Living Systematic Review report

NICE

Title

Effectiveness and safety of remdesivir for acute symptoms and complications of COVID-19 (Protocol)

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On behalf of the Living Evidence to inform health decisions research group

Living Evidence to inform health decisions research group: María Ximena Rojas, Gerard Urrutia Chuchí, Gabriel Rada, David Rigau, Pablo Alonso, Ariadna Auladell-Rispau, Josefina Bendesrky, Camila Ávila, Francisca Verdugo.

Conflicts of interest: None known

Abstract

Coronavirus disease 2019 (COVID-19) manifests as a respiratory disease caused by the SARS-CoV-2 virus. COVID-19 presents with varying clinical severity and at its most severe can cause pneumonia, acute respiratory distress syndrome and respiratory failure. Therapeutics for COVID-19 is an emerging area. 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 perturbs viral replication and therefore may be a useful theraputic strategy for managing COVID-19 infection.

Several primary studies and systematic reviews (SRs) have been published in the last year to assess the safety and effectiveness of remdesivir as a treatment for COVID-19 and further research is anticipated.

Objective

To evaluate the effectiveness and safety of remdesivir for acute symptoms and complications of COVID-19.

Methods

Recommendations on remdesivir for management of COVID-19 were published in NICE's guideline on managing COVID-19. We will maintain this evidence synthesis as a living systematic review including only randomized controlled trials (RCT) and systematic reviews of RCTs. Searches will be performed weekly across databases including Medline, Embase and the Cochrane Library and results will be incorporated into EPPI reviewer. New studies will be assessed for relevance against the protocol and any studies considered to potentially impact the current recommendations will be used to assess whether an update is needed. We will evaluate the risk of bias of the randomized trials included in any updates to the review using the ROB-2 tool and assess the certainty of evidence using the GRADE approach.

The living process will continue until end of June 2022.

Background

Condition or domain being studied

Coronavirus disease 2019 (COVID-19) manifests as a respiratory disease caused by the SARS-CoV-2 virus. COVID-19 presents with varying clinical severity and at its most severe can cause pneumonia, acute respiratory distress syndrome and respiratory failure.

Why it is important to do this review

Therapeutics for COVID-19 is an emerging area. 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 perturbs viral replication and therefore may be a useful therapeutic

strategy for managing COVID-19 infection.

Taking into account that the evidence on this therapy is on the rise (i.e. new studies have been published and other studies are going to be published in the near future), we propose to carry out a living systematic review with the aim of updating the estimates of the effect of this intervention on people with COVID-19 once new evidence emerges. This SR will be developed as part of the *Living Evidence to Inform Health Decisions* project, which supports health system organizations in the implementation of the living evidence model for the development of evidence synthesis to inform health decisions.

Objective

To evaluate the effectiveness and safety of remdesivir for acute symptoms and complications of COVID-19.

Types of studies to be included

We will include randomized controlled trials (RCTs) and systematic reviews of

RCTs. **Types of participants**

Adults, young people and children with suspected or confirmed COVID-19 (this includes all disease severities).

Setting

Studies including patients in any setting (hospital or community

dwelling). **PICO question**

What is the effectiveness and safety of remdesivir for acute symptoms and complications of COVID-19?

Intervention

Remdesivir.

Comparator

Standard care alone, standard care plus placebo, placebo or active comparator.

Note: Standard care comprises best supportive care and in certain circumstances the use of additional drugs (such as dexamethasone).

Types of outcome measures

Critical outcomes

- Mortality (n/N)
- Invasive mechanical ventilation (IMV) or intensive care admission (requirement and duration)
- Adverse events
- Hospitalisation (requirement and duration)

Important outcomes

- Supplemental oxygen, high-flow oxygen, continuous positive airway pressure or noninvasive ventilation (requirement and duration)
- Discontinuation due to adverse events
- Symptom resolution or clinical recovery (number and time until) ● Virological clearance (negative PCR)
- Clinical worsening / deterioration (number and time until)
- Sustained recovery (development of long-term effects of COVID) **Methods for identification and selection of studies**

NICE reused data from the National Australian COVID-19 clinical evidence taskforce for recommendations on remdesivir. At the time of publication (March 2021), no specific literature searches were carried out for the therapeutics section of the guideline.

