COVID-19
Treatment Summaries

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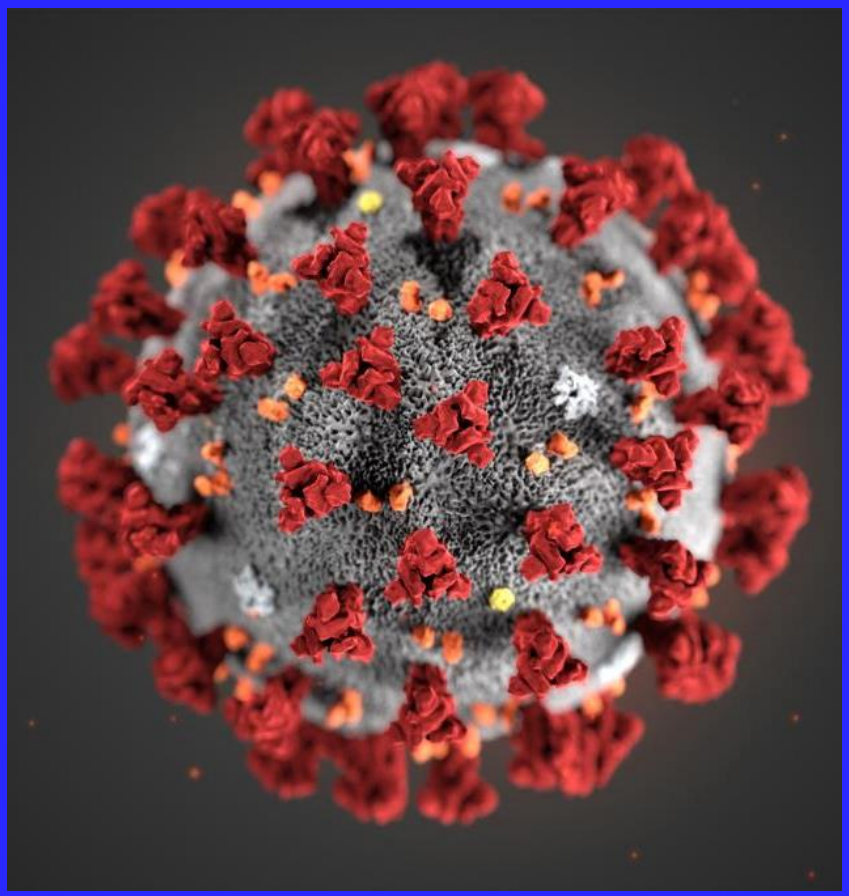

Laura Ghiggino
Rob Shulman

Version 1.0

UKCPA
CLINICAL PHARMACY ASSOCIATION

Critical Care Group

Contents

Summary

At time of publishing the NHS and World Health Organisation state that as there is no good evidence there is no specific treatment recommendations and medication outside normal management of viral infections, pneumonia, acute respiratory distress syndrome and shock should not be given outside of a registered clinical trial. This document is to give clinicians guidance on the potential therapies and as more information and guidance emerges offer concise information. There are other medications in clinical trials that currently do not have a monograph.

Lopinavir/Ritonavir Summary

- **A small trial in China found no significant benefit to using Lopinavir and Ritonavir but it may have a place in early therapy to reduce time to clinical improvement**
- **It is a licensed medication for the management of HIV but there are no licensed doses or duration of treatment in COVID-19**
- **It can be used in patients with renal dysfunction cautiously**
- **It should be avoided in patients with hepatic dysfunction**
- **There are many interactions which can be severe so they should be checked on initiation and throughout therapy**
- **There is a liquid available for swallowing difficulties and via NG tubes.**

Chloroquine Summary

- **There are currently no reported clinical trials regarding chloroquine and its usage in COVID-19 patients although there is some guidance worldwide about potential dosing schedules.**
- **There is some evidence of efficacy in vitro but not in vivo as of yet**
- **The World Health Organisation support trials investigating chloroquine**
- **Caution in patients with cardiac histories and with QT prolonging medications**
- **Use is contraindicated with amiodarone**
- **Overdose is extremely toxic**

Hydroxychloroquine Summary

- **There is a small open label clinical trials regarding hydroxychloroquine and its usage in COVID-19 patients which showed improvement but there needs to be more information and more robust trials to recommend its usage.**
- **The French trial showed benefit of hydroxychloroquine + azithromycin in combination**
- **Caution in patients with cardiac histories and with QT prolonging medications**

Ribavirin Summary

- **No current evidence for usage in COVID-19 but some unsupported dosing schedules released by China**
- **Some historic usage in the SARS epidemic 2002 with associated doses and adverse reaction information from high IV doses**
- **Lots of monitoring required especially haemoglobin, creatinine, LFTs and electrolytes**
- **Avoid in unstable cardiac disease and haemoglobinopathies**

Darunavir/Cobicistat Summary

- **Currently no evidence and only a few low power clinical trials into its usage in COVID-19**
- **Multiple serious drug interactions possible**
- **Not appropriate for use in severe hepatic disease**
- **Can confuse creatinine calculations due to artificially raised creatinine**

Nitazoxanide Summary

- **Nitazoxanide has been shown to inhibit SARS-CoV-2 in vitro but no clinical trial results have been published yet.**
- **Good safety profile**
- **Not readily available in the UK**

Remdesivir Summary

- **Gilead will not release this drug unless the patient is mechanically ventilated. Slightly unclear unlikely to release drug if the patient is on inotropes or vasopressors**

- **Most of the available drug in the compassionate use program is currently going to Italy**

- **No data on pharmacokinetics eg renal failure/haemofiltration**

Favipiravir Summary

- **Experimental treatment with currently no reported clinical trials**
- **Early information emerging from trials in China seem promising**
- **No public information regarding precautions, renal and hepatic effects or side effects**

