RCT	Spain, Lithuania, Ireland, Italy, Portugal, Slovakia, Romania, Latvia	7815	SC and remdesivir (100 mg). Additional arms include SC and chloroquine or hydroxychloroquine (not Ireland), Lopinavir + ritonavir, and interferon.	SC	All-cause mortality	27-Mar-20	NR	Ongoing
2020–002060-31	Phase 3, open-label RCT	Czech Republic	20	SC and Remdesivir (100 mg). Additional arms include SC and chloroquine or hydroxychloroquine, lopinavir + ritonavir, and interferon.	SC	All-cause mortality	22-Jun-20	NR	Ongoing
2020–001549-38	Phase 3, open-label RCT	Germany	800	SC and remdesivir (100 mg). Additional arms include SC and lopinavir + ritonavir, and interferon.	SC	Clinical status on d 15 (7-point ordinal scale)	29-Jun-20	NR	Ongoing
2020–001052-18	Phase 3, blinded RCT	Denmark, UK, Greece, Germany, Spain	333	Remdesivir.	Placebo intravenous solution or tablet	Clinical status on d 15 (8-point ordinal scale) /Time to recovery	25-Mar-20	NR	Ongoing
2020–000936-23	Phase 3, open label RCT	France, Austria	1050	Remdesivir. Additional arms include hydroxychloroquine, lopinavir + ritonavir, and interferonβ-1 (Austria only).	NA	Clinical status on d 15 (7-point ordinal scale)	09-Mar-20	NR	Ongoing

(Continues)

TABLE 2 (Continued)

Registration number	Trial design	Countries	Sample size	Interventions	Control	Primary outcome	First posted	Completion date*	Status
IRCT20200405046953N1	Phase 3 RCT	Iran	3000	SC and remdesivir (10 d, infusion). Additional arms include SC with chloroquine or hydroxychloroquine, lopinavir with ritonavir, or lopinavir with ritonavir plus interferon.	SC	All-cause mortality	06-Apr-20	NR	Recruitment complete
ISRCTN83971151	Phase 3, open-label RCT	Argentina, Brazil, Canada, Germany, Honduras, India, Indonesia, Iran, Ireland, Israel, Italy, Kenya, Lebanon, Malaysia, Norway, Peru, Philippines, Qatar, Saudi Arabia, South Africa, Spain, Switzerland, Thailand	Several thousand	SC and remdesivir (10 d). Additional arms include SC and chloroquine (or hydroxy-chloroquine), lopinavir + ritonavir (Kaletra), or interferon-β.	SC	All-cause mortality	25-Mar-20	25-Mar-21	Recruiting
jRCT2031190264	Blinded RCT	USA, Korea, Japan	100	Remdesivir (d 1: 200 mg, d 2–10: 100 mg)	Matching placebo with equivalent volume	Clinical status at d 15 (8-point ordinal scale)	24-Mar-20	NR	Not recruiting

RCT = randomized controlled trial; NA = not applicable; IV = intravenous; SC, standard care
*some registries only provide month and year.

associated with decreased 30-day all-cause mortality (adjusted OR 0.41, 95% CI 0.17 to 0.99). Pasquini *et al.*[42] retrospectively compared remdesivir-treated patients with controls (n = 51). Both groups were under mechanical ventilation. The authors reported significantly lower mortality among remdesivir-treated patients compared with those who did not receive the antiviral (56.0 *vs* 92.3% P < .001) and improved odds of survival among remdesivir-treated patients compared to the controls (OR 3.51, 95% CI 1.77 to 6.95).

