Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials

Alain Amstutz, Benjamin Speich*, France Mentré, Corina Silvia Rueegg, Drifa Belhadi, Lambert Assoumou, Charles Burdet, Srinivas Murthy, Lori Elizabeth Dodd, Yeming Wang, Kari A O Tikkinen, Florence Ader, Maya Hites, Maude Bouscambert, Mary Anne Trabaud, Mike Fralick, Todd C Lee, Ruxandra Pinto, Andreas Barratt-Due, Fridtjof Lund-Johansen, Fredrik Müller, Olli P O Nevalainen, Bin Cao, Tyler Bonnett, Alexandra Griessbach, Ala Taji Heravi, Christof Schönenberger, Perrine Janiaud, Laura Werlen, Soheila Aghlmandi, Stefan Schandelmaier, Yazdan Yazdanpanah, Dominique Costagliola, Inge Christoffer Olsen, Matthias Briel*

Summary

Background Interpretation of the evidence from randomised controlled trials (RCTs) of remdesivir in patients treated in hospital for COVID-19 is conflicting. We aimed to assess the benefits and harms of remdesivir compared with placebo or usual care in these patients, and whether treatment effects differed between prespecified patient subgroups.

Methods For this systematic review and meta-analysis, we searched PubMed, Embase, the Cochrane COVID-19 trial registry, ClinicalTrials.gov, the International Clinical Trials Registry Platform, and preprint servers from Jan 1, 2020, until April 11, 2022, for RCTs of remdesivir in adult patients hospitalised with COVID-19, and contacted the authors of eligible trials to request individual patient data. The primary outcome was all-cause mortality at day 28 after randomisation. We used multivariable hierarchical regression—adjusting for respiratory support, age, and enrollment period—to investigate effect modifiers. This study was registered with PROSPERO, CRD42021257134.

Findings Our search identified 857 records, yielding nine RCTs eligible for inclusion. Of these nine eligible RCTs, individual data were provided for eight, covering 10 480 patients hospitalised with COVID-19 (99% of such patients included in such RCTs worldwide) recruited between Feb 6, 2020, and April 1, 2021. Within 28 days of randomisation, 662 (12·5%) of 5317 patients assigned to remdesivir and 706 (14·1%) of 5005 patients assigned to no remdesivir died (adjusted odds ratio [aOR] 0·88, 95% CI 0·78–1·00, p=0·045). We found evidence for a credible subgroup effect according to respiratory support at baseline ($p_{interaction}$=0·019). Of patients who were ventilated—including those who received high-flow oxygen—253 (30·0%) of 844 patients assigned to remdesivir died compared with 241 (28·5%) of 846 patients assigned to no remdesivir (aOR 1·10 [0·88–1·38]; low-certainty evidence). Of patients who received no oxygen or low-flow oxygen, 409 (9·1%) of 4473 patients assigned to remdesivir died compared with 465 (11·2%) of 4159 patients assigned to no remdesivir (0·80 [0·70–0·93]; high-certainty evidence). No credible subgroup effect was found for time to start of remdesivir after symptom onset, age, presence of comorbidities, enrolment period, or corticosteroid use. Remdesivir did not increase the frequency of severe or serious adverse events.

Interpretation This individual patient data meta-analysis showed that remdesivir reduced mortality in patients hospitalised with COVID-19 who required no or conventional oxygen support, but was underpowered to evaluate patients who were ventilated when receiving remdesivir. The effect size of remdesivir in patients with more respiratory support or acquired immunity and the cost-effectiveness of remdesivir remain to be further elucidated.

Funding EU-RESPONSE.

Lancet Respir Med 2023

Published Online February 21, 2023 https://doi.org/10.1016/S2213-2600(22)00528-8

See Online/Comment https://doi.org/10.1016/S2213-2600(23)00036-X

*Joint first authors

CLEAR Methods Center, Division of Clinical Epidemiology , University Hospital Basel, Basel, Switzerland (A Amstutz PhD, B Speich PhD, A Griessbach MSc, A Taji Heravi MSc, C Schönenberger MSc, S Aghlmandi PhD, S Schandelmaier PhD, M Briel PhD)**; Department of Clinical Research, University Hospital Basel, Basel, Switzerland** (A Amstutz, B Speich, A Griessbach, A Taji Heravi, C Schönenberger, P Janiaud PhD, L Werlen PhD, S Aghlmandi, S Schandelmaier, M Briel)**; Université Paris Cité and Université Sorbonne Paris Nord, Inserm, IAME, Paris, France** (Prof F Mentré PhD, D Belhadi PhD, L Assoumou PhD, C Burdet PhD, Y Yazdanpanah PhD)**; Département d'Épidémiologie, Biostatistique et Recherche Clinique** (Prof F Mentré, D Belhadi, C Burdet) **and Service de Maladies Infectieuses et Tropicales** (Y Yazdanpanah)**, Hôpital Bichat, AP-HP, Paris, France; Oslo Centre for Biostatistics and Epidemiology** (C S Rueegg PhD, I C Olsen PhD) **and Department of Anesthesia and Intensive Care Medicine** (A Barratt-Due PhD, F Lund-Johansen PhD, Prof F Müller PhD)**, Oslo University Hospital, Oslo, Norway; Department of Pediatrics, Faculty of Medicine, University of British Columbia,**

Introduction

Since the outbreak of the COVID-19 pandemic, immense efforts have been made to find effective treatments for the disease.[1–3] The broad-spectrum antiviral medication remdesivir was identified as a promising therapeutic candidate because of its ability to inhibit coronaviruses in vitro—including SARS-CoV-2, which causes COVID-19.[4–6] For patients with a high risk of severe COVID-19 who had not been vaccinated or hospitalised with the disease, a single randomised controlled trial (RCT) showed that intravenous remdesivir reduced COVID-19-associated hospitalisation.[7] For patients treated in hospital, RCTs have shown conflicting results.[8–11] The National Institutes of Health (NIH),[12] the Infectious Diseases Society of America (IDSA),[13] and WHO[14] generally recommend remdesivir for patients hospitalised with mild to severe COVID-19. However, the National Institute for Health and Care Excellence (NICE) interprets the evidence differently[15] and uncertainty remains, especially in terms of which subgroup of patients is most likely to benefit.

An individual patient data meta-analysis has advantages over individual RCTs or a standard meta-analysis as it

Vancouver, BC, Canada (S Murthy MHSc); Clinical Trials Research Section, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, MD, USA (L E Dodd PhD); Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing, China (Y Wang MD, Prof B Cao PhD); Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Beijing, China (Y Wang, Prof B Cao); National Clinical Research Center for Respiratory Diseases, Beijing, China (Y Wang, Prof B Cao); Department of Urology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland (Prof K A O Tikkinen PhD); Department of Surgery, South Karelian Central Hospital, Lappeenranta, Finland (Prof K A O Tikkinen); Département des Maladies Infectieuses et Tropicales (Prof F Ader MD) and Laboratoire de Virologie, Institut des Agents Infectieux de Lyon, Centre National de Référence des Virus Respiratoires France Sud (M Bouscambert PharmD, M A Trabaud PharmD), Hospices Civils de Lyon, Lyon, France; Legiopath, Centre International de Recherche en Infectiologie, Inserm 1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, École Normale Supérieure de Lyon, Univ Lyon, Lyon, France (Prof F Ader); Cliniques Universitaires de Bruxelles Hôpital Érasme, Université Libre de Bruxelles, Clinique des Maladies Infectieuses, Brussels, Belgium (M Hites PhD); Department of Medicine, University of Toronto, Toronto, ON, Canada (M Fralick PhD); Clinical Practice Assessment Unit, Department of Medicine, McGill University Health Centre, Montreal, QC, Canada (T C Lee MSc); Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, Toronto, ON, Canada (R Pinto PhD); Hatanpää Health Centre, Tampere, Finland (O P O Nevalainen PhD); Clinical Monitoring Research Program Directorate, Frederick National Laboratory for Cancer Research,