Corticosteroid Summary

- **The WHO advises that corticosteroids should not be routinely used to treat acute lung injury or adult respiratory distress syndrome in critically ill patients with suspected or proven COVID-19 infection outside of clinical trials.**

- **Surviving Sepsis guidelines state that 'Low dose' corticosteroid therapy for refractory shock states should be used cautiously at the lowest dose and shortest duration possible and in accordance with the Surviving Sepsis Campaign guidelines and also in the sickest patients with ARDS[65].**

- **The evidence in COVID-19 is not currently available and the available guidelines are controversial and conflicting. The clinician should use their best judgement in the situation and monitor the patient for side effects of steroid usage of the decision is made to use them.**

Introduction

Ghiggino, L*, Shulman, R**
*Critical Care Pharmacist – Oxford University Hospitals NHS Foundation Trust ** Lead Critical Care Pharmacist – University College London Hospital

COVID-19 is a disease caused by the novel virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which appeared in Wuhan China at the end of 2019[1]. It is of the coronavirus family and is a relation of the previous human SARS virus which caused an epidemic in 26 countries in 2002. Currently there is little information available about the virus and its treatments since it is a novel agent and more research needs to be undertaken. The World Health Organisation (WHO) has issued guidance that no treatment should be undertaken unless the patient is enrolled in one of the many small emergency clinical trials that are being undertaken[2]. Data from epicentres of the virus (Wuhan, China and Northern Italy) shows a high proportion (9-11% in Italy)[3] of cases requiring intensive care treatment. The death rate varies by country which may be due to demographics as the virus seems to be particularly deadly to patients of advanced age and those with pre-existing co-morbidities.

The virus itself is a RNA virus with a lipid shell and protein spikes. Research has shown similarities with SARS virus which emerged from bats in 2002. The origin of the current virus is unknown. The spike (S) protein facilitates entry into cells through binding of the surface unit, S1, of the S protein to a cellular receptor. In addition, entry requires S protein priming by cellular proteases, which entails S protein cleavage at the S1/S2 and the S2 site. This allows fusion of the viral and cellular membranes. One study showed similar cell entry between SARS and SARS-CoV-2 implying that they target similar entry receptors on the cell surface. This study showed that SARS-CoV-2 seems to use ACE2 as a target protein for cell entry although this relevance to therapeutics is still unclear. This study also showed that serine protease TMPRSS2 primes SARS-CoV-2 for entry into cells and could be a target for future therapies[4].

Risk factors for severe disease

First reports from Wuhan, in admitted patients, overall, 91 (48%) of the 191 patients had comorbidity. Most common was hypertension (30%), followed by diabetes (19%) and coronary heart disease (8%). The odds of dying in the hospital increased with age (odds ratio 1.10, 95% confidence interval [CI], 1.03 - 1.17, per year increase in age), higher Sequential Organ Failure Assessment (SOFA) score (5.65, 2.61 - 12.23; $P < .0001$), and D-dimer level exceeding 1 µg/L on admission

Potential treatments and their considerations are listed below. As this is a new area of research information is likely to change quickly but the basic pharmacokinetics of existing licensed treatments should not be variable.

Ongoing Clinical Trials

[1] Gov.UK COVID-19: UK response; Accessed from https://www.gov.uk/government/publications/wuhan-novel-coronavirus-background-information/wuhan-novel-coronavirus-epidemiology-virology-and-clinical-features Accessed on 20/03/2020
[2] World Health Organisation; Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected; Interim Guidance; 13/03/2020
[3] Remuzzi,A and Remuzzi G; COVID-19 and Italy: what next?; The Lancet; March 2020
[4] Hoffmann, M et al; SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is Blocked by a Clinically Proven Protease Inhibitor; Cell; March 2020;

Currently there is no standout treatment for COVID-19 due to the lack of data and evidence. There are a number of ongoing clinical trials in the UK and if treatment with an agent is desired it should be sort out through enrolling in an existing clinical trial.

Name of the trial	Arms of the trial	Other Information	Link
RECOVERY	Usual care vs Usual care + lopinavir-ritonavir (PO or NG) vs Usual care + nebulised Interferon-β-1a vs Usual care + low dose dexamethasone (PO or IV)	Trial of each add on therapy is for 10 days Eligible criteria: - Over 18 - Hospitalised - Have a positive PCR for SARS-CoV-2 - No medical history that might put the patient at significant risk if he/she were to participate in the trial	https://www.recoverytrial.net/
REMAP-CAP	4 domains: Evaluation of prolonged macrolide therapy Corticosteroids: no corticosteroids vs low dose hydrocortisone vs hydrocortisone in septic shock Antiviral: no antiviral therapy vs lopinavir-tironavir Immune Modulation therapy: no immune modulation therapy vs interferon-β-1a vs interleukin-1 receptor antagonist (anakinra)	The trial is adaptive and intended to evolve over time. - Adult patients - ICU admission for severe CAP within 48 hours with symptoms of LRTI and radiological evidence of infiltrates - Up to 48 hours after ICU admission receiving organ support as detailed in protocol - All cause mortality at day 90 - Split into intervention domains and regional domains	https://www.remapcap.org/protocol-documents
ACTT (Adaptive COVID-19 Treatment Trial)	Placebo vs Remdesivir	Adaptive, randomised, double blind, placebo controlled trial - Adult patients - Confirmed SARS-CoV-2 via PCR - Any stage of disease but must have confirmed infiltrates or clinical assessment with crackles or mechanical ventilation/or supplemental oxygen	https://clinicaltrials.gov/ct2/show/NCT04280705
REALIST (Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration)	Human umbilical cord derived CD363 enriched MSCs vs placebo	Phase 1 – open label trial followed by phase 2 – randomized, double-blind, allocation concealed placebo controlled - Patient over 16 - Patients with ARDS - Patient on mechanical ventilation	https://www.clinicaltrials.gov/ct2/show/NCT03042143

Lopinavir/Ritonavir (Kaletra®)

Background

Currently licensed for the management of human immune deficiency virus (HIV) as a combined therapy at the dose of 400mg/100mg BD or 800mg/200mg OD[5]. Lopinavir is an antiretroviral by inhibiting HIV1 and HIV2 proteases. Ritonavir is used as a booster to further the action of lopinavir through augmentation of liver enzymes[6]. As a result there are many interactions which must be checked during its use.

