Treatment of COVID-19 with investigational antiviral agents:

Interim Decision Support Tool for clinicians

16 March 2020
v1.0

Meera Chand, Jake Dunning, Michael Jacobs
on behalf of the UK Airborne High Consequence Infectious Diseases Network

The authors wish to thank Professor Frederick Hayden, University of Virginia School of Medicine, for his expert comments and advice.

1 Document scope

This evolving document is intended to provide an overview of available evidence and experience on investigational therapeutics for UK clinicians treating confirmed cases of COVID-19.

It was produced on behalf of the UK Airborne High Consequences Diseases network, for the use of UK clinicians. Due to the urgency for interim guidance, only a limited number of agents have been assessed and a wholly systematic approach to assessing the evidence (such as GRADE) has not been performed. Further agents and therapeutic combinations will be added to updated versions of this document. Some subjective judgments are solely the consensus opinion of the authors and consulted experts.

The focus here is on investigational antiviral treatments for managing hospitalised COVID-19 patients. Supportive care and treatment of co-infections and complications, such as ARDS, are not addressed: generic guidance is available elsewhere and is recommended for use until specific evidence emerges relating to COVID-19. WHO clinical management guidance is available at: https://tinyurl.com/rh99jm7

2 Background

COVID-19 is caused by infection with the newly emerged betacoronavirus SARS-CoV-2.

There are currently very limited data on antiviral treatments for SARS-CoV-2, and so we draw inferences from data for other betacoronaviruses that cause severe respiratory disease in humans: SARS-CoV and the less closely related MERS-CoV. There are some differences between these viruses that are not yet sufficiently defined to understand their clinical relevance.

There are increasing data on the clinical course and viral dynamics in COVID-19, but it is not yet clear how these impact on the best timing and efficacy of specific treatments.

3 Principles for using experimental therapies

Treatment with investigational agents should occur within the context of controlled intervention trials if at all possible.

Monitored experimental use of therapy (“compassionate use”) may be appropriate if the treating clinician judges that the potential for benefit is likely to outweigh the risk. This document aims to help clinicians with these assessments.

In general, monitored experimental use of therapy should always be accompanied by systematic data collection, in order to help inform future guidance. The ISARIC-WHO Case Record Form is available here: https://isaric.tghn.org/covid-19-clinical-research-resources

4 Therapies under consideration

We reviewed the available data on treatment of betacoronaviruses and broadly hierarchised the evidence according to the following matrix:

Virus tested	Evidence of benefit	
SARS-CoV-2	Human controlled intervention trial	Greatest evidence
SARS-CoV	Human observational study	
MERS-CoV	Nonhuman primate experimental	
Other betacoronavirus	Small animal experimental	
	In vitro	
	Theoretical	Least evidence

For relevant compounds, we then also considered the available safety data.

Therapies that are plausible and supported by reasonable body of *in vitro*, animal and/or clinical data are shown in the following tables. A large number of other compounds have been evaluated for *in vitro* inhibition of SARS-CoV-2 and/or other betacoronavirus replication, and some have demonstrated an inhibitory effect at serum concentrations that might be achieved in patients. However, without animal studies or well-documented experience of clinical use in comparable contexts, these are not currently recommended for clinical use in COVID-19 patients. Similarly, some drugs have theoretical potential for benefit in COVD-19 patients but no supporting data, and are not recommended for use. Drugs in these categories are not listed in the tables, with the exception of any that have been widely proposed as current treatment options for COVID-19.

The therapies are divided into two categories in the following tables based on current evidence:

1. Benefit may exceed risk, potentially suitable for compassionate use (Table 1)
2. Inadequate data to recommended compassionate use currently, await further data (Table 2)

Table 1. Evidence base for specific therapies for SARS-CoV-2 infection: Benefit may exceed risk, potentially suitable for compassionate use

*S=SARS, M=MERS, S2=SARS-CoV-2; iv=in vitro, a=animal, c=clinical

Remdesivir				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; Miv; S2iv Sa; Ma Several non-UK S2c studies in progress and expected to report Apr 2020	Nucleotide prodrug with activity against a number of unrelated RNA viruses. Potent inhibition of SARS-CoV, MERS-CoV and bat coronaviruses with pandemic potential in human airway epithelial cells *in vitro*, with sub-micromolar EC50 values. In a mouse model of SARS-CoV, prophylactic and early therapeutic administration significantly reduces lung viral load and improves clinical signs of disease and respiratory function; later treatment, initiated at peak viral replication, reduces lung viral loads but does not alter clinical outcome. In a nonhuman primate model of MERS-CoV infection, prophylactic or early treatment improves clinical respiratory function and radiological signs, and reduces lung viral load and histopathological changes. Direct comparison with combination lopinavir/ritonavir and interferon-beta *in vitro* and in mouse models of MERS-CoV infection demonstrated greater virological, clinical and histopathological benefit with remdesivir.	Inhibits SARS-CoV-2 replication in Vero cells with a low micromolar EC50 value.	Manufacturer reports two phase 1 human trials completed, results not published. Phase 2 trial in Ebola Virus Disease (EVD) survivors (NCT 02818582) fully recruited but not yet reported. Extensive therapeutic use in 2018-20 Ebola outbreak in DRC, but trials designed for efficacy and only limited interpretation of safety is possible: no significant adverse safety signal detected.	Limited supply available for compassionate use (March 2020). Use restricted to severely ill patients. Compassionate use programme details at: https://rdvcu.gilead.com

