Rapid policy statement

Interim Clinical Commissioning Policy: Remdesivir for patients hospitalised with COVID-19 (adults and children 12 years and older) Version 2

06 November 2020

Introduction

In response to the public health emergency posed by coronavirus disease 2019 (COVID-19), NHS England, working with the Devolved Administrations (DAs), has established a rapid policy development process to aid clinicians in offering best care and advice to patients with or at risk of COVID-19 across the UK. This document sets out the interim clinical commissioning position for the use of remdesivir for patients with COVID-19.

Commissioning position

The proposal is: remdesivir is recommended to be available as a treatment option through routine commissioning for hospitalised patients (adults and children 12 years and older) with COVID-19 according to its licence and in accordance with the criteria set out in this document.

Equality statement

Promoting equality and addressing health inequalities are at the heart of the four nations' values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010 or equivalent equality legislation) and those who do not share it; and

- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain language summary

COVID-19 is a disease caused by a coronavirus (named SARS-CoV-2) causing many different symptoms, the most common being fever, loss of sense of taste and smell and cough. Remdesivir (given intravenously) is an anti-viral medicine which has been shown to improve recovery time in some hospitalised patients. This policy outlines the commissioning criteria for the use of remdesivir to treat people with COVID-19 in hospital according to its licence and in line with current evidence.

Overview

The condition

COVID-19 manifests predominantly as a respiratory illness, of widely varying clinical severity. At the most severe end of the spectrum COVID-19 results in severe pneumonia and respiratory failure with the need for mechanical ventilation. Hyperinflammatory states leading to organ dysfunction beyond the respiratory tract, have also been well described.

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 perturbs viral replication. Remdesivir is given intravenously, once daily after an initial loading dose. Reported adverse effects include transaminase elevations, infusion related reactions (hypotension, nausea, vomiting, diaphoresis) and drug hypersensitivity (www.veklury.eu). Additional adverse events may become more apparent with more widespread use.

Clinical problem

Several medical treatment options for COVID-19 have been assessed in clinical trials, many of which are ongoing. Emerging evidence of these treatment options have been reviewed (including interim results from the WHO Solidarity trial) by a national clinical expert group, which has concluded that there is insufficient further evidence to change the current commissioning position on the use of remdesivir in the treatment of COVID-19 (Beigel et al, 2020; Goldman et al, 2020; Rochwerg et al, 2020; Spinner et al, 2020; WHO Solidarity trial consortium, 2020; Wilt et al, 2020).

Criteria have been developed to define access and eligibility for remdesivir treatment based on expert consensus, including:

1. Key steps along the COVID-19 clinical pathway at which actions and review are necessary
2. Specific eligibility criteria to be followed

Evidence summary

An evidence review conducted by the National Institute for Health and Care Excellence (NICE) on 5 June 2020 indicated some benefit with remdesivir compared with placebo for reducing supportive measures – including mechanical ventilation – and reducing time to recovery in patients with mild, moderate or severe COVID-19 disease who are on supplemental oxygen treatment (https://www.nice.org.uk/advice/es27/evidence).

Implementation

Eligibility criteria

Patients are eligible for treatment with remdesivir in accordance with the product licence (European Medicines Agency, 2020). The patient characteristics are:

- Hospitalised with coronavirus disease 2019[1] (COVID-19)
- With pneumonia requiring supplemental oxygen
- Adults, and adolescents 12 years and older[2] who weigh 40kg and over
- Estimated glomerular filtration rate (eGFR) at least 30ml/minute
- Alanine aminotransferase (ALT) below 5 times the upper limit of normal at baseline.

The following criteria have been developed based on expert consensus and should be followed. A clinical pathway is presented (Appendix 1) which include steps, review points and actions outlined by these criteria[3].

- **Initiation of treatment**
  - The decision to initiate treatment with remdesivir should be made by the admitting care consultant[4].
  - Remdesivir should not be initiated in patients who present to hospital more than 10 days after symptom onset.
- **Risk assessment**
  - Clinical judgement around treatment with remdesivir can be informed by a risk score. Those with a low 4C Mortality Score[5] (0 to 3) are highly likely to recover without treatment with remdesivir.

[1] In the absence of a confirmed virological diagnosis, remdesivir should only be used when a multidisciplinary team have a high level of confidence that the clinical and radiological features suggest that COVID-19 is the most likely diagnosis.
[2] Remdesivir is available for the treatment of children aged <12 years (weighing at least 3.5kg), and those aged 12- <18 years and weighing <40kg, through the company's compassionate use scheme (this is at the discretion of Gilead Sciences)
[3] Clinical judgement in the initiation, review, escalation and de-escalation of patients receiving remdesivir treatment should be supported where possible by multidisciplinary team assessment.
[4] The decision to treat with remdesivir is not an emergency and should be made judiciously after assessment and in a timely manner.
[5] The 4C Mortality Score (available at https://isaric4c.net/risk/) is a validated risk stratification score, which can help inform clinical decision making for patients admitted to hospital with COVID-19 (Knight et al, 2020). Other clinical risk scores are available.