Research in context

Evidence before this study

Interpretation of the evidence for the use of remdesivir, an antiviral drug, in patients treated in hospital for COVID-19 is conflicting. Several randomised controlled trials (RCTs) and aggregate data meta-analyses have been conducted. Most showed that remdesivir provided a marginal, if any, reduction in mortality, progression to mechanical ventilation, and length of hospital stay. Subgroup analyses have suggested effect modification by respiratory support (ie, ventilation *vs* no ventilation), but these analyses were often underpowered, had no formal credibility assessment, and led to contradictory findings. We conducted a systematic review and individual patient data meta-analysis to evaluate the benefits and harms of remdesivir compared with placebo or usual care in patients treated in hospital for COVID-19 and whether treatment effects differed between subgroups of patients. We searched PubMed, Embase, the Cochrane COVID-19 trial registry, ClinicalTrials.gov, the International Clinical Trials Registry Platform, and preprint servers for studies published between Jan 1, 2020, and April 11, 2022. The search terms included synonyms of SARS-CoV-2, remdesivir, and randomised controlled trials; for exact search terms used, see appendix p 46. Eligible studies were RCTs (unpublished or published, in any format, in any language) that randomly assigned adult patients hospitalised with COVID-19 to either remdesivir or no remdesivir (ie, usual care as defined by the local context, with or without placebo).

Added value of this study

Including 99% of the patients involved in RCTs on this topic worldwide, our results show significant survival benefit from remdesivir and less progression to mechanical ventilation or death in patients with no or conventional oxygen support. The evidence for the effect of remdesivir in patients hospitalised with COVID-19 who were receiving high-flow oxygen or more intensified respiratory support before receiving remdesivir is inconclusive, which could be related to the small sample size. Remdesivir did not increase severe or serious adverse events compared with usual care.

Implications of all the available evidence

Patients treated in hospital for COVID-19 who are receiving no or conventional oxygen support have significant survival benefits from remdesivir. For patients requiring more respiratory support, evidence is inconclusive and treatment should therefore be individualised. The effect size of remdesivir in patients with more respiratory support or acquired immunity and the cost-effectiveness of remdesivir remain to be further elucidated.

allows for standardised outcome and subgroup definitions across trials, maximised power to assess the heterogeneity of the treatment effect across subgroups, and adjustment for baseline differences.[16,17] We therefore conducted a systematic review and individual patient data meta-analysis of all available RCTs that investigated the use of remdesivir in patients hospitalised with COVID-19. The aim of this analysis was to assess the benefits and harms of remdesivir for these patients and whether treatment effects differ between prespecified subgroups.

Methods

Search strategy and selection criteria

For this systematic review and individual patient data meta-analysis, we discussed the protocol and results with two patient representatives from Switzerland and two practising infectious disease specialists (one from Switzerland and one from Norway) to enhance clinical and patient relevance. We report the results according to the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) guidelines (appendix p 60).[18]

Eligible studies were RCTs (unpublished or published, any format, in any language) that randomly assigned adult patients (aged ≥16 years) who were treated in hospital for COVID-19 to receive either remdesivir or no remdesivir (ie, usual care as defined by the local context, with or without placebo). We searched PubMed, the Cochrane COVID-19 trial registry (covering PubMed, Embase, the International Clinical Trials Registry Platform [ICTRP] from WHO, and medRxiv), COVID-evidence (including ClinicalTrials.gov and the ICTRP), and the L·OVE platform from the Epistemonikos Foundation (including a large number of databases, trial registries, and preprint servers) for studies published between Jan 1, 2020, and March 1, 2021, and updated the search on April 11, 2022. The search terms included synonyms of SARS-CoV-2, remdesivir, and randomised controlled trials; for exact search terms used, see appendix p 46. We also searched Google and relevant published reviews that were identified during the search (see appendix p 46 for details of the search strategy for each database). Each title and abstract was assessed for potential eligibility by two of the eight reviewers (MBr, CS, AG, PJ, ATH, LW, AA, and BS). If either reviewer judged a study as potentially relevant on the basis of the title or abstract, the full text was obtained and independently assessed by two further reviewers. Disagreements were resolved by discussion or, if necessary, by a third reviewer.

All included studies obtained individual ethical approval. The Ethics Committee Northwest and Central Switzerland confirmed that no separate ethical approval was necessary for this individual patient data meta-analysis as only anonymised data were used. The study protocol is available on PROSPERO (CRD42021257134), Open Science Framework (https://osf.io/7a4wf), and in the appendix (pp 43–59).

Data analysis

For potentially eligible RCTs, we requested protocols from investigators by email to conduct a final eligibility check and prepare data-sharing agreements. If no answer was received after three attempts, we tried to contact the investigator by telephone. The data provided were checked against published results. Where necessary, we discussed and resolved discrepancies with the corresponding study team. To standardise outcomes across trials, we followed the prespecified definitions from our protocol; some results might therefore differ slightly from those in the published articles.

Missing data were addressed with the corresponding study teams and, where possible, collected retrospectively. For the remaining missing data, we used multiple imputation by chained equations techniques.[19] If a covariable or outcome was missing for an entire trial, we excluded this trial from corresponding analyses without imputation (for details see appendix p 3).

When selecting outcomes, we considered two existing core outcome sets and recommendations by WHO.[20–22] The primary outcome was mortality at 28 days after randomisation, combining data collected during treatment in hospital (in-hospital mortality) and after hospital discharge (out-of-hospital mortality). RCTs that did not provide individual patient data meta-analyses but for which the results (including mortality data) had been published were added using an aggregated data meta-analysis approach as part of a sensitivity analysis.

The secondary outcomes were (1) mortality at and within 60 days, (2) the need for new mechanical ventilation or death within 28 days, (3) the number of mechanical-ventilation-free days during the first 28 days, (4) clinical status at day 14 and (5) clinical status at day 28 on an ordinal scale (1=outside of hospital alive or reached discharge criteria [WHO clinical progression scale[22] 0–3], 2=hospitalised without a need for oxygen therapy [WHO scale 4], 3=hospitalised with a need for supplemental oxygen [WHO scale 5], 4=hospitalised with a need for high-flow oxygen or non-invasive ventilation [WHO scale 6], 5=hospitalised with a need for mechanical ventilation or extracorporeal membrane oxygenation [ECMO; WHO scale 7–9], 6=dead [WHO scale 10]), (6) days until cessation of oxygen therapy in patients with oxygenation at baseline up to day 28, (7) days until discharge or reaching discharge criteria up to day 28 (defined as reaching level 1 of the clinical status ordinal scale), (8) quality of life at day 28, (9) viral clearance (proportion of patients with absence of virus replication by PCR) up to day 5, (10) viral clearance up to day 10, (11) viral clearance up to day 15, and (12) number of participants with an adverse event (grade 3 and 4) or serious adverse event by day 28. The number of days for all outcomes refers to the number of days since randomisation. Detailed definitions of the outcomes are available in the appendix (p 13).

We prespecified potential effect modifiers in the study protocol (appendix pp 49–51) and made hypotheses about the direction of effect modification by considering the pathophysiology of acute COVID-19,[23] the mechanism of action of remdesivir,[24] and evidence from previous studies. We anticipated a larger potential benefit from remdesivir in patients who received no or only low-flow oxygen (*vs* those who received more respiratory support—ie, clinical status 4 and 5),[11] who had lower concentrations of baseline C-reactive protein (<75 mg/L),[25] who were younger (analysed continuously; <70 years of age),[26] who had no comorbidities (*vs* those who had at least one comorbidity),[26] and who started remdesivir soon after symptom onset (analysed continuously; ≤5 days *vs* >5 days and ≤10 days *vs* >10 days).[8] Dexamethasone has been shown to reduce mortality from COVID-19 in patients who are hospitalised and receiving respiratory support.[27] To assess the effect of the evolving improvement of usual care and the introduction of dexamethasone in most guidelines for the treatment of COVID-19, we used the date of the press release for the RECOVERY trial results (June 16, 2020) as a proxy and hypothesised that patients enrolled before June 16, 2020, could have a larger benefit from remdesivir than those enrolled afterwards. Furthermore, we assessed the effect of remdesivir in patients with and without antibodies against SARS-CoV-2 at baseline, hypothesising that patients infected with SARS-CoV-2 who had not yet mounted their own humoral immune response (ie, patients who were seronegative) could have a larger benefit from remdesivir, as shown for other COVID-19 treatments.[28] We assessed anti-SARS-CoV-2 receptor-binding domain antibodies and nucleocapsid antibodies, using the same cutoffs for seroconversion as the corresponding trials.