Grein *et al.*[41] administered compassionate treatment with remdesivir to 61 patients with COVID-19 and reported a cumulative incidence of clinical improvement of 84% (95% CI 70 to 99) by Kaplan–Meier analysis after 28 days of follow-up. The authors concluded, notwithstanding the limitations they recognized in their study, that remdesivir might have clinical benefits in patients with severe COVID-19. The authors responded to several criticisms and, on re-analysis, found a cumulative incidence improvement of 74%, which did not change their conclusions.[43]

Antinori *et al.*[4] conducted a prospective open-label study to describe the outcomes among 35 adult patients with confirmed SARS-CoV-2 pneumonia who received remdesivir. On day 28, 14 patients from the ward were discharged, 2 were hospitalized and 1 died; 6 patients from the ICU were discharged, 8 died, 3 were mechanically ventilated and 1 was hospitalized. The most common adverse events were hypertransaminaseaemia and acute kidney injury.

We also found 6 case series reporting the experience of a total of 32 patients who received remdesivir,[33–38] 5 of them using a 10-day course of remdesivir (14 days in Dubert *et al.*). Two of these studies[35,38] conducted with pregnant women found that all patients' clinical condition improved after receiving remdesivir. Three case series[33,34,37] reported improved clinical status of patients treated with the antiviral. Zampino[36] *et al.*, however, reported hypertransaminaseaemia after receiving the drug and suggested a direct role of remdesivir in hepatocellular toxicity. Additional adverse reactions observed in these case series included nausea, diarrhoea, chest discomfort, insomnia, acute renal injury, maculopapular rash and cytolitic hepatitis. Two studies[36,37] reported *torsade de pointes* (an uncommon and distinctive form of polymorphic ventricular tachycardia).

Finally, Montastruc *et al.*[39] conducted a pharmacovigilance analysis to describe hepatic impairment related to remdesivir use. Based on 387 patient reports of remdesivir use, they found increased risk of reporting hepatic disorders among patients treated with remdesivir compared with hydroxychloroquine, lopinavir/ritonavir, or tocilizumab (reporting OR, 1.94; 95% CI, 1.54 to 2.45). Table 3 shows the characteristics of the observational studies and case series included in our study.

4 | DISCUSSION

4.1 | Efficacy

Four published RCTs[13,28–30] test the efficacy and safety of remdesivir in 2293 hospitalized patients with COVID-19. Compared with their control groups, 2 trials[13,29] reported statistically significant improvement such as shorter median recovery time and better clinical status among patients who received remdesivir. Wang *et al.*[30] did not detect a statistically significant benefit, although their study was underpowered due to a decrease in COVID-19 cases in their study area. Olender *et al.*[31] from RCT data reported reduced odds of death from COVID-19 and greater recovery of patients in the remdesivir group *vs* standard care. These preliminary positive results help to explain the trend of active clinical trials including remdesivir as part of the standard of care for patients with COVID-19.

A panel of international experts reporting in July 2020[44] concluded that remdesivir possibly reduces both time to symptom resolution and duration of mechanical ventilation, but its impact on mortality remains uncertain. Since we found that most active trials use patient mortality as the main outcome, evidence about the impact of remdesivir on this important endpoint will be available soon. The panel mentioned this antiviral was, at the time of reporting, the only treatment where all the data stem from RCTs supported by a pharmaceutical company, making a publication bias quite likely. The panel warned that enthusiasm for the drug may deflect attention, funds, time and workforce away from other potentially effective treatments.[45]

The preliminary evidence of positive results of remdesivir treatment for patients with COVID-19 raises a concern that available doses will not be enough to cover a global demand.[46] The USA recently purchased almost all supplies of this antiviral available worldwide.[47] A partial solution to the shortage of remdesivir is decreasing the treatment duration. Goldman *et al.*[28] reported similar clinical status of patients who received a 5-day course compared with those who received a 10-day course. Additionally, Spinner *et al.*[29] reported a better clinical status of patients receiving a 5-day treatment course compared to patients receiving standard care at day 11 of treatment, although they questioned the clinical importance of their finding. The possibility that drug efficacy may be similar with 5 and 10 days of treatment could increase the net availability of the antiviral, especially for low- and middle-income countries. The finding remains to be confirmed in independent RCTs, which could take some time. Most active trials still use a 10-day course of the antiviral.