Clinical Evidence

There is little clinical evidence currently but there are ongoing trials. The COVID national guidelines in China are suggesting a dose of 400mg/100mg BD for 10 days[7]. A recent publication showed no benefit in hospitalised patients from a randomized controlled trial of 199 patients with confirmed SARS-CoV-2. 100 patients received standard care, 99 patients received 400mg/100mg BD for 14 days. They excluded patients with liver conditions, pregnant patients and patients who had HIV due to other antiretroviral usage. Patients who were unable to swallow received lopinavir/ritonavir through a nasogastric tube. There were no significant differences between the two groups. 60.3% of patients were men and the median age was 58 although there were more patients with cancer in the treatment arm (5 vs 1).

"Patients assigned to lopinavir–ritonavir did not have a time to clinical improvement different from that of patients assigned to standard care alone in the intention-to-treat population (median, 16 day vs. 16 days; hazard ratio for clinical improvement, 1.31; 95% confidence interval [CI], 0.95 to 1.85; P=0.09). In the modified intention-to-treat population (which excluded 3 patients which died before treatment was given), the median time to clinical improvement was 15 days in the lopinavir–ritonavir group, as compared with 16 days in the standard-care group (hazard ratio, 1.39; 95% CI, 1.00 to 1.91). In the intention-to-treat population, lopinavir–ritonavir treatment within 12 days after the onset of symptoms was associated with shorter time to clinical improvement (hazard ratio, 1.25; 95% CI, 0.77 to 2.05), but later treatment with lopinavir–ritonavir was not (hazard ratio, 1.30; 95% CI, 0.84 to 1.99). No significant differences were observed when the time to clinical improvement was assessed by NEWS2 score at entry in the intention-to-treat population. In addition, when the time to clinical deterioration (defined as a one-category increase on the seven-category scale) was compared between the two groups, no difference was observed (hazard ratio for clinical deterioration, 1.01; 95% CI, 0.76 to 1.34)."

With regards to secondary outcomes: "the 28-day mortality was numerically lower in the lopinavir–ritonavir group than in the standard-care group for either the intention-to-treat population (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI, −17.3 to 5.7) or the modified intention-to treat population (16.7% vs. 25.0%; difference, −8.3 percentage points; 95% CI, −19.6 to 3.0).
Patients in the lopinavir–ritonavir group had a shorter stay in the intensive care unit (ICU) than those in the standard-care group (median, 6 days vs. 11 days; difference, −5 days; 95% CI, −9 to 0), and the duration from randomization to hospital discharge was numerically shorter (median, 12 days vs. 14 days; difference, 1 day; 95% CI, 0 to 3). In addition, the percentage of patients with clinical improvement at day 14 was higher in the lopinavir–ritonavir group than in the standard-care group (45.5% vs. 30.0%; difference, 15.5 percentage points; 95% CI, 2.2 to 28.8). There were no significant differences for other outcomes such as duration of oxygen therapy, duration of hospitalization, and time from randomization to death"

[5] Lopinavir and Ritonavir monograph;NICE BNF online; Accessed from www.bnf.nice.org.uk; Accessed on 14/03/2020
[6] Kaletra 100mg/25mg film-coated tablets; AbbVie Ltd; Last updated 12/11/2019; Accessed from www.medicines.org.uk/emc on 14/03/2020
[7] Liying Dong , Shasha Hu , Jianjun Gao; Discovering drugs to treat coronavirus disease 2019 (COVID-19); Drug Discovery and Therapeutics; 2020; 14 (1); Pages 58-60

There were more gastrointestinal side effects such as nausea, vomiting and diarrhoea in the treatment arm but there were more serious adverse events in the standard care arm. Around 14% of patients in the lopinavir/ritonavir arm couldn't complete 14 days of treatment due to side effects. The authors discussed that there may be benefit in treatment with lopinavir/ritonavir in early disease but improvement is only small between the drugs. Treatment does not seem to reduce viral RNA loads or duration of viral RNA detectable. The study was not blinded[8].

Administration and dosing schedule

Presentation: Lopinavir/Ritonavir 100mg/25mg tablets, 200mg/50mg tablets, 400mg/100mg oral solution

Treatment doses in adults: Unlicensed for COVID-19 Currently licensed for the management of human immune deficiency virus (HIV) as a combined therapy at the dose of 400mg/100mg BD or 800mg/200mg OD. The Chinese covid-19 guidelines suggest 400mg/100mg BD for 10 days. The study above suggests 400mg/100mg BD for 14 days.