Bias was assessed using the Cochrane Risk of Bias 2 tool. The credibility of subgroup effects was assessed using the Instrument for Assessing the Credibility of Effect Modification Analyses (ICEMAN).[29] We judged the certainty of evidence following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, including the selection of the most patient-relevant outcomes to report in a summary of findings table.[30] All assessments were conducted in duplicate (by AA, BS, MBr, and SS); discrepancies were discussed and resolved by consensus.

All patients were analysed in the study group to which they were randomised (intention-to-treat principle). We applied an individual patient data meta-analysis one-stage approach,[31] using multilevel models with baseline patient characteristics (≥70 years of age, respiratory support, enrolled before June 16, 2020) as important prognostic factors to be included as fixed effects in addition to treatment. To account for between-trial variability, we included trial as a random intercept. We calculated the following point estimates with 95% CIs: adjusted odds ratios (aORs) for binary and ordinal outcomes (primary outcome and secondary outcomes 1, 2, 4, 5, and 9–12), adjusted hazard ratios (aHRs) for the time-to-event

National Institutes of Health, Frederick, MD, USA (T Bonnett MSc); **Sorbonne Université, Inserm, Institut Pierre-Louis d'Épidémiologie et de Santé Publique, Paris, France** (D Costagliola PhD); **Department of Health Research Methodology, Evidence, and Impact, McMaster University, Hamilton, ON, Canada** (M Briel)

Correspondence to:
Dr Benjamin Speich, CLEAR Methods Center, Division of Clinical Epidemiology, Department of Clinical Research, University Hospital Basel, Basel 4051, Switzerland
benjamin.speich@usb.ch

See **Online** for appendix

For the **L·OVE platform**, see https://iloveevidence.com/

For the **Cochrane Risk of Bias 2 tool** see https://methods.cochrane.org/risk-bias-2

outcomes (secondary outcomes 1, 6, and 7) and adjusted incidence rate ratios (aIRRs) for the count outcome (secondary outcome 3). Details about each model used are provided in the appendix (p 13).

To investigate potential effect modification, we added each of the effect modifiers in turn to the models as a fixed effect and as an interaction term with the treatment group and kept the adjustment variables in the models. We assessed heterogeneity in interaction estimates across trials using forest plots. To overcome the weaknesses of categorising continuous effect modifiers, we added these modifiers also as linear treatment interaction terms and used the multivariable fractional polynomials interaction approach to explore non-linear relationships (see appendix p 4 for details).[32]

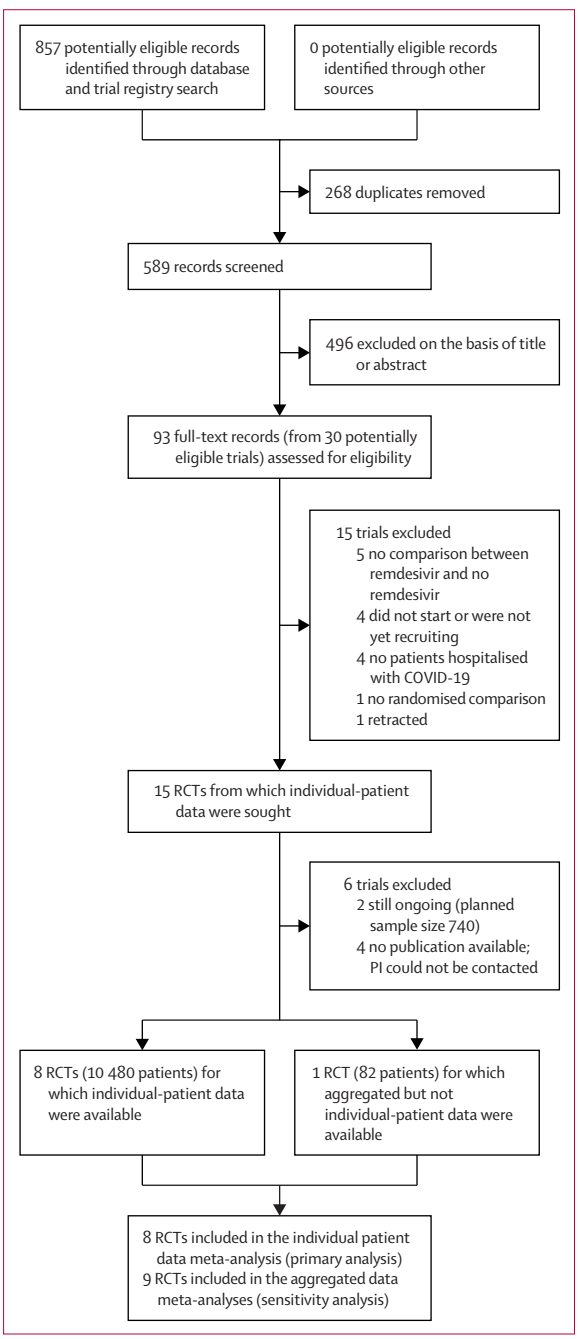

Figure 1: **Study selection**
PI=principal investigator. RCT=randomised controlled trial.

The primary analysis was based on models using the multiple imputation datasets. Effects were estimated in each of the 100 imputed datasets separately and then combined using Rubin's rule (see appendix p 3). We did a complete case analysis as a sensitivity analysis.

Four additional prespecified sensitivity analyses were conducted. First, we limited the meta-analysis to only trials that we judged to have a low risk of bias for all outcomes. Second, we conducted meta-analyses with aggregated data from the one remaining RCT that did not provide individual patient data to summarise all existing randomised evidence. For this trial, we calculated point estimates with SEs using the same model as for the main analysis but without adjustment. Then, we pooled this unadjusted effect with the adjusted point estimates from the trials included in our analysis using the inverse-variance method, and applied the Paule-Mandel estimator for τ^2, the Q-profile method for its CI, and Hartung-Knapp adjustment—including an ad-hoc modification—for random effects models.[33,34] Third, for the subgroup analyses, we chose two additional cutoffs as a time point from symptom onset to randomisation (ie, treatment start): 10 days or less versus more than 10 days, and 7 days or less versus more than 7 days. Finally, instead of dichotomising the baseline respiratory support clinical scale into non-ventilated (no oxygen or only low-flow oxygen) versus ventilated (high-flow oxygen or non-invasive ventilation, mechanical ventilation, or ECMO), we investigated all four ordinal scale levels individually as a treatment interaction. The WHO Solidarity trial data did not differentiate between patients receiving low-flow and high-flow oxygen and so we added these patients to the non-ventilated, low-flow oxygen group (ordinal scale level 3) as they did.[11] As a sensitivity analysis, we investigated the treatment interaction of baseline respiratory support without the WHO Solidarity trial data.

Two more post-hoc analyses were added during the peer-review process. First, we assessed progression to mechanical ventilation in patients who were not on mechanical ventilation at baseline and who were still alive at day 28. Second, instead of using enrolment period as a proxy for dexamethasone use and other care adaptations over time, we assessed corticosteroid use directly as a treatment interaction.

We used R version 4.1.0 for analyses, except for the multivariable fractional polynomials interaction analyses, which we did in Stata version 15.1. We chose $p<0{\cdot}05$ as the level of statistical significance and no adjustments were made for multiple comparisons. This study was registered with PROSPERO, CRD42021257134.