Available clinical evidence on the efficacy of remdesivir focuses on critically ill patients in need of supplemental oxygen. The only RCT including patients with oxygen saturation >94% on room air[29] reported better clinical status of patients who received a 5-day course of remdesivir compared with those receiving standard care. The re-analysis by Shih *et al.*[32] reported a significant effect of remdesivir treatment among patients who were moderately ill at baseline. These results support the call to investigate remdesivir treatment in patients with mild or moderate COVID-19, perhaps using administration formats such as inhaled remdesivir that do not require hospitalization.

4.2 | Effectiveness

Two observational studies are consistent with an association between remdesivir treatment and decreased mortality.[40,42] Case series

TABLE 3 Characteristics of the observational studies and case series included in our study

Authors	Type of study	Sample size	Inclusion criteria	Remdesivir scheme	Primary outcome	Main findings	Reported adverse events
Montastruc *et al.*[39]	Pharmacovigilance analysis	2921	Patients with COVID-19 registered up to 15 June 2020	Mean duration of treatment was 3.8 d (range 1–11).	Risk of hepatic disorders with remdesivir	Treatment with remdesivir was associated with an increased risk of reporting hepatic disorders (ROR, 1.94; 95% CI, 1.54–2.45) compared with hydroxychloroquine, lopinavir/ritonavir, or tocilizumab	Hypertransaminaseaemia, hyperbilirubinaemia, hepatic failure and hepatitis
Rivera *et al.*[40]	Cohort study	2186	Adult patients with cancer and laboratory-confirmed SARS-CoV-2 infection.	Not reported.	30-d all-cause mortality	In comparison with treated controls, remdesivir was associated with decreased 30-d all-cause mortality (aOR 0.41, 95% CI: 0.17–0.99). Compared to untreated controls, remdesivir was numerically associated with decreased mortality (aOR 0.76, 95% CI: 0.31–1.85).	Not reported
Grein *et al.*[41]	Cohort of patients	53	Hospitalized patients with RT-PCR confirmed SARS-CoV-2 infection, ambient-air SaO2 < 95% or need for oxygen support, creatinine clearance > 30 mL per minute, AST and ALT < 5 times the upper limit.	Loading dose of 200 mg on d 1, followed by an intravenous dose of 100 mg/d from d 2 to d 10.	Changes in oxygen-support requirements, hospital discharge, reported adverse events, and death	The cumulative incidence of clinical improvement was 84% (95% CI 70–99) by Kaplan–Meier analysis by 28 d of follow-up.	Hypertransaminaseaemia, diarrhoea, rash, renal impairment and hypotension. Multiple organ-dysfunction syndrome, septic shock, and acute kidney injury
Pasquini *et al.*[42]	Retrospective comparison of patients treated with remdesivir *vs* controls	51	Hospitalized patients >18 years old, admitted to the ICU, RT-PCR confirmed COVID-19, and mechanical ventilation	Loading dose of 200 mg on d 1, followed by an intravenous dose of 100 mg/d from d 2 to d 10.	Patient mortality	Compared with untreated patients, the mortality was significantly lower for remdesivir-treated patients (56.0 *vs* 92.3% $P < .001$). Remdesivir treatment was associated with survival	Not reported

(Continues)

TABLE 3 (Continued)

