NICE National Institute for Health and Care Excellence

Evidence review

Remdesivir for treating hospitalised patients with suspected or confirmed COVID-19

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This evidence review sets out the best available evidence on remdesivir for treating hospitalised patients with suspected or confirmed COVID-19. It should be read in conjunction with the evidence summary, which gives the key messages.

Commissioned by NHS England

Disclaimer

The content of this evidence review was up-to-date on 4 June 2020. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information. For details on the date the searches for evidence were conducted see the search strategy.

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Background

As of 26 May 2020, over 5.4 million people globally and 261,188 people in the UK have developed coronavirus disease 2019 (COVID-19) (World Health Organisation [WHO] 2020), a disease caused by a novel coronavirus which emerged in Wuhan, China in December 2019. Other diseases caused by coronaviruses include severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) as well as the common cold. It has caused a fast-moving public health crisis globally, as countries impose a range of restrictions on daily life to contain the spread of disease.

COVID-19 manifests as a predominantly respiratory illness, of widely varying clinical severity. At the most severe end of the spectrum it results in severe pneumonia and respiratory failure with the need for mechanical ventilation. Acute respiratory distress syndrome (ARDS) is often a pre-terminal event in patients with COVID-19 and is the leading cause of mortality. Observational studies have shown an association between systemic inflammation, comorbidities, age, gender, ethnic background and adverse outcomes in COVID-19 (Huang et al. 2020, Liang et al. 2020a, Ruan et al. 2020, Williamson et al. 2020, Zhou et al. 2020). COVID-19 risk scores have been developed to predict the development of critical illness among hospitalised COVID-19 infected patients (Liang et al. 2020b, Galloway et al. 2020). NICE has published guidelines for managing symptoms and complications of COVID-19.

Intervention

Remdesivir is an adenosine nucleotide prodrug that is metabolised intracellularly to form the pharmacologically active substrate remdesivir triphosphate. Remdesivir triphosphate inhibits SARS-CoV-2 RNA polymerase which prevents viral replication.

Remdesivir is the first COVID-19 treatment to receive a positive scientific opinion by the Medicines and Healthcare products Regulatory Agency (MHRA), based on advice from the Commission on Human medicines, under the rapid early access to medicines scheme (EAMS) by meeting the EAMS published access criteria. Remdesivir is indicated for the treatment of adults and young people aged 12 years and over and weighing at least 40 kg hospitalised with suspected or laboratory

confirmed SARS-CoV-2 infection and severe disease. Severe disease is defined as patients with either peripheral oxygen saturation of 94% or less on room air, or requiring supplementary oxygen, or patients requiring non-invasive or invasive ventilation or extracorporeal membrane oxygenation (ECMO) (MHRA: treatment protocol for healthcare professionals, EAMS 11972/0001 and 11972/0002, remdesivir 100 mg concentrate for solution for infusion).

The suggested dosage in adults and young people aged 12 years and over who require invasive ventilation and/or ECMO, is a single dose of remdesivir 200 mg on day 1 followed by once daily maintenance doses of remdesivir 100 mg for 9 days (10 day course in total). The suggested dosage in adults and young people aged 12 years and over, not requiring invasive ventilation or ECMO is a single dose of remdesivir 200 mg on day 1 followed by once daily maintenance doses of remdesivir 100 mg for 4 days (5 day course in total). If a patient does not demonstrate clinical improvement or deteriorates and progresses to ventilation or ECMO, treatment may be extended for up to 5 additional days (up to 10 day course in total). Remdesivir is administered by intravenous infusion.

Children aged under 12 years and pregnant women can access remdesivir through a separate compassionate use scheme operated by the manufacturer Gilead (MHRA central alerting system: Update - Early Access to Medicines Scheme for remdesivir in the treatment of COVID-19).

Clinical problem

This is a rapidly evolving pandemic globally, with countries facing different stages of the spread of disease. Initial hospital data from the UK suggest that increasing age over 50 years is a strong predictor of mortality in hospital (hazard ratio [HR] 4.02 for 50–69 years, 9.6 for 70–79 years and 13.6 for 80 years or over; Docherty et al. 2020). Children and young people appear to be less affected by the virus, with low numbers of deaths and critical care admissions in this age group (Lu et al. 2020). UK primary care record data from 17.4 million patients showed death in hospital from COVID-19 was strongly associated with male gender, older age, Black or Asian ethnicity, deprivation, uncontrolled diabetes and severe asthma. As of 28 May 2020, the Intensive Care National Audit Research Centre (ICNARC) was notified of 12,086

admissions for critical care with confirmed COVID-19 in England, Wales and Northern Ireland (ICNARC 2020).

Treatment options for COVID-19 are limited and there are trials underway to assess the efficacy of available medicines to manage the disease.

Objective

This review aims to establish the clinical effectiveness, safety and cost effectiveness of remdesivir in adults, young people and children hospitalised with suspected or confirmed COVID-19.

Methodology

A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) for this review was provided by NHS England for the topic (see the search strategy section for more information). The research questions for this evidence review are:

1. In adults, young people and children hospitalised with suspected or confirmed COVID-19[1], what is the clinical effectiveness of remdesivir compared with placebo or standard care[2]?

2. In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the safety of remdesivir compared with placebo or standard care?

3. In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the cost effectiveness of remdesivir compared with placebo or standard care?

4. From the evidence selected, are there any subgroups of patients that may benefit or be harmed from remdesivir more than the wider population of interest?

[1] COVID-19 is the acute clinical syndrome caused by SARS-CoV-2 virus
[2] Standard care can vary according to country. In the UK, standard care for COVID-19 is supportive treatment.

5. From the evidence selected:

    a. what definitions have been used/developed to describe 'moderate' and 'severe' COVID-19?

    b. what is the duration of remdesivir treatment?

A literature search was undertaken by NICE Information Services team. Results were screened using their titles and abstracts for relevance against the criteria from the PICO, by 2 reviewers. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the PICO inclusion criteria for this evidence review. More information can be found in the sections on search strategy and evidence selection.

The evidence review was developed using a modified version of the NHS England process for developing evidence reviews.

Summary of included studies

Three studies identified from the search are included in this evidence summary. Two studies (Beigel et al. 2020 and Wang et al. 2020) are phase 3 double-blinded, placebo-controlled randomised controlled trials (RCT) and 1 study is an observational study (Grein et al. 2020). A meta-analysis of the 2 included RCTs (Cochrane 2020) was also identified following the search and included.