	Country	Participants	Men (%); women (%)	Median age (IQR), years	Recruitment period	Population	Intervention	Control	Follow-up period*
ACTT-1 (2020)[8]	Denmark, Germany, Greece, Japan, South Korea, Mexico, Spain, UK, and USA	1062	684 (64%); 378 (36%)	59 (49–70)	February–April, 2020	Adults hospitalised with COVID-19 who had evidence of lower respiratory tract infection†	Intravenous remdesivir (200 mg day 1, 100 mg day 2–10)	Placebo	28 days
CATCO (2022)[35]‡	Canada	1281	767 (60%); 515 (40%)	66 (54–77)	August, 2020–April, 2021	Adults hospitalised with COVID-19†	Intravenous remdesivir (200 mg day 1, 100 mg day 2–10)	Usual care	60 days
DisCoVeRy (2022)[36,41]‡	Austria, Belgium, France, Luxembourg, Portugal	843	586 (70%); 257 (30%)	64 (54–73)	March, 2020–January, 2021	Adults hospitalised with COVID-19 presenting at least one specific symptom†	Intravenous remdesivir (200 mg day 1, 100 mg day 2–10)	Usual care	90 days
FIN-Solidarity (2022)[39,42]‡	Finland	208	134 (64%); 74 (36%)	59 (50–68)	July, 2020–January, 2021	Adults hospitalised with COVID-19†	Intravenous remdesivir (200 mg day 1, 100 mg day 2–10)	Usual care	≥60 days
NOR-Solidarity (2021)[37]‡	Norway	99	72 (73%); 27 (27%)	58 (48–72)	March–October, 2020	Adults hospitalised with COVID-19†	Intravenous remdesivir (200 mg day 1, 100 mg day 2–10)	Usual care	60 days
Wang et al (2020)[38]	China	236	140 (59%); 96 (41%)	65 (56–71)	February–March, 2020	Adults hospitalised with COVID-19, having specific symptoms†	Intravenous remdesivir (200 mg day 1, 100 mg day 2–10)	Placebo	28 days
Spinner et al (2020)[9]	USA, China, France, Germany, Italy, Japan, South Korea, Netherlands, Singapore, Spain, Sweden, Switzerland, Taiwan, and UK	584	369 (63%); 215 (37%)	55 (45–65)	March–April, 2020	Adults hospitalised with COVID-19† and moderate COVID-19 pneumonia	(1) Intravenous remdesivir (200 mg day 1, 100 mg day 2–5); (2) Intravenous remdesivir (200 mg day 1, 100 mg day 2–10§)	Usual care	28 days
Additional WHO-Solidarity (2021, 2022)[10,11]¶	Albania, Argentina, Brazil, Colombia, Egypt, Ethiopia, Honduras, India, Indonesia, Iran, Ireland, Italy, Kuwait, Lebanon, Lithuania, Malaysia, North Macedonia, Oman, Pakistan, Peru, Philippines, Saudi Arabia, South Africa, Spain, Switzerland	6167¶	3878 (63%); 2289 (37%)	55 (44–65)	March, 2020–January, 2021	Adults hospitalised with COVID-19 (in the view of the responsible physician; no PCR confirmation required)	Intravenous remdesivir (200 mg day 1, 100 mg day 2–10)	Usual care	≥60 days

RCT=randomised controlled trial. *All RCTs systematically followed up patients after discharge from hospital until day 28 after randomisation, after which follow-up differed between trials. †Confirmed by a positive laboratory test. ‡These RCTs were part of the WHO Solidarity trial, but individual patient data were received from the study teams directly with more detailed data points. The CATCO trial continued recruitment for another 3 months after the WHO Solidarity trial stopped recruitment (Jan 29, 2021) and therefore provided more individual patient data. §This was a three-arm trial, in which the two intervention arms assessed different treatment durations (remdesivir 10 days *vs* 5 days), yielding similar effects. We grouped patients from both intervention arms together into our remdesivir arm. ¶The following countries also took part in the WHO Solidarity trial: Austria, Belgium, Canada, Finland, France, Luxembourg, Norway, and Portugal. However, individual patient data from these countries are part of the data included in the CATCO, DisCoVeRy, FIN-Solidarity, and NOR-Solidarity trials, and were therefore taken out of the overall WHO Solidarity trial dataset. As such, the total number of patients reported here (n=6167) does not correspond to that in the publication (n=8275).

Table 1: **Characteristics of RCTs included in the individual patient data meta-analysis**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Our search identified 857 records. After removing duplicates and ineligible records, we identified 15 RCTs from which we sought individual patient data (figure 1). Six studies were excluded, either because they were still ongoing (n=2) or because no investigator could be contacted to confirm eligibility (n=4). From the remaining nine eligible trials (with a total of 10 562 participants),[8,9,11,35–40] we received individual patient data for eight RCTs[8,9,11,35–39] that included 10 480 participants from more than 40 countries (table 1). This total represents 99% of patients with COVID-19 worldwide who participated in an RCT investigating remdesivir between Feb 6, 2020, and April 1, 2021.

The RCT without individual patient data was included in a sensitivity analysis of aggregated data (figure 1).[40] Four of the included RCTs[35–37,39] were, at the same time, part of the WHO Solidarity trial,[11] but collected more data than the WHO Solidarity trial core dataset and these results were published separately. From these four trials we received the detailed individual patient data directly from the respective country trial team and therefore removed these data from the overall WHO Solidarity trial

	Total (n=10 480)	Remdesivir group (n=5398)	No-remdesivir group (n=5082)	Missing data (%)
Age, years	58 (46–68)	58 (47–68)	58 (46–68)	15 (0·1%)
Sex	..	..	..	19 (0·2%)
Male	6610 (63·1%)	3371 (62·4%)	3239 (63·7%)	..
Female	3851 (36·8%)	2018 (37·4%)	1833 (36·1%)	..
Patients enrolled after June 16, 2020*	7620 (72·7%)	3824 (70·8%)	3796 (74·7%)	0%
Time from symptom onset to randomisation, days	9 (6–12)	9 (6–12)	9 (7–12)	6414 (61·2%)
Patients admitted to intensive care unit	1131 (30·5%)	557 (29·4%)	574 (31·7%)	6781 (64·7%)
Patients with any comorbidities	5845 (58·1%)	3040 (58·8%)	2805 (57·3%)	419 (4·0%)
Clinical status on ordinal scale	10 466	5387	5079	14 (0·1%)
2: Hospitalised without need for oxygen therapy (WHO score 4)	2381 (22·7%)	1285 (23·9%)	1096 (21·6%)	..
3: Hospitalised with need for supplemental low-flow oxygen (WHO score 5)	6355 (60·7%)	3236 (60·1%)	3119 (61·4%)	..
4: Hospitalised with need for high-flow oxygen or non-invasive ventilation (WHO score 6)	753 (7·2%)	380 (7·1%)	373 (7·3%)	..
5: Hospitalised with need for mechanical ventilation or ECMO (WHO score 7–9)	976 (9·3%)	485 (9·0%)	491 (9·7%)	..
6: Dead (WHO score 10)	1 (<0·1%)	1 (<0·1%)	0 (0%)	..
C-reactive protein concentration, mg/L†	113 (60–182)	110 (62–174)	118 (58–187)	8875 (84·7%)
Seroconversion (patients with detectable anti-SARS-CoV-2 antibodies [anti-RBD or anti-N])‡	475 (63·1%)	234 (62·4%)	241 (63·8%)	9727 (92·8%)

Data are median (IQR) or n (%). RCT=randomised controlled trial. ECMO=extracorporeal membrane oxygenation. N=nucleocapsid. *The date of the press release for the RECOVERY trial results (June 16, 2020) was used as a proxy for evolving clinical practice over time and for when dexamethasone became part of usual care. †Data only available for DisCoVeRy (n=843; 165 missing), NOR-Solidarity (n=99; 1 missing), and ACTT-1 (n=1062; 233 missing); no data from the other trials. ‡Data only available from DisCoVeRy (n=843; 162 missing) and NOR-Solidarity (n=99; 27 missing); no data from the other trials.