Authors	Type of study	Sample size	Inclusion criteria	Remdesivir scheme	Primary outcome	Main findings	Reported adverse events
						(OR 3.51; 95% CI 1.77–7.00)	
Antinori *et al.*[4]	Prospective open-label study	35	Male or non-pregnant female, >17 years old, positive RT-PCR, and X-ray or CT-confirmed pneumonia, mechanically ventilated or SaO2 < 95% on room air.	Loading dose of 200 mg on d 1, followed by an intravenous dose of 100 mg/d from d 2 to d 10.	Change in clinical status (7-point ordinal scale) on the 10th and 28th d of treatment	At d 28, 14 (82.3%) patients from the ward were discharged, 2 remained hospitalized and 1 died. Of the patients in the ICU, 6 (33.3%) were discharged, 8 (44.4%) died, 3 (16.7%) were mechanically ventilated and 1 (5.6%) improved but was still hospitalized.	Hypertransaminaseaemia, acute kidney injury, maculo-papular rash
Lee *et al.*[33]	Retrospective case series	10	PCR and X-ray or CT confirmed SARS-CoV-2 pneumonia, >17 years old, SaO2 < 95% on room air.	Loading dose of 200 mg on d 1, followed by 100 mg/d from d 2–5 or d 2–10 according to randomization.	Clinical, laboratory and imaging data	3 patients fully recovered and were discharged from the hospital. 5 patients symptoms improved but remained in hospital. 2 patients fully recovered (but remained SARS-Cov-2 positive) and were transferred to an isolation facility.	Hypertransaminaseaemia, nausea, diarrhoea, chest discomfort and insomnia.
Dubert *et al.*[34]	Retrospective case series	5	Patients diagnosed with COVID-19 treated with remdesivir and signs of severe illness	Loading dose of 200 mg followed by 100 mg/d for up to 14 d.	Clinical, laboratory and imaging data.	Most patients had a significant decrease in viral load in the upper respiratory tract. 3 patients had a favourable outcome, but 2 patients died.	Acute renal injury, maculopapular rash and cytolytic hepatitis.
McCoy *et al.*[35]	Retrospective case series	5	Hospitalized, pregnant patients with PCR confirmed severe COVID-19 who required supplemental oxygen.	Loading dose of 200 mg on d 1, followed by an intravenous dose of 100 mg/d from d 2 to d 10.	Clinical, laboratory and imaging data.	All patients improved their clinical condition and were discharged from the hospital.	Hypertransaminaseaemia

(Continues)

TABLE 3 (Continued)

Authors	Type of study	Sample size	Inclusion criteria	Remdesivir scheme	Primary outcome	Main findings	Reported adverse events
Zampino *et al.*[36]	Case series	5	Invasive mechanical ventilation, no multiorgan failure, no vasopressor requirement, ALT levels < 5 ULN, creatinine clearance > 30 mL/min	Loading dose of 200 mg on d 1, followed by an intravenous dose of 100 mg/d from d 2 to d 10.	Changes in AST/ALT and bilirubin	Patients had elevated ALT/AST and bilirubin with remdesivir	Torsade de pointes, hypertransaminaseaemia
Durante-Mangoni *et al.*[37]	Case series	4	Hospitalized COVID-19 patients with severe pneumonia and respiratory distress.	Loading dose of 200 mg on d 1, followed by an intravenous dose of 100 mg/d from d 2 to d 10	Clinical, laboratory and imaging data.	All patients increased lymphocyte counts and showed an in vivo virological effect of remdesivir but also reported adverse events	Torsade de pointes
Igbinosa *et al.*[38]	Case series	3	Pregnant patients who met criteria for compassionate use of remdesivir, confirmed SARS-CoV-2 infection, and imaging supportive of lower respiratory disease	Not reported	Clinical, laboratory and imaging data.	After starting remdesivir, oxygen was no longer required for the 3 patients.	Transaminitis

ROR = reporting odds rations; CI = confidence interval; aOR = adjusted odds ratio; RT-PCR = reverse transcription polymerase chain reaction; SaO2 = oxygen saturation; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ICU = intensive care unit; CT = computed tomography; ULN = upper limit of normal

reports[4,33–38] are also consistent with improved health outcomes among patients treated with the antiviral, lack of a counterfactual clearly limiting inferences about causality. Two case series reported that remdesivir was well tolerated among pregnant patients[35,38] and the cohort study by Rivera *et al*. reported positive outcomes of remdesivir treatment among patients with cancer.[40] There is still little evidence, however, on the effectiveness and safety of remdesivir in subgroups of patients.