Administration via nasogastric tube:

The tablets should not be crushed. Patient exposure to both drugs has been shown to be reduced by around 40% (range 5-75%) after crushing[9]

Better absorbed with a high fat meal[10] although the manufacture showed no difference between AUC (see pharmacokinetics)[6]

No specific information found

Use liquid and monitor response carefully although there is some information that liquid is incompatible with tubing that contains polyurethane. It is compatible with PVC or silicone feeding tubes.[11]

- Stop the enteral feed.
- Flush the enteral feeding tube with the recommended volume of water.
- Draw the required volume of liquid medication into the syringe.
- Flush the medication dose down the feeding tube.
- Finally, flush with the recommended volume of water.
- Re-start the feed, unless a prolonged break is required

Administration via nasojejenal tube

A case report suggests that lopinavir+ritonavir may not be absorbed when administered through a jejunostomy tube[12]

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[8] Cao, B et al; A trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19; The New England Journal of Medicine; 18 March 2020; Accessed 20/03/2020
[9] NEWT Guidelines; Lopinavir and ritonavir; Accessed 20/03/2020
[10] White R. Lopinavir + ritonavir monograph for inclusion in Handbook of Drug Administration via enteral feeding tubes; Medicines Complete; Accessed 20/03/2020
[11] Kaletra 80mg/20mg Oral solution; AbbVie Ltd; Last updated 12/11/19; Accessed from www.medicines.org.uk/emc on 25/03/2020
[12] Kamimura M, Watanabe K, Kobayakawa M *et al.* Successful absorption of antiretroviral drugs after gastrojejunal bypass surgery following failure of therapy through a jejunal tube. *Intern Med* (2009); 48: 1103-1104

Clinical Pharmacokinetics

Absorption[6]

Multiple dosing with 400/100 mg Kaletra twice daily for 2 weeks and without meal restriction produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 12.3 ± 5.4 µg/ml, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 8.1 ± 5.7 µg/ml. Lopinavir AUC over a 12 hour dosing interval averaged 113.2 ± 60.5 µg•h/ml. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

Effects of food on oral absorption

Administration of a single 400/100 mg dose of Kaletra tablets under fed conditions (high fat, 872 kcal, 56% from fat) compared to fasted state was associated with no significant changes in C_{max} and AUC_{inf}. Therefore, Kaletra tablets may be taken with or without food. Kaletra tablets have also shown less pharmacokinetic variability under all meal conditions compared to Kaletra soft capsules.

Distribution

At steady state, lopinavir is approximately 98 − 99% bound to serum proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin however, it has a higher affinity for AAG. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg Kaletra twice daily, and is similar between healthy volunteers and HIV-positive patients.

Biotransformation

In vitro experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolised by the hepatic cytochrome P450 system, almost exclusively by isozyme CYP3A. Ritonavir is a potent CYP3A inhibitor which inhibits the metabolism of lopinavir and therefore, increases plasma levels of lopinavir. A ^{14}C-lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg Kaletra dose was due to parent active substance. At least 13 lopinavir oxidative metabolites have been identified in man. The 4-oxo and 4-hydroxymetabolite epimeric pair are the major metabolites with antiviral activity, but comprise only minute amounts of total plasma radioactivity. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism, and likely the induction of lopinavir metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilising after approximately 10 days to 2 weeks.

Elimination

After a 400/100 mg ^{14}C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of ^{14}C-lopinavir can be accounted for in urine and faeces, respectively. Unchanged lopinavir accounted for approximately 2.2% and 19.8% of the administered dose in urine and faeces, respectively. After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in the urine. The effective (peak to trough) half-life of lopinavir over a 12 hour dosing interval averaged 5 − 6 hours, and the apparent oral clearance (CL/F) of lopinavir is 6 to 7 l/h.

Once-daily dosing: the pharmacokinetics of once daily Kaletra have been evaluated in HIV-infected subjects naïve to antiretroviral treatment. Kaletra 800/200 mg was administered in combination with emtricitabine 200 mg and tenofovir DF 300 mg as part of a once-daily regimen. Multiple dosing of 800/200 mg Kaletra once daily for 2 weeks without meal restriction (n=16) produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 14.8 ± 3.5 µg/ml, occurring approximately 6 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5.5 ± 5.4 µg/ml. Lopinavir AUC over a 24 hour dosing interval averaged 206.5 ± 89.7 µg•h/ml.

As compared to the BID regimen, the once-daily dosing is associated with a reduction in the C_{min}/C_{trough} values of approximately 50%.

Lopinavir:
Lopinavir is mainly excreted in faeces and to a smaller extent in the urine; unchanged lopinavir accounts for about 2.2% of a dose excreted in the urine and 19.8% in the faeces. After multiple dosing, less than 3% of the absorbed lopinavir dose is excreted unchanged in the urine[13].

Ritonavir:
About 86% of a dose is eliminated through the faeces (both as unchanged drug and as metabolites) and about 11% is excreted in the urine[14].

Renal Impairment

Lopinavir
Renal drug database[13]: dose as in normal renal function. Unlikely to be dialysed.

Ritonivir[14]
Renal drug database: dose as in normal renal function. Unlikely to be dialysed.

Lopinavir/Ritonavir

Manufacturer advises[6] since the renal clearance of lopinavir and ritonavir is negligible, increased plasma concentrations are not expected in patients with renal impairment. Because lopinavir and ritonavir are highly protein bound, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis.

Hepatic Impairment

Lopinavir:
LiverTox[15] reports that some degree of transaminase rises are found in 3-10% of patients but are usually mild and self- limiting and can resolve even with continuation of therapy. Clinically apparent injury is rare and usually appears 1 – 8 weeks after starting treatment which can progress to fatal outcomes.

Ritonivir:
LiverTox[16] reports moderate to severe elevation in around 15% of patients treated with full dose ritonavir. Ritonavir has been associated with clinically apparent liver concerns including cholestatic and hepatocellular but it is difficult to completely attribute this too full dose ritonavir as it is often combined with other drugs. In combination with saquinavir has been associated with rapid hepatic injury when combined with Rifampicin.

Lopinavir/Ritonavir:
The manufacturer states that Lopinavir/Ritonavir is contraindicated in severe liver disease. Increased bilirubin has been seen in as soon as 7 days from initiation. Increased monitoring is advised in existing liver impairment[6].

Highly protein bound so potentially increased exposure with reduced proteins in liver disease but studies show a limited increase of 30% of lopinavir concentrations that is unlikely to be of significance. High influences on CYP 3A4[6].