Table 2: **Baseline characteristics of 10 480 pooled patients from eight RCTs that provided individual patient data**

dataset (figure 1, table 1). The characteristics of all RCTs without available individual patient data are summarised in the appendix (p 15).

The 10 480 patients included in our individual patient data meta-analysis had a median age of 58 years (IQR 46–68); the majority were male (6610, 63·1%) and had at least one comorbidity (5845, 58·1%; table 2). Patients were randomly assigned after a median symptom duration of 9 days (IQR 6–12); 1729 (16·5%) received non-invasive or mechanical ventilation at baseline and 7620 (72·7%) were enrolled after June 16, 2020, when dexamethasone became part of usual care for the treatment of patients with severe COVID-19. Baseline characteristics were similar between randomised groups (table 2). Additional baseline characteristics are presented in the appendix (p 16). None of the included patients were vaccinated. Seven RCTs[8,9,35–39] systematically collected in-hospital and out-of-hospital data until 28 days after randomisation, and one RCT[11] collected in-hospital data only. All RCTs were judged to be at low risk of bias for the outcomes mortality at day 28 after randomisation and the need for new mechanical ventilation or death at day 28 and, for those RCTs that collected these data, low risk of bias for the outcomes number of mechanical-ventilation-free days within 28 days and viral clearance (appendix p 29). Two RCTs[8,38] additionally had a low risk of bias for the remaining secondary outcomes (appendix p 30). In the individual patient data received, few data on adjustment variables and outcomes were missing (appendix p 18).

Overall, 662 (12·5%) of 5317 patients in the remdesivir group died by day 28 compared with 706 (14·1%) of 5005 patients in the no-remdesivir group (aOR 0·88, 95% CI 0·78–1·00, p=0·045; table 3). At day 60, the mortality rate was 13·7% with remdesivir (727 of 5311 patients) versus 15·2% (760 of 5002 patients) without remdesivir (0·91, 0·81–1·02, p=0·116). There was no conclusive evidence for a difference in time to death within 60 days (aHR 0·94, 95% CI 0·85–1·04, p=0·239; absolute difference in median 0·6 days; see Kaplan-Meier plot on appendix p 31).

The number of patients either requiring new mechanical ventilation or dying up to day 28 was lower in the remdesivir group (988 [18·5%] of 5346 patients) than in the no-remdesivir group (1123 [22·3%] of 5034 patients; aOR 0·81, 95% CI 0·73–0·90, p<0·0001), and the number of mechanical-ventilation-free days was higher in the remdesivir group (aIRR 1·05, 95% CI 1·04–1·07, p<0·0001; individual patient data available from six trials only[8,9,35–38]). Patients receiving remdesivir had better clinical status on an ordinal scale—ie, less respiratory support at day 28 (aOR 0·87, 95% CI 0·80–0·96, p=0·0037) and at day 14 (0·88, 0·81–0·95, p=0·0015) than patients in the no-remdesivir group. Overall, remdesivir had no effect on time until hospital discharge (aHR 1·02, 95% CI 0·97–1·07, p=0·404; absolute difference in median 0·16 days). Days until cessation of oxygen among patients on oxygen at baseline could be assessed with individual patient data from only six trials[8,9,35–38] (n=4105 participants), in which remdesivir was associated with fewer days until oxygen cessation than no remdesivir (aHR 1·13, 95% CI 1·04–1·23, p=0·0042; absolute difference in median 0·92 days). There was no conclusive evidence for a difference between groups in terms of viral clearance at days 5, 10, and 15 (viral load data were available from only three trials[8,36,37]). Within the first 28 days, patients in the remdesivir group were less likely to have a grade 3 or 4 adverse event or a serious adverse event than patients in the no-remdesivir group (594 [27·3%] of 2179 patients *vs* 623 [32·3%] of 1926 patients; aOR 0·86, 95% CI 0·75–1·00, p=0·046; individual patient data available from only six trials[8,9,35–38]). Overall, the number of grade 3 or 4 adverse events or serious adverse events was similar in both groups when

	Remdesivir group (n=5398)	No-remdesivir group (n=5082)	Primary analysis set (including multiple imputation); intention-to-treat regression analyses		Sensitivity analysis (complete case set); intention-to-treat regression analyses	
			Point estimate (95% CI)	p value	Point estimate (95% CI)	p value
Primary						
All-cause mortality at day 28*	662/5317 (12·5%)	706/5005 (14·1%)	aOR 0·88 (0·78–1·00)	0·045	aOR 0·89 (0·79–1·00)	0·059
Secondary						
All-cause mortality at day 60*	727/5311 (13·7%)	760/5002 (15·2%)	aOR 0·91 (0·81–1·02)	0·116	aOR 0·91 (0·81–1·03)	0·128
Time to death within 60 days, days†	60 (28–60)‡	60 (28–60)‡	aHR 0·94 (0·85–1·04)	0·239	aHR 0·94 (0·85–1·04)	0·238
New mechanical ventilation or death at day 28*	988/5346 (18·5%)	1123/5034 (22·3%)	aOR 0·81 (0·73–0·90)	<0·0001	aOR 0·81 (0·73–0·90)	<0·0001
Mechanical-ventilation-free days within 28 days, days§¶	28 (28–28)§	28 (19–28)§	aIRR 1·05 (1·04–1·07)	<0·0001	aIRR 1·06 (1·04–1·07)	<0·0001
Clinical status at day 28‖	5390	5079	aOR 0·87 (0·80–0·96)	0·0037	aOR 0·88 (0·80–0·96)	0·0049
1: Outside of hospital alive or reached discharge criteria (WHO score 0–3)	4147 (76·9%)	3785 (74·5%)	..	..	..	..
2: Hospitalised without need for oxygen therapy (WHO score 4)	166 (3·1%)	129 (2·5%)	..	..	..	..
3: Hospitalised with need for supplemental low-flow oxygen (WHO score 5)	198 (3·7%)	195 (3·8%)	..	..	..	..
4: Hospitalised with need for high-flow oxygen or non-invasive ventilation (WHO score 6)	29 (0·5%)	35 (0·7%)	..	..	..	..
5: Hospitalised with need for mechanical ventilation or ECMO (WHO score 7–9)	188 (3·5%)	229 (4·5%)	..	..	..	..
6: Dead (WHO score 10)	662 (12·3%)	706 (13·9%)	..	..	..	..
Clinical status at day 14‖	5390	5079	aOR 0·88 (0·81–0·95)	0·0015	aOR 0·88 (0·82–0·96)	0·0021
1: Outside of hospital alive or reached discharge criteria (WHO score 0–3)	3429 (63·6%)	3127 (61·6%)	..	..	..	..
2: Hospitalised without need for oxygen therapy (WHO score 4)	317 (5·9%)	258 (5·1%)	..	..	..	..
3: Hospitalised with need for supplemental low-flow oxygen (WHO score 5)	764 (14·2%)	697 (13·7%)	..	..	..	..
4: Hospitalised with need for high-flow oxygen or non-invasive ventilation (WHO score 6)	76 (1·4%)	95 (1·9%)	..	..	..	..
5: Hospitalised with need for mechanical ventilation or ECMO (WHO score 7–9)	319 (5·9%)	381 (7·5%)	..	..	..	..
6: Dead (WHO score 10)	485 (9·0%)	521 (10·3%)	..	..	..	..
Time to discharge within 28 days, days†	10 (6–23)**	10 (6–25)**	aHR 1·02 (0·97–1·07)	0·404	aHR 1·02 (0·97–1·06)	0·487
Time to cessation of oxygen within 28 days among patients receiving oxygen at baseline, days†¶	11 (5–24)††	13 (6–28)††	aHR 1·13 (1·04–1·23)	0·0042	aHR 1·16 (1·07–1·26)	0·0004
Viral clearance at day 5*‡‡	209/651 (32·1%)	197/644 (30·6%)	aOR 1·06 (0·83–1·36)	0·619	aOR 1·06 (0·83–1·36)	0·619
Viral clearance at day 10*‡‡	234/429 (54·5%)	217/423 (51·3%)	aOR 1·11 (0·85–1·47)	0·442	aOR 1·11 (0·85–1·47)	0·442
Viral clearance at day 15*‡‡	303/473 (64·1%)	289/472 (61·2%)	aOR 1·13 (0·87–1·49)	0·362	aOR 1·13 (0·87–1·48)	0·361
At least one grade 3 or 4 adverse event or serious adverse event (excluding death) within 28 days*¶	594/2179 (27·3%)	623/1926 (32·3%)	aOR 0·86 (0·75–1·00)	0·046	aOR 0·87 (0·75–1·01)	0·059