4.3 | Safety

The most common adverse reaction reported in observational studies and case series was hepatic impairment, including hypertransaminaseaemia, hyperbilirubinaemia, hepatic failure and hepatitis. Additional adverse reactions observed in the case series included diarrhoea, chest discomfort, insomnia, acute renal injury, maculopapular rash, and torsade de pointes.

The only study exclusively exploring remdesivir safety[39] reported an association between treatment with the antiviral and increased risk of reporting hepatic disorders. Despite these results, 3 of the 4 published RCTs[13,28,30] reported a similar proportion of adverse events in the intervention and control groups. Only Spinner *et al*.[29] reported a higher proportion of nausea, hypokalaemia and headache among remdesivir-treated patients. Preliminary evidence from clinical studies support the need to conduct hepatic and renal monitoring in patients receiving the antiviral.

4.4 | Strengths and limitations

Compared with available reviews,[44,48–51] a strength of our study is the robust research design. Our search strategy was the only one guided by a professional librarian. Involvement of librarians in designing protocols of knowledge synthesis studies is associated with significantly higher quality of search strategies.[52] Our review included key databases plus 17 primary trial registries. Only 1 of the available reviews[50] included any trial registries other than Clinicaltrials.gov. This review did not report on patient outcomes, did not use a comprehensive search strategy, and only included studies up to 17 March 2020. Two of the available reviews explored both efficacy/effectiveness and safety of remdesivir[18,19] but their search strategy was weak. For example, 1 review[19] used only 1 search term for remdesivir, and only 4 for COVID-19. We used 39 terms related to COVID-19 and 6 terms related to remdesivir. Both the reviews that explored both efficacy/effectiveness and safety of remdesivir had searches ending 4.5 months earlier than ours. Supporting information 3 summarizes the potentially comparable reviews and the added value of our study.

Our review is limited by a scarcity of counterfactual evidence and the quality of the studies included. Several remdesivir trials are expected to report results soon, so our results will shortly need updating. Since our review was time-sensitive, we did not contact the authors or principal investigators of the included publications if some information was missing. We did not perform a quality appraisal of the included studies nor did we do a quantitative synthesis of the results; these elements are outside the standard objectives of a scoping review.[20,26,53]

5 | CONCLUSION

Four published RCTs involving a total of 2293 patients suggest remdesivir might shorten the time to clinical improvement among hospitalized adults with severe COVID-19. This could alleviate the burden on overloaded health services. A 5-day treatment course might be as effective as a 10-day course, which might increase access to the antiviral in the context of limited availability.

The clinical studies included in our scoping review reported mild adverse events after administration of remdesivir, especially hypertransaminaseaemia. RCT data, however, suggest a similar proportion of adverse events in treated and control groups. We recommend hepatic and renal monitoring in all patients treated with remdesivir.

The results of 23 currently registered and active trials with more than 30 000 participants will shed light on the efficacy and safety of the antiviral. There is an urgent need for access to any interim analyses from these trials to increase our understanding of the efficacy and safety of remdesivir for patients with mild or moderate COVID-19. Special concerns are early treatment, new administration formats and drug combinations. The findings of the trials that report results in 2020 will allow a quantitative synthesis of available evidence.

ACKNOWLEDGEMENTS

Genevieve Gore provided advice for conducting the systematic literature search.

COMPETING INTERESTS

No competing financial interests exist.

FUNDING

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Pimentel J, Laurie C, Cockcroft A, Andersson N. Clinical studies assessing the efficacy, effectiveness and safety of remdesivir in management of COVID-19: A scoping review. *Br J Clin Pharmacol*. 2021;87:2663–2684. https://doi.org/10.1111/bcp.14677

APPENDIX A: Search strategy of the scoping review

PubMed.