[13] Lopinavir monograph; Renal drug database; Accessed 14/03/2020
[14] Ritonavir monograph; Renal drug database; Accessed 14/03/2020
[15] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury; Lopinavir monograph; 01/09/2017; Accessed 14/03/2020
[16] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury; Ritonavir monograph; 01/09/2017; Accessed 14/03/2020

Drug Interactions

Lots of interactions due to ritonavir's actions on CYP450 enzymes. There is an extensive list through the Liverpool interaction checker. https://liverpool-covid19.s3.eu-west-2.amazonaws.com/landing-page/Covid_InteractionDetailsClass_Web_2020_Mar12.pdf and they can be checked through Stockleys and the BNF.

Summary

- **A small trial in China found no significant benefit to using Lopinavir and Ritonavir but it may have a place in early therapy to reduce time to clinical improvement**
- **It is a licensed medication for the management of HIV but there are no licensed doses or duration of treatment in COVID-19**
- **It can be used in patients with renal dysfunction cautiously**
- **It should be avoided in patients with hepatic dysfunction**
- **There are many interactions which can be severe so they should be checked on initiation and throughout therapy**
- **There is a liquid available for swallowing difficulties and via NG tubes.**

Chloroquine

Background

Chloroquine historically has been used malaria treatment and prevention. It is also used in for active rheumatoid arthritis/systemic lupus erythematosus (SLE). Its mechanism of action remains unclear[17].

Clinical Evidence

A systematic review[18] looking at six articles and 23 ongoing clinical trials (also included hydroxychloroquine) showed that chloroquine seems to have in vitro activity in limiting replication of SARS-CoV-2. An editorial written by French researchers, underlined in-vitro efficacy in other viral infections including SARS and discussed a favourable risk/benefit balance and wide availability and low cost of the drug. The expert consensus[19] by the Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province offers a dose of 500mg BD for 10 days but is based on unpublished in-vitro experience and there was no documentation on the method of how this consensus was reached. This panel recommended several precautions; including blood tests to rule out the development of anaemia, thrombocytopenia or leukopenia as well as serum electrolyte disturbances and/or hepatic and renal dysfunction. In addition ECG monitoring for QT prolongation and bradycardia and checks of visual and mental disturbances.

The Dutch Center of Disease control (CDC) suggests treating severe infections with chloroquine, however, it states treating sith supportive care is still a reasonable option due to lack of supporting evidence. In this document the dose suggested is 600mg of chloroquine base followed by 300mg after 12 hours on day 1 then 300mg BD on days 2-5. It highlights the need to stop treatment after day 5 to reduce side effects and the importance of differentiating between chloroquine phosphate and chloroquine base.

An Italian guideline document recommends Chloroquine phosphate 500mg BD or hydroxychloroquine 200mg OD for 10 days (with treatment variability from 5 to 20 days according to clinical severity).

The WHO and the authors of the systemic review deem usage of chloroquine experimental and there is no randomised controlled trials currently published to supports its usage outside of clinical trials.

Administration and dosing schedule

Presentation 250mg chloroquine phosphate tablets, Chloroquine phosphate 80mg/5ml syrup
Note: 250mg chloroquine phosphate = 155mg chloroquine base.

Adults Unlicensed for COVID-19 Active rheumatoid arthritis/SLE: 155mg (chloroquine base) OD (maximum 2.5mg/kg/day)
Treatment of non-falciparum malaria 620mg then 310mg after 6-8 hours then 310mg OD for 2 days (max 25mg/kg day of chloroquine base)[20]

[17] Chloroquine monograph; Martindale; The complete drug reference; Medicines Complete; Accessed 20/02/2020
[18] Cortegiani, A et al; A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19; Journal of Critical Care; 10 March 2020; Accessed 20/03/2020
[19] Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia; Zhonghua Jie He He Hu Xi Za Zhi. 2020 Mar 12;43(3):185-188
[20] Chloroquine monograph; NICE BNF online; Accessed from www.bnf.nice.org.uk; Accessed 14/03/20

Unlicensed COVID guidelines from China: Chloroquine phosphate: 500mg twice per day for 10 days for patients diagnosed as mild, moderate and severe cases of novel coronavirus pneumonia and without contraindications to chloroquine[7]

In obese patients use ideal body weight to avoid overdosing[20].

Administration via nasogastric tube:

The oral solution should be used in the first instance. The tablets can dissolve in water after about 5 minutes but have a very bitter taste[21]

The high viscosity of the liquid means it may require dilution with water immediately before administration[22]

Use liquid and monitor response carefully

- Stop the enteral feed.
- Flush the enteral feeding tube with the recommended volume of water.
- Shake the medicine bottle thoroughly to ensure mixing
- Draw the required volume of liquid medication into the syringe.
- Flush the medication dose down the feeding tube.
- Finally, flush with the recommended volume of water.
- Re-start the feed, unless a prolonged break is required

Administration via nasojejenal tube

Administration as above. High osmolality may increase incidence of GI side effects

Clinical Pharmacokinetics

Studies[23] in volunteers using single doses of chloroquine phosphate equivalent to 300mg base have found peak plasma levels to be achieved within one to six hours. Following a single dose, chloroquine may be detected in plasma for more than four weeks. Mean bioavailability from tablets of chloroquine phosphate is 89%. Chloroquine is widely distributed in body tissues such as the eyes, kidneys, liver, and lungs where retention is prolonged. The elimination of chloroquine is slow, with a multi exponential decline in plasma concentration. The initial distribution phase has a half-life of 2-6 days while the terminal elimination phase is 10-60 days. Approximately 50-70% of chloroquine in plasma is bound to the plasma proteins.

The principal metabolite is monodesethylchloroquine, which reaches a peak concentration within a few hours. Mean urinary recovery, within 3-13 weeks, is approximately 50% of the administered dose, most being unchanged drug and the remainder as metabolite. Chloroquine may be detected in urine for several months.