This evidence review reports results from the meta-analysis reported by Cochrane (2020) for which outcome results were based on 2 RCTs. Cochrane (2020) results based on a single RCT have not been used in this review as the review reports findings using results from Beigel et al (2020) and Wang et al (2020). Additional results from Grein et al (2020) have been used to supplement this review for outcomes that have not been covered by Cochrane (2020), Beigel et al (2020) and Wang et al (2020).

A summary of included studies is shown in table 1. See Appendix D for quality assessment of the included studies.

Table 1 Summary of included studies

Study	Population	Intervention	Outcome
Beigel et al. 2020 (Adaptive COVID-19 Treatment Trial-1 study [ACTT]) Double-blind, placebo-controlled RCT 73 sites: Denmark (n=8), Germany (n=3), Greece (n=4), Japan (n=1), Korea (n=2), Mexico (n=2), Singapore (n=1), Spain (n=2), UK (n=5), US (n=45)	1063 adults aged ≥ 18 years (mean age 58.9 years, 36% female, 15% European, and 33% black or Asian) Comorbidities included hypertension (50%), obesity (37%) and type 2 diabetes (30%) 89% were classed as having severe[1] disease at baseline 12% were in category 4, 40% were in category 5, 19% in category 6 and 26% in category 7 of the 8-point ordinal scale[2] of clinical status at baseline Median time from symptom onset to randomisation was 9 days (IQR 6–12)	IV remdesivir 200 mg on day 1 followed by 100 mg on days 2–10 or until discharge or death Comparator: placebo Follow-up: 29 days	**Primary outcome:** Time to recovery[3] **Key secondary outcomes:** Mortality at days 14 and 28 Difference in clinical status, defined by the 8-category scale at day 15[2] Grade 3 and 4 adverse events Serious adverse events
Cochrane 2020 Meta-analysis of Beigel et al. 2020 and Wang et al. 2020	See RCTs	Remdesivir, see RCTs	Clinical improvement WHO progression score (level 6/7 or above) All-cause mortality Serious adverse events
Grein et al. 2020 Case series Austria (n=1 patient), Canada (n=1). France (n=4), Germany (n=2), Italy (n=12), Japan (n=9), Netherlands (n=1),	53 adults with median age of 64 years (IQR 48–71), 25% female[4] 64% on invasive ventilation of which 57% and 8% were on invasive	IV remdesivir 200 mg on day 1 followed by 100 mg for 9 days No comparator Follow-up 28 days	Endpoints were not prespecified. The following were quantified in the study: Changes in oxygen support requirements[5] Hospital discharge

Study	Population	Intervention	Outcome
Spain (n=1), and US (n=22)	mechanical ventilation and ECMO Comorbidities included hypertension (25%), diabetes mellitus (17%), hyperlipidaemia (11%) and asthma (11%) Median duration of symptoms before remdesivir was 12 days (IQR 9–15) Median ALT, AST and creatinine levels were 37 IU/l, 26 IU/l and 79 micromoles/l		Adverse events Clinical improvement[6]
Wang et al. 2020 Double-blind, placebo-controlled, multicentre RCT 10 hospitals in China	237 adults aged ≥ 18 years (median age of 65 years [IQR 56–71], 41% female)[7] Comorbidities included hypertension (43%), diabetes (24%) and CHD (7%) 18% were taking lopinavir-ritonavir at baseline 4% were in category 2, 82% were in category 3, 16% were in category 4, 1% in category 5 and 1% in category 6 of the 6-point ordinal scale[8] of clinical status at baseline	IV remdesivir 200 mg on day 1 followed by 100 mg on days 2–10 Comparator: placebo Follow-up: 28 days	**Primary outcome:** Time to clinical improvement up to day 28[9] after randomisation **Key secondary outcomes:** Proportion of patients in each category of the 6-point scale at days 7,14 and 28 All-cause mortality at day 28 Frequency of invasive mechanical ventilation Duration of oxygen therapy Duration of hospital admission Proportion of patients with viral RNA detected and viral RNA load

Study	Population	Intervention	Outcome
	Median time from symptom onset to starting study treatment was 10 days (IQR 9–12)		Treatment-emergent adverse events Serious adverse events Discontinuations

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHD, coronary heart disease; ECMO, extracorporeal membrane oxygenation; IU/l, international units/litre; IV, intravenous; IQR, interquartile range; NIPPV, non-invasive positive pressure ventilation; RCT, randomised controlled trial; RT-PCR, reverse transcription, polymerase-chain-reaction; RNA, ribonucleic acid; SpO_2, peripheral oxygen saturation

[1] Beigel et al (2020) defined severe disease as participants meeting 1 or more of the following criteria: requiring invasive or non-invasive mechanical ventilation, requiring supplemental oxygen, an SpO2≤ 94% on room air, or tachypnoea (respiratory rate ≥ 24 breaths per minute). Mild or moderate disease was defined by an SpO2 > 94% and respiratory rate < 24 breaths per minute without supplemental oxygen requirement.

[2] The 8-point categories are as follows: 1=not hospitalised, no limitations of activities; 2=not hospitalised, limitation of activities, home oxygen requirement, or both; 3=hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalisation was extended for infection-control reasons); 4=hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19–related or other medical conditions); 5=hospitalised, requiring any supplemental oxygen; 6=hospitalised, requiring non-invasive ventilation or use of high-flow oxygen devices; 7=hospitalised, receiving invasive mechanical ventilation or ECMO; and 8=death.

[3] The time to recovery was defined as the first day, during the 28 days after enrolment, on which a patient satisfied categories 1, 2, or 3 on the 8-category ordinal scale

[4] Approved use was in hospitalised patients who had SARS-CoV-2 infection confirmed by RT-PCR and either an oxygen saturation of 94% or less while the patient was breathing ambient air or a need for oxygen support.

[5] This included ambient air, low-flow oxygen, nasal high-flow oxygen, NIPPV, invasive mechanical ventilation, and ECMO.

[6] This was defined by live discharge from hospital, a decrease of at least 2 points from baseline on a modified ordinal scale see footnote 8, similar scale used as in Wang et al (2020)

[7] Patients were RT-PCR, positive for SARS-CoV-2, had confirmed pneumonia, oxygen saturation of ≤ 94% on room air/ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤ 300 mm Hg and within 12 days of symptom onset.

[8] The 6-point scale was as follows: 1=discharged or having reached discharge criteria (defined as clinical recovery such as normalisation of pyrexia, respiratory rate <24 breaths per minute, SpO_2>94% on room air, and relief of cough, all maintained for at least 72 h); 2=hospital admission but not requiring oxygen therapy; 3=hospital admission for oxygen therapy (but not requiring high-flow or non-invasive ventilation); 4=hospital admission for non-invasive ventilation or high-flow oxygen therapy; 5=hospital admission for ECMO or mechanical ventilation; 6=death.