Data are median (IQR) or n (%), unless otherwise specified. See appendix p 18 for missing data by trial for each of the outcomes. ECMO=extracorporeal membrane oxygenation. aOR=adjusted odds ratio. aHR=adjusted hazard ratio. aIRR=adjusted incidence rate ratio. *Mixed-effects logistic regression adjusted for age >70 years, enrolment before June 16, 2020, and ventilated at baseline, and a random intercept for trial. The additional WHO Solidarity trial data provided only in-hospital mortality data, whereas all other RCTs (CATCO,[35] DisCoVeRy,[36,41] NOR Solidarity,[37] FIN Solidarity,[39,42] Wang et al,[38] ACTT-1,[8] and Spinner et al[9]) also collected out-of-hospital mortality data. †Mixed-effects Cox model adjusted for age >70 years, enrolment before June 16, 2020, and ventilated at baseline, and a random intercept for trial. ‡Descriptively, among only patients who reached the event (death), the median survival time was 10 days (IQR 5–18) in the remdesivir group and 10 days (5–17) in the no-remdesivir group, with a converted absolute difference of a median of 0·6 days. §Mixed-effects Poisson regression adjusted for age >70 years, enrolment before June 16, 2020, and ventilated at baseline, and a random intercept for trial. According to the study protocol, if a patient was discharged before day 28 it was assumed that the patient had mechanical-ventilation-free days until day 28; without this assumption, the median is 15 days (IQR 7–22) in the remdesivir group and 11 days (6–21) in the no-remdesivir group. ¶No data were available from the FIN-Solidarity trial (n=208) and the additional WHO Solidarity trial (n=6167); these missing data were not imputed. ‖Mixed-effects cumulative link model for ordinal regression adjusted for age >70 years, enrolment before June 16, 2020, and a random intercept for trial. Ventilation at baseline had to be excluded from the model owing to collinearity with the outcome. **Descriptively, among only patients who reached the event (discharge from hospital), the median time to discharge was 9 days (IQR 5–12) in the remdesivir group and 8 days (5–12) in the no-remdesivir group, with a converted absolute difference in median of 0·08 days. ††Descriptively, among only patients who reached the event (cessation of oxygen), the median time until cessation of oxygen was 8 days (IQR 5–14) in the remdesivir group and 8 days (5–14) in the no-remdesivir group, with a converted absolute difference in median of 1·04 days. ‡‡Only data from the DisCoVeRy, ACTT-1, and NOR-Solidarity trials were available.

Table 3: **Primary and secondary outcomes, by complete case set and multiple imputation set**

stratified by organ-specific subtypes (appendix p 19). None of the included RCTs reported on health-related quality of life.

Sensitivity analyses on the complete case dataset yielded similar results (table 3). The two RCTs that were judged to be at low risk of bias for all outcomes showed

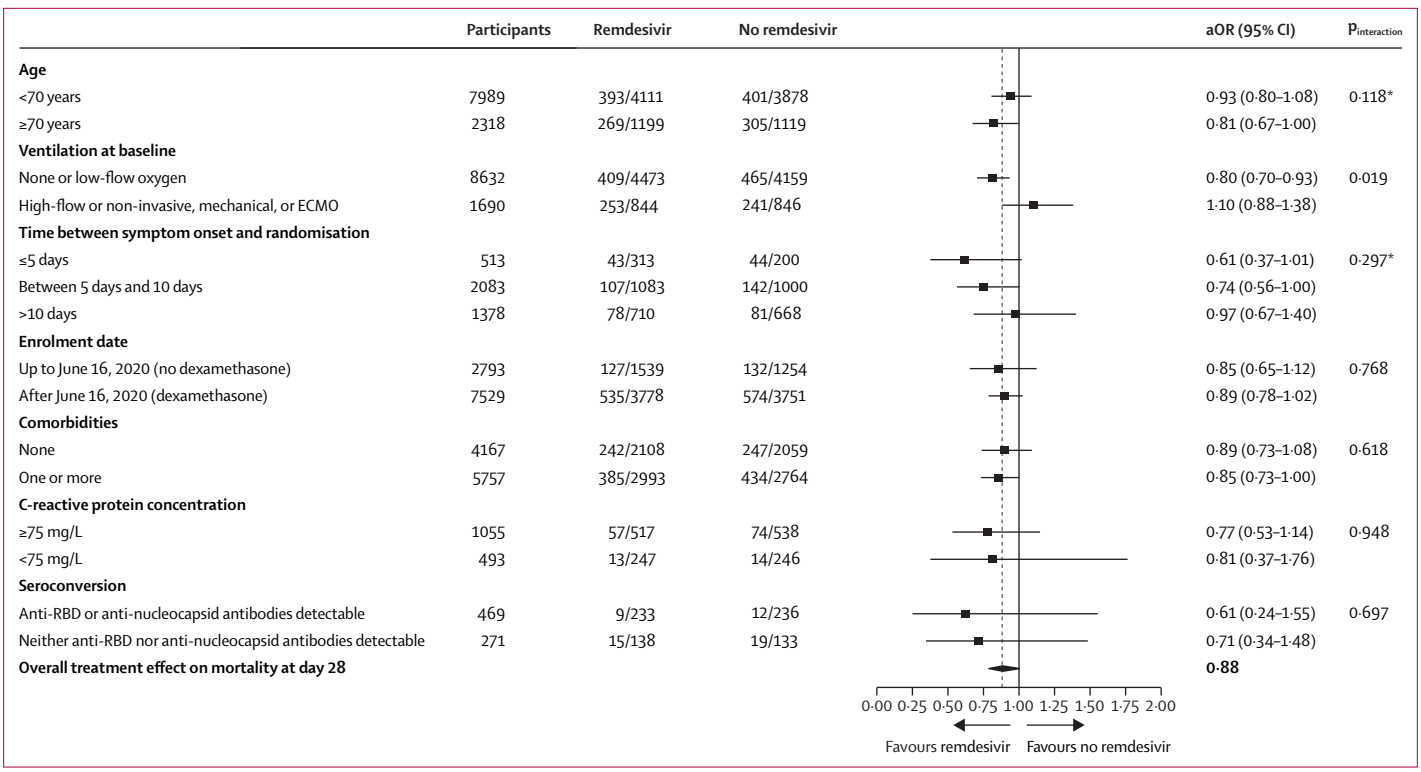

Figure 2: **Forest plot presenting subgroup analyses for the primary endpoint**
aOR=adjusted odds ratio. ECMO=extracorporeal membrane oxygenation. RBD=receptor-binding domain. *$p_{interaction}$ from the main model using the covariate as the continuous linear interaction term.

similar results, except for the outcome days until discharge (appendix p 20): patients in the remdesivir group spent on average 2·25 days less in hospital than those in the no-remdesivir group (aHR 1·29, 95% CI 1·12–1·48, p=0·0003), whereas no difference was observed in the primary analysis using all individual patient data. The meta-analysis with aggregated data from the trial without individual patient data yielded identical results (appendix p 32). The post-hoc sensitivity analysis assessing progression to mechanical ventilation among patients who were not ventilated at baseline and were still alive at day 28 showed that patients who were assigned to remdesivir were less likely to require mechanical ventilation than those who were not (aOR 0·63, 95% CI 0·48–0·83, p=0·0009; appendix p 21).