Chloroquine and its metabolites are excreted in the urine, with about half of the dose appearing as unchanged drug and about 10% as the monodesethyl metabolite. Chloroquine may be detected in urine for several months[24]

[21] NEWT Guidelines; Chloroquine; Accessed 20/03/2020
[22] White R. Chloroquine monograph for inclusion in Handbook of Drug Administration via enteral feeding tubes; Medicines Complete; Accessed 20/03/2020
[23] Avloclor 250mg tablets; Alliance Pharmaceuticals; Last updated 12/10/2016; Accessed from medicines.org.uk/emc on 14/03/2020
[24] Chloroquine monograph; Renal drug database; Accessed 14/03/2020

Renal Impairment

Renal Drug Database: Dose as in normal renal function above GFR of 10, less than 10 GFR reduce dose by 50%.

HD: Not dialysed (reduce dose by 50%)
HDF/High Flux: Unknown dialysability (reduce dose by 50%)
Continuous arteriovenous/venovenous HD: Not dialysed (dose as in normal renal function)

Excretion is increased in alkaline urine

Manufacturer[23] advises caution.

Hepatic Impairment

LiverTox: Usage of chloroquine over 50 years has rarely linked to transferase elevations or clinically apparent liver injury. In patients with acute porphyria and porphyria cutanea tarda, chloroquine can trigger an acute attack with fever and transferase elevations, sometimes resulting in jaundice.

Chloroquine undergoes minor metabolism by the liver (30%) and most is excreted unchanged in the urine[25].

Manufacturer[23] advises caution – can cause LFT and bilirubin changes especially in patients with cirrhosis

Monitor LFTs, Bilirubin and signs of toxicity. Overdose is very toxic and should be manged as per ToxBase.

Precautions[17,23]

- Chloroquine can prolong QTc interval and should be used with caution with patients with risk factors and taking other medications that can prolong QTc.
- Cardiomyopathy has been reported in patients being treated with chloroquine
- Caution in renal and liver disease (see relevant sections)
- Ophthalmic monitoring should occur in patients on long courses
- Caution in those with Glucose-6-phosphate dehydrogenase deficiency – risk of haemolysis
- Full blood counts due to potential bone marrow suppression
- DRESS syndrome reported with chloroquine
- Caution in epilepsy as seizure reported
- Caution in porphyria
- Caution in psoriasis
- Small number of cases of parenchymal lung disease reported
- Caution in myasthenia gravis

Drug Interactions

Always check for interactions. Caution with drugs that prolong the QT interval or have potential to cause arrhythmias. Amiodarone is contra-indicated.

Care with drugs that reduce the seizure threshold.

[25] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury; Chloroquine; 02/02/2017; Accessed 14/03/2020

Overdose

See Toxbase in addition to manufacturer[23] guide below

Features

Chloroquine is highly toxic in overdose and children are particularly susceptible. The chief symptoms of overdosage include circulatory collapse due to a potent cardiotoxic effect, respiratory arrest and coma. Symptoms may progress rapidly and include:

- General features include nausea and vomiting. Hypokalaemia is common in severe poisoning and metabolic acidosis may also develop. Rarely hepatotoxicity, nephritis, gastric haemorrhage, haematological abnormalities and psychiatric features may occur.

- Neurological features include headache, dizziness, drowsiness, blurred vision, diplopia and, rarely, blindness, may precede restlessness, increased excitability and convulsions. Coma is less common.

- Cardiac features often appear at an early stage. Cardiac arrest may be a presenting feature. Hypotension is very common and may progress to cardiogenic shock and pulmonary oedema.

With serious intoxication, width-increased QRS complex, bradyarrhythmias, nodal rhythm, QT prolongation, atrioventricular block, ventricular tachycardia, torsades de pointes, ventricular fibrillation may occur.

Intraventricular conduction defects with a wide QRS, and prolongation of the QT interval are more common than A-V (atrioventricular) conduction defects. Ventricular tachycardia and fibrillation tend to occur early while torsade de pointes develops after about 8 hours.

Management

Acute overdose with chloroquine can be rapidly lethal and intensive supportive treatment should be started immediately.

Death may result from circulatory or respiratory failure or cardiac arrhythmia but is usually due to cardiac arrest related to the direct effects on the myocardium. If there is no demonstrable cardiac output due to arrhythmias, asystole or electromechanical dissociation, external chest compression should be persisted with for as long as necessary, or until adrenaline and diazepam can be given (see below).

Firstly, maintain a clear airway and ensure adequate ventilation. The benefit of gastric decontamination is uncertain, but activated charcoal can be considered for adults and children aged over 5 years, within 1 hour of ingestion of more than 10 mg/kg of chloroquine base as a single dose or for any amount in a child aged 5 years and under, as it may reduce absorption of any remaining chloroquine from the gut. Activated charcoal should also be considered within 1 hour of ingestion of a weekly dose taken on 2 or more consecutive days. Alternatively, gastric lavage may be considered in adults within 1 hour of a potentially life threatening overdose. There is a risk of cardiac arrest following aspiration of gastric contents in more serious cases.

Monitor circulatory status (with central venous pressure measurement), cardiac rhythm, respiration, conscious level and urinary output. Check urea & electrolytes, liver function and full blood count in symptomatic patients. Consider arterial blood gas analysis in patients who have a reduced level of consciousness or have reduced oxygen saturation on pulse oximetry.

It is not clear if correction of hypokalaemia is essential but it may have a protective effect and should not be corrected in the early stages of poisoning. The degree of hypokalaemia may be correlated with the severity of chloroquine intoxication. If it persists beyond 8 hours, cautious correction should be undertaken with frequent biochemical monitoring of progress. Rebound hyperkalaemia is a risk during recovery.