(((((remdesivir[Text Word] OR "GS 5734"[Text Word]) OR GS5734[Text Word]) OR compound 4b[Text Word]) OR D11472[Text Word]) OR "remdesivir"[Supplementary Concept]) AND ((((((((((((((coronavirus[All Fields] OR coronavirus'[All Fields] OR coronavirus's[All Fields] OR coronavirusapplikation[All Fields] OR coronavirusassociated[All Fields] OR coronaviruscpe[All Fields] OR coronavirusdisease[All Fields] OR coronaviruse[All Fields] OR coronaviruserkrankung[All Fields] OR coronaviruses[All Fields] OR coronaviruses'[All Fields] OR coronavirusinfektion[All Fields] OR coronavirusinfektionen[All Fields] OR coronaviruslike[All Fields] OR coronavirusreplikation[All Fields] OR coronavirussen[All Fields] OR coronavirustissue[All Fields] OR coronavirusurile[All Fields]) OR "covid 2019"[All Fields]) OR "covid 19"[All Fields]) OR "SARS2"[All Fields]) OR "SARS-CoV-2"[All Fields]) OR "SARS-CoV-19"[All Fields]) OR "COVID-19"[nm]) OR ("severe acute respiratory"[All Fields] AND (pneumonia outbreak[All Fields] OR pneumonia outbreaks[All Fields]))) OR "novel cov"[All Fields]) OR "2019ncov"[All Fields]) OR "cov2"[All Fields]) OR "ncov"[All Fields]) OR "covid19"[All Fields]) OR "coronaviridae"[All Fields]) OR (corona virus[All Fields] OR corona viruses[All Fields])) OR (("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "Coronavirus Infections"[Mesh]) OR "Coronavirus"[Mesh])) AND ("2019/01/01"[PDAT]: "2020/05/09"[PDAT])

Embase

1. exp Coronavirinae/
2. exp Coronavirus infection/
3. exp SARS-related coronavirus/or exp SARS coronavirus/or coronavirus*.mp
4. covid 2019.mp.
5. SARS2.mp.
6. SARS-CoV-2.mp.
7. SARS-CoV-19.mp.
8. COVID-19.mp.
9. ("severe acute respiratory" and "pneumonia outbreak*").mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word].
10. ("novel cov" or 2019ncov or "cov2" or "covid19" or "coronaviridae" or "corona virus*" or "nCov").mp.
11. (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11.
13. exp remdesivir/.
14. ("remdesivir*" or "GS 5734" or "GS5734" or "compound 4b" or "D11472").mp.
15. 13 or 14.
16. 12 and 15 (yr: 2019 and 2020).

Scopus

TITLE-ABS-KEY ("remdesivir*" OR "GS 5734" OR "GS5734" OR "compound 4b" OR "D11472") AND TITLE-ABS-KEY ("coronavirus*" OR "covid 2019" OR "SARS2" OR "SARS-CoV-2" OR "SARS-CoV-19" OR "COVID-19" OR ("severe acute respiratory" AND "pneumonia outbreak*") OR "novel cov" OR 2019ncov OR "sars cov2" OR "cov2" OR "covid19" OR "coronaviridae" OR "corona virus*" OR "nCov") AND (LIMIT-TO (PUBYEAR, 2020) OR LIMIT-TO (PUBYEAR, 2019)).

Number of clinical trials included by database.*

Database name	Link	Hits	Included
Clinical Trials from U.S. National Library of Medicine	https://clinicaltrials.gov	56	13
Australian New Zealand Clinical Trials Registry (ANZCTR)	anzctr.org.au	2	0
Brazilian Clinical Trials Registry (ReBec)	ensaiosclinicos.gov.br	0	0
Chinese Clinical Trial Registry (ChiCTR)	chictr.org.cn	0	0
Clinical Research Information Service (CRiS), Republic of Korea	cris.nih.go.kr	0	0
Clinical Trials Registry - India (CTRI)	ctri.nic.in/Clinicaltrials/advsearch.php	unavailable	unavailable
Cuban Public Registry of Clinical Trials (RPCEC)	registroclinico.sld.cu/en/home	0	0
EU Clinical Trials Register (EU-CTR)	clinicaltrialsregister.eu	12	7
German Clinical Trials Register (DRKS)	drks.de/drks_web	0	0
Iranian Registry of Clinical Trials (IRCT)	irct.ir	4	1