A moderately credible interaction was found between the level of baseline respiratory support and mortality at day 28 after randomisation (ICEMAN, appendix p 5). Specifically, for patients who did not require oxygen or who were on low-flow oxygen at baseline, mortality in those assigned to remdesivir was 409 (9·1%) of 4473 patients compared with 465 (11·2%) of 4159 patients assigned to no remdesivir (aOR 0·80, 95% CI 0·70–0·93), whereas for patients receiving higher baseline respiratory support, mortality in those assigned to remdesivir was 253 (30·0%) of 844 patients compared with 241 (28·5%) of 846 patients assigned to no remdesivir (1·10, 0·88–1·38; $p_{interaction}$=0·019; figure 2 and appendix pp 22, 33).

The sensitivity analysis, which investigated oxygenation in more detail (appendix p 36), suggested that patients who were receiving no oxygen at baseline derived a similar relative benefit (aOR 0·86, 95% CI 0·53–1·39 with and 0·77, 0·34–1·74 without additional WHO Solidarity data) to patients receiving low-flow oxygen (0·79, 0·68–0·92 with and 0·59, 0·43–0·82 without additional WHO Solidarity data). Similarly, patients requiring high-flow or non-invasive ventilation (1·04, 0·71–1·52 both with and without additional WHO Solidarity data) had similar outcomes to patients requiring mechanical ventilation (1·15, 0·86–1·52 with and 1·07, 0·70–1·65 without additional WHO Solidarity data).

Furthermore, we observed a possible but uncertain effect modification with larger benefit from remdesivir for patients who received the treatment early after symptom onset (figure 2, appendix pp 23, 34, 35; low credibility according to ICEMAN, appendix p 7).

We did not find credible evidence for effect modification by age (figure 2, appendix pp 11, 24, 37, 38), presence of comorbidities (figure 2, pp 9, 25, 39), enrolment period (figure 2, pp 26, 40), or corticosteroid use (appendix p 36).

Evidence for effect modification by C-reactive protein concentration and humoral immune status at baseline (figure 2, appendix pp 27, 28, 41) was inconclusive because

	Study results and measurements	Absolute effect estimates*			Certainty in effect estimates (quality of evidence)	Summary
		Remdesivir	No remdesivir	Absolute difference		
Patients receiving no or low-flow oxygen at start of treatment						
All-cause mortality at day 28	aOR 0·80 (0·70–0·93); based on data from 8632 patients from 8 trials	92 events per 1000 patients	112 events per 1000 patients	20 fewer events per 1000 patients (95% CI 31 fewer to 7 fewer); NNT=50 (if ACR* is 2·5%, NNT=205)	High	Remdesivir reduces 28-day mortality in this patient subgroup
New mechanical ventilation or death at day 28	aOR 0·78 (0·69–0·87); based on data from 8662 patients from 8 trials	155 events per 1000 patients	190 events per 1000 patients	35 fewer events per 1000 patients (95% CI 51 fewer to 21 fewer)	High	Remdesivir reduces progression to mechanical ventilation or death
Time to discharge or to reach discharge criteria up to day 28	aHR 1·02 (0·98–1·07); based on data from 8737 patients from 8 trials	7 days (median)	7 days (median)	0 days (95% CI 0 days to 1 day less for remdesivir)†	Moderate‡	Remdesivir probably has little or no effect on days to hospital discharge
Grade 3 or 4 adverse event or serious adverse event within 28 days	aOR 0·82 (0·68–0·99); based on data from 2810 patients from 6 trials	214 events per 1000 patients	249 events per 1000 patients	35 fewer events per 1000 patients (95% CI 65 fewer to 2 fewer)	Moderate§	Remdesivir probably reduces the risk of severe and serious adverse events
Patients receiving high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO at start of treatment						
All-cause mortality at day 28	aOR 1·10 (0·88–1·38); based on data from 1690 patients from 8 trials	305 events per 1000 patients	285 events per 1000 patients	20 more events per 1000 patients (95% CI 26 fewer to 70 more); NNH=51 (if ACR* is 2·5%, NNH=412)	Low¶	Remdesivir might have little or no effect on 28-day mortality
New mechanical ventilation or death at day 28	aOR 0·91 (0·74–1·11); based on data from 1718 patients from 8 trials	365 events per 1000 patients	387 events per 1000 patients	22 fewer events per 1000 patients (95% CI 69 fewer to 25 more)	Moderate‖	Remdesivir probably has little or no effect on progression to mechanical ventilation or death
Time to discharge or to reach discharge criteria up to day 28	aHR 0·97 (0·84–1·12); based on data from 1729 patients from 8 trials	13 days (median)	13 days (median)	0 days (95% CI 1 day less to 2 days more)†	Low**	Remdesivir might have little or no effect on time to hospital discharge
Grade 3 or 4 adverse event or serious adverse event within 28 days	aOR 0·96 (0·76–1·21); based on data from 1281 patients from 6 trials	463 events per 1000 patients	473 events per 1000 patients	10 fewer events per 1000 patients (95% CI 68 fewer to 48 more)	Low††	Remdesivir might have little or no effect on severe and serious adverse events

aOR=adjusted odds ratio. NNT=number needed to treat. ACR=assumed control risk. aHR=adjusted hazard ratio. ECMO=extracorporeal membrane oxygenation. NNH=number needed to harm. *Assumed control risks: weighted mean baseline risk across all trials (total number of events in control/total observations in control). Alternative ACR for in-hospital mortality (2·5%) based on recent data (May, 2022) from the US Centers for Disease Control.[43] †Median (event-free) survival time (ie, median hospitalisation time), converted according to Grading of Recommendations, Assessment, Development and Evaluations guidelines.[44] ‡Outcome was rated down for risk of bias. §Outcome was rated down for inconsistency. ¶Outcome was rated down twice for imprecision. ‖Outcome was rated down for imprecision. **Outcome was rated down for imprecision and risk of bias. ††Outcome was rated down for imprecision and inconsistency.

Table 4: **Summary of findings and certainty of evidence, by respiratory support**

baseline C-reactive protein concentration was available from only three trials[8,36,37] and serology data from only two trials (table 2).[36,37] On the basis of the observed credible treatment effect modifier, we summarised the main findings in a stratified way following the GRADE approach (table 4).

Discussion

This individual patient data meta-analysis of eight RCTs, for which we obtained individual patient data for 10 480 patients with COVID-19 treated in hospitals worldwide, found a credible subgroup effect of remdesivir by respiratory support at baseline. Results were inconclusive for patients receiving high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO, which might be due to the small sample size. By contrast, in patients receiving no or only low-flow oxygen support, remdesivir reduced mortality within 28 days after randomisation, resulting in 20 fewer deaths per 1000 patients (95% CI 31 fewer to 7 fewer) or a number needed to treat of 50 (high-certainty evidence; table 4).

Although subgroup effects in RCTs need to be viewed critically, the consistent direction of effect modification across individual trials, statistical evidence ($p_{interaction}$=0·019 based on individual patient data), and previous evidence for a similar effect modification[11,45] strengthened the credibility of this subgroup effect (appendix p 5). The pathophysiological reasoning is that respiratory support serves as a proxy measure for disease severity; however it is a rather crude representation of the biological course of COVID-19 and is highly dependent on resources available at local study sites.

Although remdesivir does have specific side-effects (eg, severe bradycardia), we found no empirical evidence from our pooled analysis for any increase in grade 3 or 4 adverse events or serious adverse events, both overall and when stratified by organ system (appendix p 19).

These subgroup findings do not support the recommendations in the NICE guidelines; however, these

guidelines in addition consider cost-effectiveness.[15] The findings do align with several aspects of the NIH guidelines.[12] Remdesivir is recommended for patients treated in hospital for COVID-19 who require only conventional oxygen and not for patients who are receiving mechanical ventilation or ECMO. For patients who require high-flow oxygen or non-invasive ventilation, our detailed subgroup analysis on respiratory support (appendix p 36) suggested that these patients have similar outcomes to patients who receive mechanical ventilation, and therefore does not support recommending remdesivir as part of their treatment. Our findings are in line with the IDSA guidelines[13] and the most recent update of the WHO COVID-19 treatment guidelines,[14] both of which recommend using remdesivir for patients with severe but not critical COVID-19.