In case of persistent metabolic acidosis consider intravenous sodium bicarbonate. Rapid correction is particularly important if there is prolongation of the QRS interval. DC (direct current) shock is indicated for ventricular tachycardia and ventricular fibrillation.

Cardiac arrhythmias should be treated with caution. The use of anti-arrhythmic drugs (such as those with quinidine-like effects) is best avoided since they may depress the myocardium further and exacerbate hypotension.

Early administration of the following has been shown to improve survival in cases of serious poisoning:

1. Adrenaline infusion until adequate systolic blood pressure (more than 100mg/Hg) is restored; adrenaline reduces the effects of chloroquine on the heart through its inotropic and vasoconstrictor effects.

2. Diazepam infusion; diazepam may decrease the cardiotoxicity of chloroquine.

Acidification of the urine, haemodialysis, peritoneal dialysis or exchange transfusion have not been shown to be of value in treating chloroquine poisoning. Chloroquine is excreted very slowly, therefore cases of overdosage require observation for several days.

Summary

- **There are currently no reported clinical trials regarding chloroquine and its usage in COVID-19 patients although there is some guidance worldwide about potential dosing schedules.**
- **There is some evidence of efficacy in vitro but not in vivo as of yet**
- **The World Health Organisation support trials investigating chloroquine**
- **Caution in patients with cardiac histories and with QT prolonging medications**
- **Use is contraindicated with amiodarone**
- **Overdose is extremely toxic**

Hydroxychloroquine Sulphate

Background

Hydroxychloroquine sulphate is a derivative of chloroquine and has similar characteristics. Usually used in rheumatoid conditions in the UK but also used for malaria in the USA. It's mechanism of action is not fully understood[26].

Clinical Evidence

Currently there is little evidence of the use of chloroquine or hydroxychloroquine. Please see information above for chloroquine.

A small French open label non randomised study of 36 COVID-19 patients showed a significant improvement in viral load when treated with 600mg a day (200mg three times a day for 10 days) of hydroxychloroquine. The patients were grouped by severity of disease and included asymptomatic patients, patients with upper respiratory tract infection and lower respiratory tract infection. 26 patients received hydroxychloroquine and 16 patients were control. 6 patients of the 26 in the hydroxychloroquine arm were lost to follow up as 3 were admitted to intensive care, 1 patient died, 1 self discharged and 1 stopped taking hydroxychloroquine due to nausea. The hydroxychloroquine arm was older than the control arm. 6 patients were also given azithromycin. The study showed that at day 6 57.1% of those treated with hydroxychloroquine and 100% of those treated with hydroxychloroquine + azithromycin were virologically cured compared with 12.5% of the control group. 1 patient in the hydroxychloroquine + azithromycin arm tested positive with a low titre on day 8 after testing negative on day 6. The authors published early due to the significant findings but the trial is still ongoing[27].

Administration and dosing schedule

Presentation 200mg tablet; Oral suspension and solution may be available as a special
Adults
Treatment dose **Unlicensed for COVID-19** Acute rheumatoid arthritis, Systemic and discoid lupus erythematosus and dermatological condtions caused or aggravated by sunlight: 200 – 400mg OD (6.5mg/kg/day)

Based on ideal body weight in obese patients[28]

Administration via enteral tube:
The tablet can be crushed and dispersed in water[29]

No information from The Handbook of Drug Administration via enteral feeding tubes

Clinical Pharmacokinetics[30]

Absorption

[26] Hydroxychloroquine monograph; Martindale The complete drug reference; Medicines Complete; Accessed 20/02/2020
[27] Gautret, P; Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial; International Journal of Antimicrobial Agents; March 2020
[28] Hydroxychloroquine monograph; NICE BNF online; Accessed from www.bnf.nice.org.uk; Accessed 14/03/20
[29] NEWT Guidelines; hydroxychloroquine; Accessed 20/03/2020
[30] Quinoric 200mg Film-Coated Tablets; Bristol Laboratories Ltd; Last updated 13/11/17; Accessed from medicines.org.uk/emc on 14/03/2020

Following oral administration, hydroxychloroquine is rapidly and almost completely absorbed. In one study, mean peak plasma hydroxychloroquine concentrations following a single dose of 400mg in healthy subjects ranged from 53-208ng/ml with a mean of 105ng/ml. The mean time to peak plasma concentration was 1.83 hours.

Distribution

The parent compound and metabolites are widely distributed in the body.

Metabolism

The metabolism of Hydroxychloroquine is similar to that of Chloroquine.

Elimination

The mean plasma elimination half-life varied, depending on the post-administration period, as follows; 5.9 hours (at C max- 10 hours), 26.1 hours (at 10-48 hours) and 229 hours (at 48-504 hours). Elimination is mainly via the urine, where 3% of the administered dose was recovered over 24 hours in one study.

Renal Impairment

Manufactures[30]: Advises caution in patients with renal and hepatic disorders. Estimation of plasma levels should be undertaken in patients with renal or hepatic disease and doses adjusted accordingly.

Renal Drug Database[31]:
GFR 30 – 50ml/min: 150mg daily
GFR 10 -30ml/min: 50mg-100mg daily (caution)
GFR less than 10ml/min: 50mg-100mg daily (caution)
*These doses may not be practical consider prolonging dosing interval

HD: Not dialysed – dose as in <10ml/min
HDF/High flux: Unknown dialysability - dose as in GFR <10ml/min
Continuous arteriovenous/venovenous HD: Unknown dialysability – dose as in GFR = 10-30ml/min

Hydrocychloroquine and its metabolites are slowly excreted via the kidneys. Attempt to avoid prolonged use in renal failure. There are some case reports of toxicity in patients with CKD stage 3.