(Continues)

We used the terms ("remdesivir" OR "GS 5734" OR "GS5734" OR "compound 4b" OR "D11472")

Database name	Link	Hits	Included
ISRCTN	isrctn.com	2	1
Japan Primary Registries Network (JPRN)	rctportal.niph.go.jp	4	1[a]
Lebanese Clinical Trials Registry (LBCTR)	http://lbctr.moph.gov.lb:8080/lbctr	0	0
Thai Clinical Trials Registry (TCTR)	http://www.clinicaltrials.in.th	0	0
The Netherlands National Trial Register (NTR)	trialregister.nl	0	0
Pan African Clinical Trial Registry (PACTR)	pactr.samrc.ac.za	0	0
Peruvian Clinical Trial Registry (REPEC)	ensayosclinicos-repec.ins.gob.pe/	0	0
Sri Lanka Clinical Trials Registry (SLCTR)	https://slctr.lk	0	0

[a] 2 records were duplicates, included In records from ClinicalTrials.gov

APPENDIX B: PRISMA extension for reporting scoping reviews checklist[1]

Section/topic	#	PRISMA-ScR Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants and interventions; study synthesis methods; results; limitations; conclusions and implications of key findings.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review question(s)/objective(s) lend themselves to a scoping review approach.	1 and 2
Objectives	4	Provide an explicit statement of the question(s) and objective(s) being addressed with reference to their key elements (e.g. population or participants, concepts and context), or other relevant key elements used to conceptualize the review question(s) and/or objective(s)).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g. Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify the characteristics of the sources of evidence (e.g. years considered, language, publication status) used as criteria for eligibility, and provide a rationale.	2
Information sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional sources) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence	9	State the process for selecting studies (i.e. screening, eligibility) included in the scoping review.	2 and 3
Data charting process	10	Describe the methods of charting data from the	2 and 3

(Continues)

(Continues)

Section/topic	#	PRISMA-ScR Checklist item	Reported on page #
		included sources of evidence (e.g. piloted forms; forms that have been tested by the team before their use, whether data charting was done independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	3
Critical appraisal of individual sources of evidence	12	**If done,** provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	NA
Summary measures	13	Not applicable for scoping reviews.	NA
Synthesis of results	14	Describe the methods of handling and summarizing the data that were charted.	3
Risk of bias across studies	15	Not applicable for scoping reviews.	NA
Additional analyses	16	Not applicable for scoping reviews.	NA
RESULTS			
Selection of sources of evidence	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Figure 1
Characteristics of sources of evidence	18	For each source of evidence, present characteristics for which data were charted and provide the citations.	Tables 1, 2, and 3
Critical appraisal within sources of evidence	19	If done, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	20	For each included source of evidence, present the relevant data that were charted that relate to the review question(s) and objective(s).	Tables 1, 2, and 3
Synthesis of results	21	Summarize and/or present the charting results as they relate to the review question(s) and objective (s)	3 to 15
Risk of bias across studies	22	Not applicable for scoping reviews.	NA
Additional analysis	23	Not applicable for scoping reviews.	NA
DISCUSSION			
Summary of evidence	24	Summarize the main results (including an overview of concepts, themes, and types of evidence available), explain how they relate to the review question(s) and objectives, and consider the relevance to key groups	15 and 16
Limitations	25	Discuss the limitations of the scoping review process.	16
Conclusions	26	Provide a general interpretation of the results with respect to the review question(s) and objective(s), as well as potential implications and/or next steps.	16
FUNDING			
Funding	27	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	16

(Continues)

1. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med 2018;169 (7):467–73.