Lopinavir/ritonavir				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; Miv Ma Sc Several non-UK S2c studies in progress and expected to report imminently	Protease inhibitor developed for HIV, a completely unrelated virus. In vitro data for both MERS and SARS-CoV are variable but suggest low potency inhibition at clinically achievable concentrations. No animal studies of SARS-CoV. In a nonhuman primate model of MERS, early treatment improved clinical, radiological and pathological features and reduced viral loads. In two retrospective, matched cohort studies of SARS, early but not rescue LPV/r treatment was associated with improved clinical outcomes, but interpretation is difficult because of multiple other uncontrolled interventions (ribavirin, corticosteroids) in these patients. Compassionate use in the S. Korea MERS outbreak was not informative about efficacy; no preliminary results available from ongoing MERS clinical trial in KSA. Combination LPV/r and ribavirin appeared beneficial in a small study of post-exposure prophylaxis against MERS in healthcare workers. Direct comparison between remdesivir, lopinavir/ritonavir, and interferon-beta *in vitro* and in mouse models of MERS-CoV infection demonstrated greater virological, clinical and histopathological benefit with remdesivir.	Unpulished data indicate that lopinavir is inhibitory at uM concentrations for SARS-CoV-2 in Vero cell culture. One observational study in COVID-19 patients did not find reduced duration of viral RNA detection in those receiving lopinavir-ritonavir. An open-label RCT of lopnavir-ritonavir in hospitlalized COVID-19 patients has been completed but results are not yet publically available.	Well established agent with well understood toxicity profile. Gastrointestinal side effects are very common. Note multiple significant drug-drug interactions.	Routinely available (licensed for the treatment of HIV-1 infection).

Table 2. Evidence base for specific therapies for SARS-CoV-2 infection: Inadequate data to recommended compassionate use currently, await further data

*S=SARS, M=MERS, S2=SARS-CoV-2; iv=in vitro, a=animal, c=clinical

Chloroquine (CQ)				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; S2iv	Inhibitory *in vitro* for SARS-CoV but the selective index is low. In one murine model of SARS intraperitoneal chlorquine was ineffective in inhibiting lung virus titers. For multiple other viruses, potent *in vitro* activity has not translated into benefit in animal or clinical studies. In some cases, CQ has been shown to enhance viral replication in animal models, probably because of its immunomodulatory effects. In both a nonhuman primate model and clinical trial in chickungunya infection (which is unrelated to SARS-CoV-2), CQ treatment resulted in worse outcomes, despite promising antiviral activity *in vitro*.	Effective inhibition of SARS-CoV-2 replication *in vitro.* Early announcements from China have reported significant clinical benefit of CQ treatment in COVID-19, but supporting data awaited.	Well established agent, defined safety profile as antimalarial drug; however, safety in acute viral illness is not established and studies, albeit with unrelated viruses, raise concerns (see data).	Routinely available (various licensed indications, including malaria and rheumatoid arthritis).

Interferon (systemic)				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; Miv Sa; Ma Sc; Mc	Type I (α, β), type II (γ), and type III (λ) IFNs all show activity against SARS-CoV in extensive *in vitro* studies. Type I (α, β) IFNs have shownactivity in limited animal and observational clinical studies. Dose-related reductions in lung viral titers were found in In mice dosed intraperitoneally with IFN- B/D beginning 4 h after SARS-CoV exposure. One small observational study of IFN-aflacon-1 combined with corticosteroids reported improved clinical outcomes in SARS. *In vitro*, MERS-CoV appears to be more sensitive to type I IFNs than SARS-CoV, especially IFN-β. Some animal evidence of benefit of early treatment with IFN-β1b in nonhuman primate model of severe disease. Observational studies of IFN-α combined with ribavirin have yielded inconclusive results; the largest study found no evidence for reduced mortality or for an antiviral effect. There are no preliminary results available from ongoing MERS clinical trial of systemic IFN-β-1b combined with lopinavir-ritonavir in the Kingdom of Saudi Arabia.	Unpublished in vitro data indicate that SARS-CoV is more susceptible to IFN- β-1a and -1b than to IFN-α.	Well established agent with defined but complex safety profile. Clinicians experienced in managing side effects should be consulted e.g. those who have treated hepatitis C virus (HCV) infection and multiple sclerosis.	Several different interferons are available for systemic administration. There are insufficient data to strongly recommend a particular preparation, although IFN-β appears more promising based on available data.