[9] Defined as the time (in days) from randomisation to the point of a decline of 2 levels on a 6-point ordinal scale of clinical status (from 1=discharged to 6=death) or discharged alive from hospital, whichever came first.

Details of the excluded studies are listed in the section on evidence selection.

Effectiveness and safety

Research question 1. In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the clinical effectiveness of remdesivir compared with placebo or standard care?

Mortality

Cochrane (2020) found no statistically significant difference in all-cause mortality at days 14 to 28 with remdesivir compared with placebo (2 RCTs, n=1299: relative risk [RR] 0.74, 95% confidence interval [CI] 0.40 to 1.37, I^2 58%; low certainty).

Clinical improvement

Beigel et al (2020) found that patients with mild or moderate, or severe COVID-19 in the remdesivir group had a statistically significant shorter time to recovery than patients in the placebo group (median time 11 days compared with 15 days, recovery rate ratio 1.32, 95% confidence interval [CI] 1.12 to 1.55, p<0.001).

Wang et al (2020) found that for patients with severe COVID-19, the median time to clinical improvement was 21 days (13–28 days) in the remdesivir group compared with 23 days in the placebo group (15–28 days). Remdesivir was not associated with a statistically significant difference in time to clinical improvement (HR 1.23, 95% CI 0.87 to 1.75) compared with placebo. (Note Wang et al. 2020 reported the statistical power of the study to be 58% due to reduced enrolment of patients in the study.)

Length of hospital stay

Wang et al (2020) found no statistically significant difference between the remdesivir and placebo groups in the duration of hospital stay (25 days compared with 24 days respectively, difference 0 days [–4 to 4 days]).

Supportive measures

Cochrane (2020) found a statistically significant reduction in the incidence of WHO progression score level 6 or above at days 14 to 28 with remdesivir compared with placebo (2 RCTs, n=1299: RR 0.76, 95% CI 0.62 to 0.93, I^2 0%; high certainty). This outcome included non-invasive ventilation/high-flow oxygen or mechanical ventilation with or without additional organ support (ECMO, vasopressors or dialysis) or death.

Similar results were seen for the incidence of WHO progression score level 7 or above at days 14 to 28 (2 RCTs, n=1299: RR 0.73, 95% CI 0.58 to 0.91, I^2 0%; high certainty). This outcome included mechanical ventilation with or without additional organ support (ECMO, vasopressors or dialysis) or death.

Wang et al. 2020 found that the duration of invasive mechanical ventilation was shorter in the remdesivir group compared with the placebo group (8 days and 16 days respectively, difference –8 days [–19 to 0 days], reported as not statistically significant). The authors state that the number receiving this supportive measure was small, 21 people in total (7% in the remdesivir group and 11% in the placebo

group). The duration of oxygen support was also shorter in the remdesivir group compared with placebo group (19 days and 21 days respectively, difference –2 days [–6 to 1 days], reported as not statistically significant).The median or mean unit of measure was not reported for these results.

SARS-CoV-2 viral measures

Wang et al (2020) reported the baseline viral load of nasopharyngeal and oropharyngeal swabs to be 4.7 $\log_{10}$ copies/ml (standard error [SE] 0.3) in the remdesivir group and 4.7 $\log_{10}$ copies/ml (SE 0.4) in the control group. By day 28 the viral load was reported to have decreased over time similarly in both groups to approximately less than 1 $\log_{10}$ copies per ml (exact figures not reported). No differences were seen between the 2 treatment groups for patients who were treated within or after 10 days of symptom onset. The cumulative rate of undetectable viral RNA of nasopharyngeal and oropharyngeal swabs by day 28 was not different between the remdesivir and placebo groups (75.6% and 83.1% respectively, difference –7.5 [95% CI –19.2 to 4.2]). These results were not statistically significant.

Research question 2. In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the safety of remdesivir compared with placebo or standard care?

Cochrane (2020) found there were statistically significantly fewer serious adverse events (not clearly defined in the studies) with remdesivir compared with placebo (2 RCTs, n=1296: RR 0.77, 95% CI 0.63 to 0.94, I^2 0%; moderate certainty). Beigel et al (2020) reported respiratory failure to be the most common serious adverse events in remdesivir and placebo groups (5.2% and 8.0% respectively). Wang et al (2020) reported that the most common serious adverse events in remdesivir and placebo groups were respiratory failure or acute respiratory distress syndrome (10.3% and 7.6% respectively) and cardiopulmonary failure (5.1% vs 8.9%).

Beigel et al (2020) found that adverse events (occurring in 5 or more patients) were reported in 28.8% (n=156) of remdesivir group compared with 33.0% (n=172) of the placebo group. Most commonly reported in the remdesivir group compared with placebo were anaemia or decreased haemoglobin (7.9% and 9% respectively); acute kidney injury, decreased estimated glomerular filtration rate or creatinine clearance, or increased blood creatinine (7.4% compared with 7.3%), pyrexia (5.0%

compared with 3.3%); hyperglycemia or increased blood glucose level (4.1% compared with 3.3%), and increased aminotransferase levels including alanine aminotransferase, aspartate aminotransferase, or both (4.1% compared with 5.9%). Treatment discontinuations were similar in the 2 groups where 36 patients in each group discontinued treatment because of an adverse event or serious adverse event other than death.

Wang et al. found that adverse events (occurring in 2% or more patients) were reported in 65.8% (n=102) of remdesivir group compared with 64.1% (n=50) of the placebo group. Common adverse events in the remdesivir and placebo groups included constipation (13.5% and 15.3% respectively), hypoalbuminaemia (12.9% and 15.3%), hypokalaemia (11.6% and 14.1%), anaemia (11.6% and 15.3%), thrombocytopenia (10.3% and 6.4%), aspartate aminotransferase (4.5% and 11.5%) and increased total bilirubin (9.6% and 8.9%). More patients in the remdesivir group discontinued treatment because of adverse events or serious adverse events compared with placebo group (11.6% and 5.1% respectively), of which 4.5% were due to respiratory failure or acute respiratory distress syndrome in the remdesivir group.

Beigel et al (2020) and Wang et el (2020) state that deaths reported in the study were not related to remdesivir.

Research question 3. In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the cost effectiveness of remdesivir compared with placebo or standard care?

No studies were found to assess cost effectiveness.

Research question 4. From the evidence selected, are there any subgroups of patients that may benefit or be harmed from remdesivir more than the wider population of interest?

Beigel et al (2020) and Grein et al (2020) both advise caution in interpreting data their subgroup analyses (with the exception of severity of disease) because the widths of the confidence intervals have not been adjusted for multiplicity.