- Remdesivir should not be initiated in patients who present to hospital and are unlikely to survive (determined by clinical judgment). The 4C Mortality Score might be helpful in this assessment.

- **Duration**

  All patients must receive a maximum of 5 days of remdesivir in total (comprising a loading dose plus 4 further days of maintenance doses).

- **Reassessment and review**

  The use of remdesivir should be reassessed daily. Consider stopping remdesivir if:

  - The patient clinically improves and no longer requires supplemental oxygen 72 hours after commencement of treatment; or
  - The patient continues to deteriorate despite 48 hours of sustained mechanical ventilation.

Pregnancy

Remdesivir should be avoided in pregnancy unless clinicians believe the benefits of treatment outweigh the risks to the individual (please see SmPC for further information).

Dose

The recommended dosage is a single loading dose of remdesivir 200mg intravenously on day 1, followed by a once daily maintenance dose of remdesivir 100 mg for the remainder of the treatment course, which should not exceed five days.

Monitoring

Renal and liver function should be monitored carefully during treatment with remdesivir as clinically appropriate.

Stopping criteria

Remdesivir should be discontinued in patients who develop **any** of the following:

- ALT ≥ 5 times the upper limit of normal during treatment with remdesivir (remdesivir may be restarted when ALT is < 5 times the upper limit of normal)
- ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR)
- eGFR <30 mL/min

Safety reporting

Any suspected adverse drug reactions (ADRs) for patients receiving remdesivir should be reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/

Co-administration

Corticosteroids

Administration of systemic dexamethasone or hydrocortisone is recommended in the management of patients with severe or critical COVID-19. Corticosteroids are not suggested in non-severe COVID-19 disease. Updated WHO guidance on the use of systemic corticosteroids in the management of COVID-19 can be found here.

There is no interaction of remdesivir with either dexamethasone or hydrocortisone expected. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

Hydroxychloroquine

Coadministration of remdesivir and chloroquine phosphate or hydroxychloroquine sulphate is not recommended based on in vitro data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir.

Governance

Data collection requirement

Provider organisations in England should register all patients using prior approval software (alternative arrangements in Scotland, Wales and Northern Ireland will be communicated) and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Clinical outcome reporting

Hospitals managing COVID-19 patients are encouraged to submit data through the ISARIC 4C Clinical Characterisation Protocol (CCP) case report forms (CRFs), as coordinated by the COVID-19 Clinical Information Network (CO-CIN) (https://isaric4c.net/protocols/).

Effective from

This policy will be in effect from the date of publication.

Policy review date

This is an interim rapid clinical policy statement, which means that the full process of policy production has been abridged: public consultation has not been undertaken. This policy may need amendment and updating if, for instance, new trial data emerges, supply of the drug changes, or a new evidence review is required. A NICE Technology Appraisal or Scottish Medicines Consortium (SMC) Health Technology Assessment or All Wales Medicines Strategy Group (AWMSG) appraisal of remdesivir for COVID-19 would supersede this policy when completed.

Definitions

COVID-19	Refers to the disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus.
Mechanical ventilation	A life support treatment which helps people breathe when they are not able to breathe enough on their own.
Extra Corporeal Membrane Oxygenation	A life support machine for people who have a severe and life-threatening illness that stops their heart or lungs from working properly.

References

Beigel, J.H., Tomashek, K.M., Dodd, L.E. (2020) Remdesivir for the treatment of COVID-19 – final report. NEJM. NEJMoa2007764. doi: 10.1056/NEJMoa2007764.

Deng, G., Yin, M., Chen, X. et al (2020) Clinical determinants for fatality of 44,672 patients with COVID-19. Crit. Care 24, 179 (2020)

Docherty, A.B., Harrison, E.M., Green, C.A. et al (2020) Features of 20133 UK patients in hospital with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 369: m1985. doi: 10.1136/bmj.m1985.

Goldman, J.D., Lye, D.C.B., Hui, D.S. et al. (2020) Remdesivir for 5 or 10 days in patients with severe COVID-19. NEJM. NEJMoa2015301. doi: 10.1056/NEJMoa2015301.

ICNARC (2020) ICNARC report on COVID-19 in critical care: England, Wales and Northern Ireland 23 October 2020. https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports Accessed on 28 October 2020.

Knight, S.R., Ho, A., Pius, R. et al. (2020) Risk stratification of patients admitted to hospital with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. BMJ. 370: m3339. doi:10.1136/bmj.m3339.

Rochwerg, B., Agarwal, A., Zeng, L. (2020) Remdesivir for severe COVID-19: a clinical practice guideline. BMJ. 370: m2924. doi: 10.1136/bmj.m2924.