There was some evidence to suggest that earlier initiation of remdesivir after symptom onset led to larger treatment effects (appendix p 34). However, owing to insufficient consistency across trials and a $p_{interaction}$ value of 0·297 (assessed as a linear trend), the credibility of this effect modification was low (appendix p 7). We found no evidence for a subgroup effect with respect to age, presence of comorbidities, enrolment period, or corticosteroid use.

Patients in the remdesivir group were not discharged from hospital earlier than those in the no-remdesivir group (table 3). In the sensitivity analysis including only the two placebo-controlled RCTs, patients in the remdesivir group were, on average, discharged 2·25 days earlier than patients in the no-remdesivir group (appendix p 20). This discrepancy might illustrate the difference between efficacy (placebo-controlled RCTs) and effectiveness (pragmatic, open-label RCTs). Although analysis of efficacy is important to assess the pharmacological effects of remdesivir, estimates of effectiveness are crucial to reflect effects under real-life circumstances—eg, that patients might be kept longer in hospital to complete an intravenous treatment.

To our knowledge, this is the first and only individual patient data meta-analysis on the effects of remdesivir in patients treated in hospital for COVID-19, summarising all existing randomised evidence on the topic including adverse events stratified by organ systems. Strengths include a rigorous study protocol with prespecified analyses; standardised outcome definitions across all included trials; robust analysis models accounting for clustering by trial; analysis strictly according to group allocation (intention-to-treat); less than 5% missing data in adjustment variables, subgroup variables and outcome variables (except for viral load, C-reactive protein concentrations, and serology data); and hypothesis-driven, prespecified subgroup analyses, including the assessment of non-linear subgroup effects using the multivariable fractional polynomials interaction approach. We followed current standards for the analysis and reporting of an individual patient data meta-analysis,[16] the interpretation of subgroup effects (ICEMAN[29]), and the assessment of risk of bias, and we present a summary of evidence using the GRADE approach.[30]

Our study has several limitations. First, the study team from one additional eligible RCT,[40] an investigator-initiated trial involving 82 patients with COVID-19 from India, did not provide individual patient data. This trial was included in an aggregate data meta-analysis that yielded similar results. Second, data collection regarding respiratory support was not as detailed in the WHO Solidarity trial as in the other seven included trials and did not differentiate between low-flow and high-flow oxygen use. Four included RCTs[35–37,39] were also part of the WHO Solidarity trial and collected detailed respiratory support data, enabling us to directly compare the two data sources: only 27% of the patients from these four trials who were categorised as receiving low-flow or high-flow oxygen at baseline in the WHO Solidarity dataset received high-flow oxygen (data not shown). The remaining WHO Solidarity trial dataset, without the four abovementioned RCTs, contained individual patient data mostly from the southern hemisphere, where the use of high-flow oxygen or non-invasive ventilation is expected to be even lower. Therefore, classifying the patients from the additional WHO Solidarity trial dataset as receiving low-flow and not high-flow oxygen seemed appropriate. Of note, similar results were obtained with and without the WHO-Solidarity trial data (appendix p 36). Third, our analysis included only two placebo-controlled RCTs, which is important when investigating treatment efficacy, particularly for outcomes that might be biased by knowledge of treatment assignment, such as time to discharge. Fourth, some subgroup analyses (C-reactive protein concentrations and antibody response) lacked statistical power. Therefore, conclusive evidence on the effect of remdesivir among patients who have not or not yet mounted an immune response, as has been investigated for other COVID-19 treatments, could not be obtained.[28] Similarly, a substantial amount of data were missing for the secondary outcome of viral clearance (only three trials provided data), and these analyses were therefore underpowered to resolve previous conflicting evidence.[46,47] Additional virological data, such as viraemia or antigen concentrations, were not available from any included trial. Fifth, our data did not include patients with SARS-CoV-2 variants that were in widespread circulation only after April, 2021—ie, delta (B.1.617.2), omicron (B.1.1.529), or their sublineages. Remdesivir targets the RNA polymerase and, therefore, maintains efficacy against emerging SARS-CoV-2 variants of concern,[48,49] and has regained importance in clinical care owing to increasing resistance to current monoclonal antibodies.[50] However, whether a young patient admitted to intensive care with any given dominant variant of SARS-CoV-2 would benefit from remdesivir remains uncertain. Finally, our analysis included only patients who had not received any doses of a COVID-19 vaccine, and few

patients received monoclonal antibodies or another immunomodulatory therapy (appendix p 16). The absolute risk reductions with remdesivir will be smaller in a better-protected population. As an example, assuming a control group mortality risk of 2·5% among non-ventilated patients hospitalised with COVID-19—based on recent in-hospital mortality data from the USA[43]—the number needed to treat increases from 50 to 205.

This work also provides lessons for the clinical research community. Single trials, even those powered for moderate effects, will often fail to provide definitive answers, let alone answers regarding effect modification. A culture of international collaboration—ideally using large, pragmatic, coordinated trial protocols with outcomes of importance to patients[51] and prospective meta-analyses of individual patient data—is required to maximise the clinical information obtained from expensive and arduous clinical trials.

In summary, this individual patient data meta-analysis showed that remdesivir reduced mortality in the subgroup of patients hospitalised with COVID-19 who required no or only low-flow oxygen support, but was inconclusive in patients requiring more respiratory support. The effect size of remdesivir in patients who have received a complete dose of a COVID-19 vaccine, a booster dose, or who have pre-existing immunity from previous infection remain to be further elucidated.

Contributors

AA, BS, CB, CSR, DB, DC, FMe, ICO, LA, MBr, and SS developed the concept and designed the study. FMe, CB, SM, LED, YW, KAOT, FA, MH, MBo, MAT, MF, TCL, RP, AB-D, FL-J, FMü, OPON, BC, and TB collected the data. AG, ATH, BS, CS, MBr, and PJ conducted systematic searches. AA, ATH, and LW managed the data. AA did the statistical analysis. MBr, SA, and SS were responsible for statistical supervision. AA, BS, and MBr accessed and verified the data. AA, BS, MBr, SA, and SS interpreted the results. AA, BS, and MBr wrote the first draft of the manuscript and all authors critically revised the manuscript for important intellectual content. YY obtained funding and provided administrative and technical support. MBr supervised the study. All authors were responsible for the decision to submit the manuscript to the journal.

Declaration of interests

DC reports an HIV grant from Janssen and personal fees from Gilead Sciences and Pfizer for lectures outside of the submitted work. MBr and BS report an unrestricted grant from Moderna for a study outside of the submitted work. TCL reports salary support from the Fonds de Recherche du Québec Santé. MH reports personal fees from Gilead Sciences and Pfizer for lectures outside of the submitted work, and congress and travel fees from Pfizer and Gilead Sciences. ICO reports funding from BerGenBio for a study outside of the submitted work. All other authors declare no competing interests.

Data sharing

Data from individual RCTs were provided by trial groups for the specific purpose of conducting this individual patient data meta-analysis. Any requests by other researchers for those data should be directed to the responsible party for individual trials.

Acknowledgments

We thank Benjamin Kasenda for his advice and support regarding multifractional polynomial interaction analysis; Marius Trøseid and Nina Khanna for reviewing the protocol as infectious disease experts; Lars Hemkens for methodological input on the protocol; and Marco Cattaneo, Fabrice Helfenstein, and Nikki Rommers for statistical advice. We are grateful to our patient representatives, Stephan Schobinger and Rosine Mucklow, who gave valuable input during development of the study protocol and drafting of the manuscript. This systematic review and individual patient data meta-analysis was initiated and funded by EU-RESPONSE (grant number 101015736). BS is supported by an Advanced Postdoc.Mobility return grant (grant number P4P4PM_194496) from the Swiss National Science Foundation and the Research Foundation of the University of Basel.

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