Time to starting treatment

Beigel et al (2020) found that the time to recovery was statistically significantly shorter with remdesivir compared with placebo in patients who received treatment

both within and after 10 days of onset of symptoms (recovery rate ratio 1.28 days [95% CI 1.05 to 1.57] and 1.38 days [95% CI 1.05 to 1.81] p-values not reported, respectively).

Wang et al (2020) found that there was no statistically significant difference in 28-day mortality between remdesivir and placebo groups in patients who started treatment within 10 days (11.2% vs 14.8% respectively, difference –3.6% [–16.2 to 8.9]) or after 10 days of onset of symptoms and 14.2% vs 9.6% respectively, difference 4.6% [–8.2 to 17.4]).

Wang et al (2020) also found that the time to clinical improvement was faster with remdesivir compared with placebo in patients who started treatment within 10 days of symptom onset (median 18 days and 23 days respectively, HR 1.52 [95% CI 0.95 to 2.43]) although this was not statistically significant. In patients who started treatment after 10 days of symptom onset there was no difference found between remdesivir and placebo groups for this outcome (median 23 days and 24 days respectively, HR 1.07 [95% CI 0.63 to 1.83], not statistically significant).

Severity of disease

Beigel et al (2020) found that patients with severe disease had a statistically significantly shorter time to recovery in the remdesivir group than the placebo group (median time of 12 days and 18 days respectively, rate ratio 1.37 [95% CI 1.15 to 1.63], p-value not reported). Patients with mild or moderate disease had similar times to recovery (not statistically significant) in the remdesivir and the placebo groups, median of 5 days (rate ratio 1.09, 95% CI 0.73 to 1.62, p-value not reported).

Beigel at el (2020) also found that in patients with severe disease, 14-day mortality was found to be lower in the remdesivir group (31 deaths) compared with the placebo group (53 deaths) (HR 0.71 [95% CI 0.48 to 1.05], p-value not reported). Number of deaths reported in patients with mild or moderate disease was 1 in each group (HR 0.48 [95% CI 0.04 to 5.27], p-value not reported). Both results were not statistically significant.

Geographic region

Beigel et al (2020) found that the time to recovery was statistically significantly shorter with remdesivir compared with placebo for patients treated in North America (recovery rate ratio 1.33, [95% CI 1.11 to 1.59], p-value not reported, n=844). No statistically significant difference was found between the 2 groups for patients treated in Europe (recovery rate ratio 1.40, [95% CI 0.90 to 2.16], p-value not reported, n=163) or Asia (recovery rate ratio 1.20, [95% CI 0.65 to 2.22], p-value not reported, n=52).

Race

Beigel et al (2020) found that the time to recovery was statistically significantly shorter with remdesivir compared with placebo in white patients (recovery rate ratio 1.39 [95% CI 1.12 to 1.73], p-value not reported, n=563). No statistically significant differences were found between the 2 groups in the Asian and black minority groups (recovery rate ratio 1.04 [95% CI 0.68 to 1.57], n=134 and 1.14 [95% CI 0.81 to 1.61], n=219, respectively, p-values not reported).

Age

Beigel et al (2020) found that the time to recovery was statistically significantly shorter with remdesivir compared with placebo in patients aged between 18 and 39 years and in patients aged 65 years or over (recovery rate ratio 2.03 [95% CI 1.31 to 3.15], n=119 and 1.37 [95% CI 1.02 to 1.83], n=382, respectively, p-values not reported). No statistically significant difference was found between the 2 groups in patients aged between 40 and 64 years (recovery rate ratio 1.16 [95% CI 0.94 to 1.14], p-value not reported, n=558).

Grein et al (2020) found that the risk of death was statistically significantly greater among patients who were aged 70 years or over who had COVID-19 and were taking remdesivir (HR as compared with patients younger than 70 years, 11.34 [95% CI 1.36 to 94.17]).

Gender

Beigel et al (2020) found that the time to recovery was statistically significantly shorter with remdesivir compared with placebo in both female and male subgroups

(recovery rate ratio 1.38 [95% CI 1.05 to 1.81], n=377 and 1.31 [95% CI 1.07 to 1.59], n=682, respectively, p-values not reported).

Comorbidities

Grein et al (2020) found that having comorbidities such as hypertension, diabetes mellitus, hyperlipidaemia and asthma were not associated with statistically significant clinical improvements with remdesivir (HR 0.73 [95 % CI 0.32 to 1.69], HR 0.53 [95% CI 0.16 to 1.76], HR 0.70 [95% CI 0.21 to 2.30] and HR 2.00 [95% CI 0.75 to 5.34] respectively). This was also true for mortality (authors report the median interval between remdesivir treatment initiation and death was 15 days). The risk of death with remdesivir was not statistically significantly associated with having diabetes mellitus (HR 2.05 [95% CI 0.40 to 10.57]), hyperlipidaemia (HR 1.28 [95% CI 0.15 to 10.67]) or asthma (HR 1.54 [95% CI 0.18 to 13.04)]. However, the risk of death was reported to be statistically significantly greater in patients who had a higher serum creatinine at baseline (HR 1.91 [95% CI 1.22 to 2.99]). No deaths were observed in patients with hypertension.

Effects of invasive and non-invasive ventilation

Grein et al (2020) found that clinical improvement was statistically significantly less common in patients receiving invasive ventilation compared with those receiving non-invasive ventilation (HR 0.33 [95% CI 0.16 to 0.68]). There was no statistically significant difference in mortality in patients receiving invasive ventilation (0.57 per 100 hospitalisation days, [95% CI 0.0 to 1.20]) compared with those receiving non-invasive ventilation (0.51 per 100 hospitalisation days, [95% CI 0.07 to 1.10]).

Research question 5. From the evidence selected:

a. what definitions have been used/developed to describe 'moderate' and 'severe' COVID-19?

There were some differences in how 'severe disease' was described in the included studies. Beigel et al (2020) described 'severe' as requiring invasive or non-invasive mechanical ventilation, requiring supplemental oxygen, a peripheral oxygen saturation of 94% or less on room air, or a respiratory rate 24 breaths per minute or more). Mild or moderate disease was defined by a peripheral oxygen saturation of more than 94% and respiratory rate of less than 24 breaths per minute without

supplemental oxygen requirement. Wang et al (2020) did not explicitly define 'severe', however the study only included patients with 'severe disease' who had to have confirmed pneumonia, oxygen saturation of 94% or less on room air or ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less. Grein et al (2020) did not explicitly define 'severe' however use of remdesivir was only approved in hospitalised patients who had SARS-CoV-2 infection confirmed by RT-PCR and either an oxygen saturation of 94% or less while the patient was breathing ambient air or a need for oxygen support. See section on Intervention for the definition described in the remdesivir treatment protocol.

b. what is the duration of remdesivir treatment?