Spinner, C.D., Gottlieb, R.L., Criner, G.J. (2020) Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA. 324(11): 1048-1057. doi: 10.1001/jama.2020.16349.

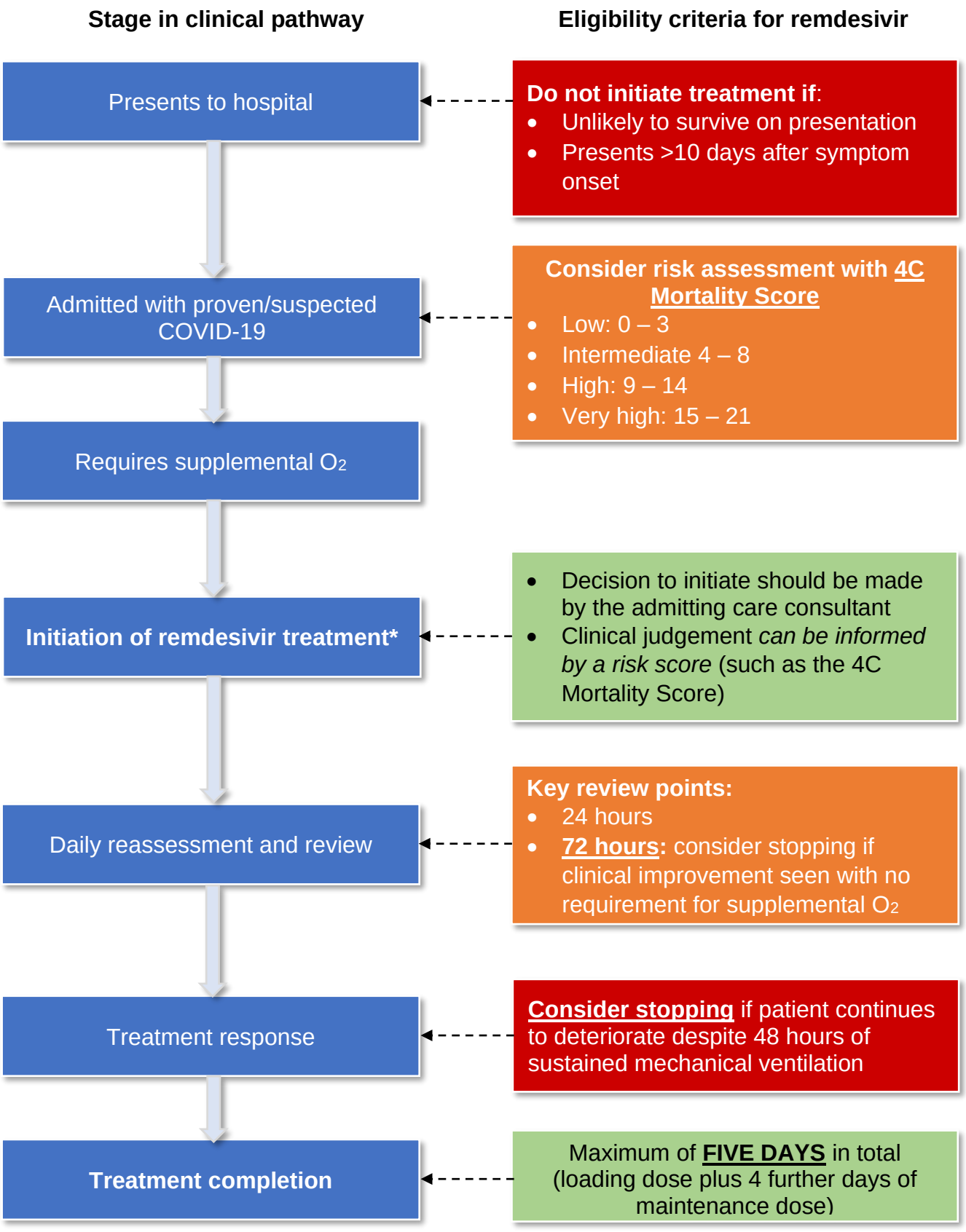
WHO Solidarity Trial Consortium (2020) Repurposed antiviral drugs for COVID-19 – interim WHO solidarity trial results. Pre-print. doi:10.1101/2020.10.15.20209817.

Williamson, E., Walker, A.J., Bhaskaran, K.J et al (2020) Factors associated with COVID-19-related hospital death using OpenSAFELY. Nature. 584: 430-436. doi: 10.1038/s41586-020-2521-4.

Wilt, T.J., Kaka, A.S., MacDonald, R. (2020) Remdesivir for adults with COVID-19: a living systematic review for an American College of Physicians practice points. Annals of Internal Medicine. doi: 10.7326/M20-5752.

Appendix 1

Clinical pathway and criteria for the use of remdesivir in patients hospitalised with COVID-19 (adults and children 12 years and older)



*There should be careful consideration before initiating remdesivir treatment