Surveillance and update plan

Following the initial publication of recommendations on remdesivir for management of COVID-19, any new emerging evidence that could impact on the guidance and prompt an update is identified through the Surveillance process. The surveillance search for COVID-19 covers:

- Medline
- Embase
- Cochrane Library
- Pre-print sources

The sources are monitored on a weekly basis. The surveillance process began on Monday 30 March 2020. The database searches on the first day covered 16-30 March 2020 inclusive.
The development of NICE's main database search strategy for COVID-19 is covered in: Levay P and Finnegan A (2021) The NICE COVID-19 search strategy for Ovid MEDLINE and Embase: developing and maintaining a strategy to support rapid guidelines. *MedRxiv preprint*. https://doi.org/10.1101/2021.06.11.21258749

Boolean search strategy

Ovid MEDLINE ALL

Search Strategy:

#	Searches
1	SARS-CoV-2/ or COVID-19/
2	(corona* adj1 (virus* or viral*)).ti,ab,kw,kf.

3	(CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab,kw,kf.
4	(coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw,kf.
5	(longcovid* or longcoronavirus* or longcorona* virus* or longCov or longsars* or longncov*).ti,ab,kw,kf
6	((postcovid* or postcoronavirus* or postcorona virus* or postCov or postsars* or postncov*) adj3 (syndrome* or disorder* or illness* or sickness* or disease* or condition* or symptom* or sign* or prognos* or followup* or "follow up*" or feature* or comorbid* or "co morbid*" or multimorbid* or "multi morbid*" or survivor* or survival* or risk* or care* or convalescen* or recuperat* or aftercare* or ambulatory* or outpatient* or "out patient*")).ti,ab,kw,kf.
7	COVID-19 Vaccines/
8	(Abdala or "Ad26.CoV2.S" or Ad26COVS1 or "Ad5-nCoV" or "AG0302-COVID19" or "ARCT-154" or AZD1222 or AZD2816 or "BBIBP-CorV" or BBV152 or BNT162 or BNT162b1 or BNT162b2 or BNT162b2s01 or Brilife or "ChAdOx1 nCoV-19" or "ChAdOx1-S" or CIGB 66 or Comirnaty or CoronaVac or Convidicea or "Covax-19" or Covaxin or Covilo or "COVIran Barekat" or CoviShield or COVOVAX or CVnCoV or "DelNS1-2019-nCoV-RBD-OPT" or EpiVacCorona or "ERUCOV-VAC" or FAKHRAVAC or "FINLAY-FR-1A" or "FINLAY-FR-2" or "Gam-COVID-Vac" or GBP510 or "GRAd-COV2" or "GX-19" or "IIBR-100" or "INO-4800" or "JNJ-78436735" or KoviVac or KCONVAC or "mRNA-1273" or "mRNA-1273.211" or "mRNA-1273.617.2" or "MVC-COV1901" or Nanocovax or "NVX-CoV2373" or PakVac or "QazCovid-in" or QazVac or "Razi Cov Pars" or "RBD-Dimer" or "SCB-2019" or SCTV01C or "Soberana 1" or "Soberana 2" or "Soberana Plus" or Spikevax or SpikoGen or "Sputnik Light" or "Sputnik V" or "TAK-919" or Tozinameran or "UB-612" or VAC31518 or Vaxzevria or Vidprevtyn or "Vietnam domestic vaccine" or VLA2001 or VLA2101 or "WIBP-CorV" or ZF2001 or Zifivax or "ZyCoV-D").ti,ab,kw,kf.

9	or/1-8

10	(9 and english.lg.) not (letter or historical article or comment or editorial or news or case reports).pt. not (Animals/ not humans/)
11	limit 10 to ed=20210720-20210729
12	limit 10 to dt=20210720-20210729
13	11 or 12

Lines 11 and 12 are amended for each weekly search to cover the previous 10 days.