None of the included studies reported data on average treatment duration. However, in the studies reported in Beigel et al (2020) and Wang et al (2020), remdesivir was administered for a duration of 2 to 10 days in both. In Grein et al (2020) remdesivir was administered for a total duration of 10 days.

Discussion and limitations of the evidence

Remdesivir has not been studied in the paediatric population or in pregnant women with COVID-19 and there are currently limited safety data. In addition, no data were found for the outcomes of disease complications, ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) and cost effectiveness. The included studies compared remdesivir with placebo and no data are available for its effects compared with a different active comparator (as there are limited treatment options for treating COVID-19).

The definition of severe COVID-19 disease differed in the included studies, the common feature was having a peripheral oxygen saturation of 94% or less on room air. Of the included studies, Beigel et al (2020) had a clear definition for both severe and mild or moderate COVID-19 disease. No average duration of remdesivir was reported in the studies. All studies used a treatment duration of up to 10 days. A study by Goldman et al (2020) looked at the efficacy of remdesivir when taken for 5 days or 10 days and reported that there was no statistically significant difference between the 2 treatment durations. This study was excluded from this review because it did not meet the relevant comparator criteria.

In terms of efficacy, the Cochrane (2020) meta-analysis reported fewer deaths with remdesivir compared with placebo and there was no significant difference for mortality at days 14 to 28. However, the meta-analysis reported remdesivir to be significantly better than placebo for reducing the need for supportive measures such as non-invasive ventilation/high-flow oxygen or mechanical ventilation with or without additional organ support in patients on WHO progression score level 6/7 or above at days 14 to 28. Beigel et al (2020) reported that the time to recovery was significantly shorter (by 4 days) with remdesivir compared with placebo. Wang et al (2020) reported remdesivir was better in reducing the time to clinical improvement and the duration of invasive mechanical ventilation and oxygen support compared with placebo (not statistically significant for both). However, Wang et al (2020) reported no statistically significant difference between remdesivir and placebo in length of hospital stay, viral RNA load and viral RNA detectability. The study by Wang et al (2020) was not powered to assess significant difference in the outcomes reported, consequently the findings should be interpreted with caution.

In terms of subgroup analyses, in patients receiving treatment within or after 10 days of symptom onset: Beigel et al (2020) reported that the remdesivir group recovered within a shorter time compared with placebo (statistically significant difference) in both subgroups; Wang et al (2020) reported that there was faster clinical improvement with remdesivir compared with placebo when starting treatment within 10 days of symptom onset (although not statistically significant), however no statistically significant difference was observed when treatment was started after 10 days of symptom onset; no statistically significant differences were seen for 28-day mortality when remdesivir was compared with placebo for these 2 subgroups. Beigel et al (2020) reported that patients with severe disease in the remdesivir group had a shorter time to recovery (statistically significant) and lower 14-day mortality (not statistically significant) compared with placebo, whereas no difference was reported in people with mild or moderate disease. Beigel et al (2020) found the time to recovery was statistically significantly shorter with remdesivir compared with placebo in patients for the following: from North America; of a white origin; aged from 18 to 39 years or aged 65 or over. Grein et al (2020) reported that clinical improvement was statistically significantly less common in patients receiving invasive ventilation compared with those receiving non-invasive ventilation. Grein et al (2020)

reported that in patients on remdesivir, death was statistically significantly greater in patients aged 70 or over and in patients who had a higher serum creatinine at baseline (this was not defined by the authors). Subgroup analyses reported by Beigel et al (2020) and Grein et al (2020) should be interpreted with caution because the authors state that inferences on treatment effects cannot be made because of wide confidence intervals and presence of multiplicity.

In terms of safety, Cochrane (2020) found there were significantly fewer serious adverse events with remdesivir compared with placebo. The individual RCTs reported the common serious adverse events with remdesivir and placebo to be respiratory failure, acute respiratory distress syndrome and cardiopulmonary failure. Beigel et al (2020) reported that 4 of the 114 serious adverse events were thought to be due to remdesivir or placebo (2 in each group) which may indicate that the rest of the adverse events may have been related to COVID-19 or underlying comorbidities. It was unclear in Wang et al (2020) and Grein et al (2020) whether serious adverse events were related to COVID-19 or remdesivir. Adverse events relating to kidney and liver biomarkers were not significantly different when remdesivir was compared with placebo in the 2 RCTs. This may have been due to the studies excluding patients with impaired renal function and alanine aminotransferase or aspartate aminotransferase 5 times the upper limit of the normal range. Consequently, there are no data in patients with renal or liver impairment. Wang et al (2020) reported that a higher proportion of patients in the remdesivir group compared with placebo group had dosing prematurely stopped by the investigators because of adverse events, including gastrointestinal symptoms (anorexia, nausea, and vomiting), aminotransferase or bilirubin increases and worsened cardiopulmonary status.

Patients included in all the studies were hospitalised and required supplemental oxygen or other supportive treatments such as invasive ventilation. Enrolled patients were, on average, older with comorbidities such as hypertension and diabetes (type 2 reported in 2 studies) and were required to have stable renal and hepatic function. The median time from symptom onset to starting treatment was between 9 and 12 days. The dose of remdesivir was the same in all the included studies. Patients could receive supportive care and use other interventions if allowed according to the treatment protocols (for example in Wang et al. 2020 patients could continue with

lopinavir-ritonavir; in Beigel et al. 2020 and Grein. et al. 2020 specific concomitant treatments were not clearly reported).

The Cochrane (2020) meta-analysis included results from 2 moderate quality RCTs (Beigel et al. 2020 and Wang et al. 2020) and both were assessed using Cochrane risk of bias 2 tool as having 'some concerns'. Overall, the quality and applicability of the meta-analysis reported by Cochrane (2020) was considered as high and fully applicable to practice. No sensitivity analyses were conducted and for the mortality outcome the heterogeneity value was high (I^2 58%, random-effects model) indicating inconsistency in the 2 RCTs. For the outcome incidence of WHO progression score level 6/7 or above at days 14 to 28, the heterogeneity measure was reported to be 0%. The RCTs used for this outcome included patients with different severity of disease (Beigel et al. 2020 included mild or moderate and severe disease and Wang et al. 2020 included severe disease only). Also, different ordinal scales were used by Beigel et al (2020) (used an 8-point ordinal scale) and Wang et al (2020) (use 6-point ordinal scale) which were mapped against the WHO 10-item progression scale. The limitations of the meta-analyses were not presented and it is unclear if the data reported by Cochrane (2020) have been formally peer-reviewed before publication.