APPENDIX C: List of included publications

1. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med. May 2020: NEJMoa2015301. https://doi:10.1056/NEJMoa2015301
2. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With

Moderate COVID-19. JAMA. August 2020. https://doi:10.1001/jama.2020.16349
3. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. N Engl J Med. May 2020:NEJMoa2007764. https://doi:10.1056/NEJMoa2007764
4. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569–1578. https://doi:10.1016/S0140-6736(20)31022-9
5. Olender SA, Perez KK, Go AS, et al. Remdesivir for Severe COVID-19 versus a Cohort Receiving Standard of Care. Clin Infect Dis. July 2020. https://doi:10.1093/cid/ciaa1041
6. Shih WJ, Shen X, Zhang P, Xie T. Remdesivir is Effective for Moderately Severe Patients: A Re-Analysis of the First Double-Blind, Placebo-Controlled, Randomized Trial on Remdesivir for Treatment of Severe COVID-19 Patients Conducted in Wuhan City. Open Access J Clin Trials. 2020;Volume 12:15–21. https://doi:10.2147/OAJCT.S262606
7. Lee C, Ahn MY, Byeon K, et al. Clinical Experience with Use of Remdesivir in the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2: a Case Series. Infect Chemother. July 2020. https://doi.org/10.3947/ic.2020.52.e46
8. Dubert M, Visseaux B, Isernia V, et al. Case report study of the first five COVID-19 patients treated with remdesivir in France. Int J Infect Dis. 2020;98:290–293. https://doi:10.1016/j.ijid.2020.06.093
9. McCoy JA, Short WR, Srinivas SK, Levine LD, Hirshberg A. Compassionate use of remdesivir for treatment of severe coronavirus disease 2019 in pregnant women at a United States academic center. Am J Obstet Gynecol MFM. 2020;2 (3):100164. https://doi:10.1016/j.ajogmf.2020.100164
10. Zampino R, Mele F, Florio LL, et al. Liver injury in remdesivir-treated COVID-19 patients. Hepatol Int. July 2020. https://doi:10.1007/s12072-020-10 077-3
11. Durante-Mangoni E, Andini R, Bertolino L, et al. Early experience with remdesivir in SARS-CoV-2 pneumonia. Infection. May 2020. https://doi:10.1007/s15010-020-01448-x
12. Igbinosa I, Miller S, Bianco K, et al. Use of remdesivir for pregnant patients with severe novel coronavirus disease 2019. Am J Obstet Gynecol. August 2020. https://doi:10.1016/j.ajog.2020.08.001
13. Montastruc F, Thuriot S, Durrieu G. Hepatic Disorders With the Use of Remdesivir for Coronavirus 2019. Clin Gastroenterol Hepatol. July 2020. https://doi:10.1016/j.cgh.2020.07.050
14. Rivera DR, Peters S, Panagiotou OA, et al. Utilization of COVID-19 treatments and clinical outcomes among patients with cancer: A COVID-19 and Cancer Consortium (CCC19) cohort study. Cancer Discov. July 2020:CD-20-0941. https://doi:10.1158/2159-8290.CD-20-0941
15. Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med. April 2020:NEJMoa2007016. https://doi:10.1056/NEJMoa2007016
16. Pasquini Z, Montalti R, Temperoni C, et al. Effectiveness of remdesivir in patients with COVID-19 under mechanical ventilation in an Italian ICU. J Antimicrob Chemother. August 2020. https://doi:10.1093/jac/dkaa321
17. Antinori S, Cossu MV, Ridolfo AL, et al. Compassionate remdesivir treatment of severe Covid-19 pneumonia in intensive care unit (ICU) and Non-ICU patients: Clinical outcome and differences in post_treatment hospitalisation status. Pharmacol Res. May 2020:104899. https://doi:10.1016/j.phrs.2020.104899