Selection of studies

The results of the literature searches will be automatically incorporated into the EPPI review for COVID-19 surveillance. Titles and abstracts of studies will be assessed by one reviewer for relevance against the protocol. Only studies with a definite impact will be coded as an include. Excludes will be coded as:

- supporting evidence
- potential future impact
- covered in guideline development
- exclude

Supporting evidence is used to code studies which reinforce or are consistent with the existing guideline recommendation(s)

Potential future impact is used to code studies which may challenge the guideline recommendation(s) but are insufficient in isolation to impact and require further confirmatory research to trigger an update. When further
confirmatory evidence does emerge, the studies can be re-coded as includes if the cumulative impact indicates a trigger for updating.

We will resolve disagreements by consensus or by discussion with another author. We will obtain the full reports for all records that appear to meet the inclusion criteria and could be potential includes. We will record the reasons for excluding studies and show the study selection process in a PRISMA flow diagram.

The living process for this question will end after June 2022.

Data extraction and management

In the event of an update, we will use EPPI reviewer to extract information about studies characteristics (characteristics of participants; inclusion-exclusion criteria; intervention and comparison description, outcomes and results). Data extraction will be performed by one author.

Assessment of risk of bias of included studies

In the event of an update, we will evaluate the risk of bias of the included randomized trials using the Cochrane ROB-2 tool.

Measures of treatment effect

Study results would be reported as pooled relative risks (RR), odds ratios (OR) for categorical outcomes or mean differences (MD) (or standardized mean differences, (SMD)) for continuous outcomes with the corresponding 95% confidence intervals (95% CI).

Data synthesis

We will evaluate the heterogeneity of the included studies with I^2 as follows: I2 < 50% as low, heterogeneity, I2 > 50% and < 75% as high, and > 75% as very high. When heterogeneity is below 75%, we will perform a meta-analysis in RevMan 5.4.

Subgroup analysis

We will perform the following subgroup analyses if data is available:

- Adults > 50 years
- Children <12 years of age
- Disease severity (asymptomatic/mild/moderate/severe/critical) ● Sex
- Ethnic background
- Pregnant women
- Comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity)
- Time from symptom onset
- Treatment with other therapeutics used for COVID-19
- Community vs hospital
- Confirmed versus negative for COVID
- Tested vs untested for COVID
- PCR confirmed versus clinically suspected COVID
- Vaccination status
- Different variants

Sensitivity analysis

If appropriate, we will perform a sensitivity analysis excluding the studies with high risk of bias.

Certainty of evidence

We will assess the certainty of evidence using the GRADE approach, both for the evidence found as part of the initial or baseline review, and for the updates resulting from the living evidence process.

One reviewer will independently define the certainty of evidence. We will present the results using summary of findings tables.

Statistical considerations for the living evidence synthesis

The inclusion of new studies identified as part of evidence surveillance and reporting on the outcomes of interest will follow this approach: We will perform a meta-analysis for each of the outcomes of interest reported by the new studies using a fixed-effect model in order to evaluate the statistical heterogeneity among included studies by using the I^2statistics. If new heterogeneity is detected (i.e. increase the heterogeneity previously identified or new heterogeneity arises where it was previously undetected), we will explore its potential sources by reviewing the new studies against previously included studies in order to identify reasons that may explain inconsistent results among studies. In presence of unexplained heterogeneity (I2> 75%), we will consider not to meta-analyze them and explain the evidence synthesis narratively. If the $I^2$is below 90%, we will perform a meta-analysis by using the fixed effects or the random effects model, whichever pertinent. We will also consider a random effects model when there are meaningful differences, methodologically, between the studies which would affect the true effect estimate they were trying to identify.

Dissemination plan

We plan to communicate our updated review results as updates to recommendations on remdesivir in NICE's guideline on managing COVID-19.

Acknowledgement

We would like to acknowledge the contribution of the COVID-19 team in the design and development of this protocol.