Beigel et al (2020) was the larger study (n=1,063) of the individual studies included in this review that had patients from 10 countries including the UK. This paper reported preliminary results up to day 14 (total follow-up was reported to be 29 days) from a trial that is still ongoing and it is unclear if it has been peer-reviewed. A short follow-up time may not be sufficient to assess treatment effects. The shorter time to recovery led the data and safety monitoring board for the study to recommend unblinding of the data to the National Institute of Allergy and Infectious Diseases. The authors state that this was to enable patients in the placebo group, as well as patients elsewhere, to benefit from treatment with remdesivir. There is a possibility that the results may be favourable earlier on in the study than might have been if the full duration was completed. In addition, the primary outcome changed from difference in clinical status to time to recovery. The authors provide an explanation for this decision, which took place before interim analysis, and was proposed by statisticians who had no knowledge of outcome data. The primary and secondary outcomes were adequately powered to show statistical significance.

Wang et al (2020) was a small RCT (n=237) that was limited to a Chinese population. The limitations of this study that affect its applicability to clinical practice include insufficient power to detect assumed differences in clinical outcomes, remdesivir and placebo groups were not well matched for baseline characteristics, treatment was started late in COVID-19, and the absence of data on infectious virus recovery or on possible emergence of reduced susceptibility to remdesivir. In the remdesivir group there were more patients with comorbidities and a higher respiratory rate. There were also fewer patients who were symptomatic for 10 days or less before starting treatment. The results were based on a slightly longer follow-up time of 28 days compared with 14 days in Beigel et al (2020). Data on the proportion of patients with viral RNA detected and viral RNA load were based on 196 patients as there was data missing from 40 patients (27 in remdesivir group and 13 in placebo group).

Grein et al (2020) was a small case series (n=53) that included patients from Europe (no UK patients), Canada and Japan. The limitations of this study that affect its applicability to clinical practice include small size, retrospective nature, missing data, lack of information on 8 patients that were initially treated, short follow-up of 28 days and lack of an active control arm. The authors state that factors contributing to differences in outcomes include type of supportive care such as concomitant medicines, variations in ventilatory practices, differences in institutional treatment protocols and thresholds for hospitalisation. The authors also state that the use of invasive ventilation as a proxy for disease severity may be influenced by the availability of ventilators in a given location.

Many trials are planned or underway to assess remdesivir for treating COVID-19. These include:

- A phase 3 randomised study to evaluate the safety and antiviral activity of remdesivir in participants with severe COVID-19 (NCT04292899, estimated primary completion date June 2020).
- A phase 3 randomised study to evaluate the safety and antiviral activity of remdesivir in participants with moderate COVID-19 compared to standard of care treatment (NCT04292730, estimated primary completion date June 2020).

- A multicentre, adaptive, randomised blinded controlled trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in hospitalised adults (NCT04280705, estimated primary completion date April 2023, note preliminary results have been published by Beigel et al 2020).
- Public health emergency SOLIDARITY trial of treatments for COVID-19 infection in hospitalised patients (ISRCTN83971151, WHO funded, overall trial end date March 2021).

Conclusion

The included studies in this review suggest some benefit with remdesivir compared with placebo for reducing supportive measures including mechanical ventilation and time to recovery in patients with mild or moderate, or severe COVID-19 disease who are on supplemental oxygen treatment. However, no statistically significant differences were found for mortality and serious adverse events (fewer reported with remdesivir compared with placebo). More treatment discontinuations were reported with remdesivir compared with placebo due to adverse events (Wang et al. 2020). A subgroup analysis reported in Beigel et al (2020) suggests that some groups may benefit more than others however this data needs to be interpreted with caution given the wide confidence intervals and lack of adjustment for multiplicity. Therefore, this limits the applicability to clinical practice when assessing which patients are most likely to benefit from remdesivir.

The findings in the review suggest that factors to consider when using remdesivir as a treatment option for COVID-19 in patients with mild or moderate, or severe disease include the timing of initiation of treatment at the onset of symptoms, disease severity (this includes the need for oxygen support, non-invasive ventilation, invasive ventilation or organ support, most of the patients in the studies had severe COVID-19) and the underlying clinical status of the patient and age. These may have important effects on the outcomes of treatment. Remdesivir should only be administered by intravenous infusion which may limit its use.

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Ruan Q, Yang K, Wang W, et al (2020). Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Medicine 46: 846–848

Wang W, Zhang D, Du G et al. (2020) Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet 395: 1569–78.

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Zhou F, Yu T, Du R, et al (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395: 1054–62

Appendices

Appendix A: Research questions

Research questions

1. In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the clinical effectiveness of remdesivir compared with placebo or standard care?

2. In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the safety of remdesivir compared with placebo or standard care?

3. In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the cost effectiveness of remdesivir compared with placebo or standard care?

4. From the evidence selected, are there any subgroups of patients that may benefit or be harmed from remdesivir more than the wider population of interest?

5. From the evidence selected:

    a. what definitions have been used/developed to describe 'moderate' and 'severe' COVID-19?

    b. what is the duration of remdesivir treatment?

Population, Intervention, Comparator and Outcomes (PICO) table

P – Population and Indication	Adults, young people and children hospitalised with suspected or confirmed COVID-19 Subgroups: • Adults >50 years • Children <12 years of age • Disease severity on admission • Gender • Ethnic background • Pregnant women • Comorbidities (e.g. chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity)

	• Time from symptom onset
I – Intervention	Remdesivir and standard care (Do not exclude studies where remdesivir is given in combination with other therapeutic interventions)
C – Comparator(s)	Placebo or standard care (care can vary according to country. In the UK standard care for COVID-19 is supportive treatment)
O – Outcomes	**Critical to decision-making:** • Mortality (e.g. overall, 1-month mortality) • Time to recovery or SARS-CoV-2 RT-PCR negativity • Length of stay (hospital or critical care) • Requirement for or duration of: • mechanical ventilation • non-invasive ventilation (e.g. CPAP, NIV or HFOT) • organ support (e.g. extracorporeal membrane oxygenation, vasopressors, renal replacement treatment) • Serious adverse events (e.g. grade 3 or 4) **Important to decision-making:** • Disease progression / change in clinical status • Complications of disease (such as multi-organ failure, pulmonary impairment, renal impairment, disturbed coagulation) • PaO2/FiO2 ratio • Adverse events (e.g. transfusion related reactions, acute respiratory failure) • Cost effectiveness
Inclusion criteria:	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, observational studies including case series.
Language	English
Patients	Human studies only
Age	All ages
Date limits	2019-present
Exclusion criteria:	
Publication type	Pre-prints
Study design	Case reports