Key references

Al Ghamdi M, Al Ghamdi KM, Ghandoora Y, Alzahrani A, Salah F, Alsulami A, et al. Treatment outcomes for patients with Middle Eastern Respiratory Syndrome Coronavirus (MERS CoV) infection at a coronavirus referral center in the Kingdom of Saudi Arabia. BMC Infect Dis. 2016 Apr 21;16:174.

Arabi YM, Alothman A, Balkhy HH, Al-Dawood A, AlJohani S, Al Harbi S, et al. Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon-β1b (MIRACLE trial): study protocol for a randomized controlled trial. Trials. 2018 Jan 30;19(1):81.

Arabi YM, Shalhoub S, Mandourah Y, Al-Hameed F, Al-Omari A, Al Qasim E, et al. Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study. Clin Infect Dis. 2019 Jun 25. pii: ciz544. doi: 10.1093/cid/ciz544. [Epub ahead of print]

Barnard DL, Day CW, Bailey K, Heiner M, Montgomery R, Lauridsen L, et al. Evaluation of immunomodulators, interferons and known in vitro SARS-coV inhibitors for inhibition of SARS-coV replication in BALB/c mice. Antivir Chem Chemother. 2006;17(5):275-84.

Chan JF, Chan KH, Kao RY, To KK, Zheng BJ, Li CP, et al. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. J Infect. 2013 Dec;67(6):606-616.

Chan JF, Yao Y, Yeung ML, Deng W, Bao L, Jia L, et al. Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. J Infect Dis. 2015 Dec 15;212(12):1904-1913.

Chan KS, Lai ST, Chu CM, Tsui E, Tam CY, Wong MM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. Hong Kong Med J. 2003 Dec;9(6):399-406.

Chen F, Chan KH, Jiang Y, Kao RY, Lu HT, Fan KW, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol. 2004 Sep;31(1):69-75.

Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Kao RY, et al. Group HUSS. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004 Mar;59(3):252-256.

de Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, van Nieuwkoop S, Bestebroer TM, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrob Agents Chemother. 2014 Aug;58(8):4875-4884.

de Wilde AH, Raj VS, Oudshoorn D, Bestebroer TM, van Nieuwkoop S, Limpens RWAL, et al. MERS-coronavirus replication induces severe in vitro cytopathology and is strongly inhibited by cyclosporin A or interferon-α treatment. J Gen Virol. 2013 Aug;94(Pt 8):1749-60.

de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A. 2020 Feb 13. [Epub ahead of print].

Falzarano D, de Wit E, Rasmussen AL, Feldmann F, Okumura A, Scott DP, et al. Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV–infected rhesus macaques. Nat Med. 2013 Oct;19(10):1313-1317.

Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem. 2020 Feb 24. [Epub ahead of print]

Katz SJ, Russell AS. Re-evaluation of antimalarials in treating rheumatic diseases: re-appreciation and insights into new mechanisms of action. Curr Opin Rheumatol. 2011 May;23(3):278-281.

Keyaerts E, Vijgen L, Maes P, Neyts J, Ranst MV. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun. 2004 Oct 8;323(1):264-268.

Loutfy MR, Blatt LM, Siminovitch KA, Ward S, Wolff B, Lho H, et al. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. JAMA. 2003 Dec 24;290(24):3222-8.

Omrani AS, Saad MM, Baig K, Bahloul A, Abdul-Matin M, Alaidaroos AY, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. Lancet Infect Dis. 2014 Nov;14(11):1090-1095.

Park SY, Lee JS, Son JS, Ko JH, Peck KR, Jung Y, et al. Post-exposure prophylaxis for Middle East respiratory syndrome in healthcare workers. J Hosp Infect. 2019 Jan;101(1):42-46.

Roques P, Thiberville SD, Dupuis-Maguiraga L, Lum FM, Labadie K, Martinon F, et al. Paradoxical effect of chloroquine treatment in enhancing chikungunya virus infection. Viruses. 2018 May 17;10(5):268.

Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017 Jun 28;9(396):eaal3653.

Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020 Jan 10;11(1):222.

Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med. 2006 Sep;3(9):e343.

Touret F, de Lamballerie X. Of chloroquine and COVID-19. Antiviral Res. 2020 Mar. [Epub ahead of print].

Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020 Mar;30(3):269-271.

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 11. pii: S0140-6736(20)30566-3. doi: 10.1016/S0140-6736(20)30566-3. [Epub ahead of print]

Consultation

Rapid review was undertaken by the UK Airborne HCID Network lead clinicans:

- Mike Beadsworth, Royal Liverpool and Broadgreen University Hospitals NHS Trust
- Nicholas Price, Guys and St Thomas' NHS Foundation Trust
- Matthias Schmid, The Newcastle upon Tyne Hospitals NHS Foundation Trust
- Anne Tunbridge, Sheffield Teaching Hospitals NHS Foundation Trust