Appendix B: Search strategy

The following sources were searched to find research literature on remdesivir:

Database	Platform	Segment searched	Date searched

MEDLINE ALL	Ovid	Ovid MEDLINE(R) ALL <1946 to May 26, 2020>	27th May 2020
Embase	Ovid	Embase <1974 to 2020 Week 21>	27th May 2020
Cochrane Library	Wiley	Issue 5 of 12, May 2020	27th May 2020
Pre-prints – bioRxiv and medRxiv	RIS file of contents downloaded into EPPI-Reviewer 5 review	27th May 2020 (time 9.43am)	27th May 2020
WHO COVID-19 database	WHO website	27th May 2020	27th May 2020

The MEDLINE literature search strategy that was used is presented below. It was translated for use as appropriate in the other sources listed above:

1 Remdesivir*.af.
2 (GS-5734 or GS5734).af.
3 1 or 2
4 exp coronavirus/
5 exp Coronavirus Infections/
6 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw,kf.
7 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw,kf.
8 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw,kf.
9 (respiratory* adj2 (symptom* or disease* or illness* or condition*) adj5 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf.
10 (("seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf.
11 (pneumonia* adj3 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf.

12 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf.
13 "severe acute respiratory syndrome*".ti,ab,kw,kf.
14 or/4-13
15 limit 14 to yr="2019 -Current"
16 3 and 15
17 limit 16 to yr="2020"

There were no limits on the search for language, animal studies or type of study. The search was date limited to retrieve results published from 2020.

The Information Services team at NICE peer-reviewed the principal database strategies according to the standard NICE checklist that was adapted from the 2015 Peer review of electronic search strategies (PRESS) checklist.

The following sources were also used to identify additional evidence on remdesivir in the form of evidence reviews and guidelines. Browsing or simple keyword searches were used to find relevant information.

Source	Website	Segment searched
Canadian Agency for Drugs and Technologies in Health	https://covid.cadth.ca/category/treatment/	27 May 2020
National Centre for Pharmacoeconomics (Ireland)	http://www.ncpe.ie/research/covid-19/	27 May 2020
Centre for Evidence-based medicine (CEBM) COVID-19 Evidence Service	https://www.cebm.net/oxford-covid-19/	27 May 2020
Agency for Care Effectiveness (ACE), Singapore	https://www.cebm.net/oxford-covid-19/	27 May 2020
Australian National COVID-19 Clinical Evidence Taskforce	https://covid19evidence.net.au/	27 May 2020
Infectious Diseases Society of America (IDSA)	https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/	27 May 2020
National Institutes for Health (NIH, US)	https://covid19treatmentguidelines.nih.gov/whats-new/	27 May 2020
BMJ Best Practice Coronavirus disease 2019 (COVID-19)	https://bestpractice.bmj.com/topics/en-gb/3000168	29 May 2020
Cochrane COVID-19 living evidence project	https://covid-nma.com/living_data/index.php#table1	29 May 2020
Norwegian Institute of Public health – map of COVID-19 evidence	https://www.fhi.no/en/qk/systematic-reviews-hta/map/	29 May 2020

Appendix C: Evidence selection

A total of 464 references were found from the database searches. After duplicate search results were removed, 327 references remained. On 28 May 2020 notification was received that a new RCT on remdesivir (Goldman et al, 2020) had been published on 27 May 2020. This reference was not retrieved during the databases searches because it was published after the searches had been completed. This reference was added to the search results.

The 328 references were screened using their titles and abstracts and 17 references were obtained and assessed for relevance. Of these, 3 are included in the evidence summary. A meta-analysis of the 2 included RCTs was also identified following the search and included.

The excluded references are listed in the following table with reasons for their exclusion.

Study reference	Reason for exclusion
Blasiak A, Lim JJ, Seah SG et al (2020). Artificial Intelligence Pinpoints Remdesivir in Combination with Ritonavir and Lopinavir as an Optimal Regimen Against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) medrxiv preprint	Not relevant study type (pre-print)
Davies M, Osborne V, Lane S et al (2020). Remdesivir in treatment of COVID-19: A systematic benefit-risk assessment medrxiv preprint	Not relevant study type (pre-print)
Gebrie D, Getnet D, Manyazewal T et al (2020). Efficacy of remdesivir versus placebo for the treatment of COVID-19: A protocol for systematic review and meta-analysis of randomized controlled trials medrxiv preprint	Not relevant study type (pre-print)
Goldman JD, Lye DCB, Hui DS et al (2020). Remdesivir for 5 or 10 Days in Patients with Severe Covid-19 New England Journal of Medicine	Not a relevant comparison
Grein, Jonathan; Myers, Robert P; Brainard, Diana Compassionate Use of Remdesivir in Covid-19. Reply. New England Journal of Medicine 382	Not relevant study type (correspondence on included study)
Hillaker E, Belfer JJ, Bondici A et al (2020). Delayed Initiation of Remdesivir in a COVID-19-Positive Patient. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy	Not relevant study type (case study)
Holshue ML, DeBolt C, Lindquist S et al (2020). First Case of 2019 Novel Coronavirus in the United States New England Journal of Medicine, 382, 10, 929-936	Not relevant study type (case study)
Hsu, C-Y, Lai C-C, Yen A et al (2020). Efficacy of remdesivir in COVID-19 patients with a simulated two-arm controlled study medrxiv preprint	Not relevant study type (pre-print)
Kujawski SA, Wong KK, Collins JP et al (2020). First 12 patients with coronavirus disease 2019 (COVID-19) in the United States medRxiv, 2020030920032896	Not relevant study type (pre-print)
Lin, Ting-Yu; Chang, Wei-Jung; Hsu, Chen-Yang; Lai, Chao-Chih; Yen Amy, Ming-Fang; Chen Sam, Li-Sheng; Chen, Hsiu-Hsi Impacts of remdesivir on dynamics and efficacy stratified by the severity of COVID-19: a simulated two-arm controlled study medrxiv preprint,,	Not relevant study type (pre-print)
Paul AE, Piticaru J, Lewis K et al (2020). Remdesivir use in patients with coronavirus COVID-19 disease: a systematic review and meta-analysis medrxiv preprint	Not relevant study type (pre-print)
Spinello A, Cossu MV, Ridolfo AL et al (2020). 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. Pharmacological research 104899	Higher quality evidence available for outcomes reported
Wang Y, Zhou F, Zhang D et al (2020). Evaluation of the efficacy and safety of intravenous remdesivir in adult patients with severe COVID-19: study protocol for a phase 3 randomized, double-blind, placebo-controlled, multicentre trial. Trials, 21, 1, 422	Not relevant study type (protocol for included study)

Wu J, Wu B, Lai T et al (2020). Compassionate Use of Remdesivir in Covid-19. The New England Journal of Medicine 382	Not relevant study type (correspondence on included study)

Appendix D: Quality assessment

Beigel et al (2020)

Overall risk of bias assessed by Cochrane authors as 'some concerns' due to deviations from intervention using Cochrane risk of bias 2 tool. See Description of primary studies for full details.

Cochrane (2020)

Assessed using the PRISMA NMA checklist

Question	Cochrane (2020) living data collaboration (accessed 29 May 2020)
Domain 1: Background	-
Has the rationale for the review been described in context?	Yes The NMA outlined the study context and a rationale which is based on a rapidly developing evidence base to produce pairwise and network meta-analytic data on the effectiveness of treatment interventions for COVID-19
Domain 2: Study selection	-
2.1. Have the study characteristics used as criteria for eligibility been specified, with rationale given for the choices made?	Yes The review protocol outlines clear PICO, the length of follow-up and report characteristics with rationales outlined explaining eligibility.
2.2. Have eligible treatments included in the treatment network been clearly described?	Yes The anti-infectious, specific immunomodulatory and non-specific immunomodulatory interventions included are described with rationales outlined for inclusion
2.3. Has it been noted whether any treatments have been clustered or merged into the same node (with justification)?	No Node merging/clustering not present in the NMA – although studies combining relevant interventions was allowed
Domain 3: Methods and data for handling statistics	-
3.1. Have the methods used to explore the geometry of the treatment network and potential biases related to it been described?	Yes The network is well described and graphically presented, relationships between direct and indirect comparisons are outlined. Quality appraisal undertaken using Cochrane RoB 2; GRADE undertaken. Publication bias was addressed through selection models with assumptions regarding the probability of publication based on study results.
3.2. Have the summary measures (e.g., risk ratio, difference in means) been described?	Yes – The NMA and pairwise comparisons are outlined as relative risk, mean differences or SMD (as appropriate) with 95% CI and absolute

	effects per 1000 people. To rank interventions, in the absence of excessive uncertainty in the relative effects SUCRA is planned (surface under the cumulative ranking curve).
3.3. Has the methodology for data handling been described?	Partially yes – To date trials are pairwise comparisons with Cochrane RoB tools used to assess bias. The code underpinning the NMA is not outlined in the study. Narrative outlines that data linked is linked to identified RCTs. A random-effects frequentist NMA has been planned and the between study heterogeneity impact will be assessed using prediction intervals. The handling of multi-arm trials, variance structure and assessment of model fit is not described.
3.4. Have the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied been described?	Yes – The consistency between direct and indirect evidence checked by use of loop-specific side-splitting method and the design-by-treatment interaction model.
3.5. Has a description of subgroup, sensitivity and meta-regression analyses been provided, where applicable?	Yes – Sensitivity analysis was undertaken that excluded studies at higher risk of bias as well as using numbers analysed versus numbers randomised.
Domain 4: Reporting of results and discussion	
4.1 Is a network diagram presented?	Yes – A network diagrams are presented within the study for each comparison.
4.2 Are the characteristics of the treatment network described?	Yes – A narrative overview of pairwise findings, treatments and the findings of the network itself are outlined. Heterogeneity and bias were assessed and outlined.
4.3 Have the results, including confidence/credible intervals, of each pairwise meta-analysis carried out been presented?	Yes – The study presents relative risks, 95% CI and absolute effects per 1000 patients for each treatment in the meta-analysis.
4.4 Have investigations of inconsistency been carried out?	Yes - The consistency between direct and indirect evidence checked by use of loop-specific side-splitting method and the design-by-treatment interaction model.
4.5 Have the results been presented for any additional analyses (e.g. sensitivity or subgroup analyses, meta-regression analyses) if done?	No – Both studies for the intervention of remdesivir (intervention of interest) were adjudged to have been of 'some concerns' using Cochrane RoB. Therefore, no sensitivity analyses could be conducted as planned for higher risk of bias. No mention is made sensitivity analysis by numbers analysed versus numbers randomised.
4.6 Is there a discussion of the limitations of the NMA study?	No – Limitations are concerned with an inability to extract information from pre-print only.
Overall quality and applicability	**-**
Overall quality	High
Applicability as a source of data	Fully applicable

Grein et al (2020)

Assessed using JBI critical appraisal checklist for case series

Question	Grein et al (2020)
Were there clear criteria for inclusion in the case series?	Yes Hospitalised patients with SARS-CoV-2 (RT-PCR confirmed) with SaO2 ≤94% on air or O2 support therapy, creatinine clearance >30 ml/min and serum ALT/AST <5X ULN
Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes Daily measurement of oxygen support requirement, adverse events, laboratory values including serum creatinine, ALT/AST at days 1 to 10, with additional follow-up at day 28 (survival, discharge, clinical improvement using an ordinal scale)
Were valid methods used for identification of the condition for all participants included in the case series?	Yes Diagnosis was by laboratory confirmed (RT-PCR assay) for SARS-CoV-2
Did the case series have consecutive inclusion of participants?	Unclear Authors do not report if they consecutively included all participants for whom an appropriate application for compassionate treatment was made
Did the case series have complete inclusion of participants?	Yes Population is reported to include all patients who received their first dose on or before 7 March 2020
Was there clear reporting of the demographics of the participants in the study?	No Age, gender, geographic region are reported. Ethnicity and education status are not reported
Was there clear reporting of clinical information of the participants?	Yes Oxygen support requirement, median duration of symptoms before treatment, coexisting conditions and median ALT/AST and serum creatinine are reported
Were the outcomes or follow-up results of cases clearly reported?	Yes Clinical improvement, mortality, safety (adverse events) and laboratory values were reported
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Yes Country of origin and region are detailed
Was statistical analysis appropriate?	Yes Note that for the Cox proportional hazards model for age (cumulative incidence of clinical improvement [%] by age group) there is a violation of the assumption of proportion hazard

Question	Grein et al (2020)
	(i.e. the lines for ≥70 years and 50 to <70 years cross at days 4 to 8 and for <50 years and 50 to <70 years cross at days 24 to 28). These data should be treated with caution

Wang et al (2020)

Overall risk of bias assessed by Cochrane authors as 'some concerns' due to deviations from intervention using Cochrane risk of bias 2 tool. See Description of primary studies for full details.

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