Hepatic Impairment

LiverTox: Hydrocychloroquine has not been associated with increased enzyme elevation. A single case series (2 cases) twenty years ago reported acute liver failure but no reports since. Therefore incidence is likely rare. With the exception of use of hydroxychloroquine in porphyria cutanea tarda when used in high doses it can trigger an acute liver injury. This reaction is associated with sudden movement of prophyrins and is often followed by an improvement in porphyrin symptoms. This is often avoided by starting with low doses[32].

Manufactures[30]: Advises caution in patients with renal and hepatic disorders. Estimation of plasma levels should be undertaken in patients with renal or hepatic disease and doses adjusted accordingly.

Precautions

- Visual disturbances[30]
- QT prolongation and cardiac history
- Renal and hepatic dysfunction
- Can cause hypoglycaemia in patients treated with or without antidiabetic medications

[31] Hydroxychloroquine monograph; Renal drug database; Accessed 14/03/2020
[32] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury; Hydroxychloroquine; Last updated 25/03/2018; Accessed 14/02/2020

- Risk of bone marrow suppression
- Muscle and tendon weakness
- Steven Johnson Syndrome and Toxic Epidermal Necrolysis have been reported
- Extrapyramidal disorders

Drug Interactions

Can increase digoxin and ciclosporin levels – monitor carefully. Potentially can impair action of antiepiletics. Caution with drugs that prolong the QT interval.

Summary

- **There is a small open label clinical trials regarding hydroxychloroquine and its usage in COVID-19 patients which showed improvement but there needs to be more information and more robust trials to recommend its usage.**
- **The French trial showed benefit of hydroxychloroquine + azithromycin in combination**
- **Caution in patients with cardiac histories and with QT prolonging medications**

Ribavirin Treatment

Background

Ribavirin is a guanosine analogue that likely exhibits multiple mechanisms of action, both direct and indirect.[33] It has a wide spectrum of activity against RNA and DNA viruses, with the oral and nebulised forms being licensed for the treatment of chronic hepatitis C in combination with other agents and for respiratory syncytial virus (RSV) bronchiolitis in infants and children, respectively. It has been used experimentally in haemorrhagic fevers such as Lassa and in SARS[34]. Ribavirin should not be used by itself but in conjunction with other treatments.

Clinical Evidence

There is currently very little evidence of the use of ribavirin in COVID-19. There was multiple papers produced for IV and aerosol ribavirin in the SARS outbreak in 2002-2003 but its efficacy was not well established due to the lack of clinical trials and small number of cases. Ribavirin was shown to inhibit the SARS-CoV-2 virus in vitro but was less potent than other agents tested[35]. The combination of harmful side effects such as anaemia, poor outcomes and in vitro studies the WHO does not consider the drug viable in the fight against COVID-19.

[33] Beigel J, Bray M. Current and future antiviral therapy of severe seasonal and avian influenza. Antiviral Research 2008; 78(1): 91-102.
[34] Ribavirin Monograph; Martindale: The complete drug reference; Medicines Complete; Accessed 21/03/2020
[35] Wang, M et al; Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro; Cell Research; 2020; 30; 269-271

Administration and dosing schedule

Presentation Ribavirin 200mg tablets / capsules, 400mg tablets, 40mg/ml oral solution, 6g lyophylisate / 100ml vial for aerosolisation, 1.2g/12ml ampoules for infusion (unlicensed).

Treatment dose in adults:

Enteral Unlicensed for COVID-19
Chronic Hepatitis C treatment[36]
Dose is weight dependent from 400mg BD up to 600mg in the morning and 800mg in the evening (oral). See NICE BNF.

Dose can be adjusted according to haemoglobin.

Aerosol / Nebulised
Greatest experience is with the use of a small particle aerosol generator (SPAG) or Aiolos nebuliser. Most studies that examine ribavirin therapy in influenza use this approach and the licensed product for ribavirin aerosol production for treatment of RSV uses the same method to generate 190microg/l air ribavirin concentration.

Dissolve the powder in a minimum of 75ml water for injections in the 100ml vial. The solution should be adequately mixed to ensure complete dissolution. Shake well. When using the SPAG generator, transfer the solution to the clean, sterilised 500ml flask and dilute to a final volume of 300ml with water for injections. When using the Aiolos nebuliser, transfer the solution into an infusion bag and dilute to a final volume of 300ml with water for injections. The final ribavirin concentration should be 20mg/ml[37].

The aerosol dose recommended in the SARS outbreak of 2002 was 20mg/ml aerosol for 18hours of the day[38].

For children with life-threatening RSV, parainfluenza virus and adenovirus[34] in immunosuppressed children
33mg/kg (max 2grams) for 1 dose over 15mins, then 16mg/kg (max 1gram) every 6 hours for 4 days then 8mg/kg (max 500mg) every 8 hours for 3 days (IV). This matches a recognised dose for Haemorrhagic Fever with Renal Syndrome[39] and a review of the literature in 2009[40]

UNLICENSED

In the SARS epidemic a regime of 2gram loading dose IV followed by 1gram 8hourly IV for 4 days then 500mg 6 hourly for 3 days was used which was considered very-high dose treatment.

Ribavirin[19] dosage in China for COVID-19 500mg (IV) BD or TDS in combination with INF-alpha or lopinovir/ritonavir for 10 days

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[36] Ribavirin monograph; British National Formulary; NICE; Accessed 14/03/2020
[37] Virazole (Ribavirin) Aerosol; Summary of Product Characteristics; Last updates 14/11/14 (no longer available online)
[38] Koren, G et al; Ribavirin in the treatment of SARS: A new trick for an old drug; CMAJ; 2003; 168 (10); 1289 - 1292
[39] Huggins JW, Hsiang CM, Cosgriff TM, Guang MY, Smith JI, Wu ZO. Prospective, Double-Blind, Concurrent, Placebo-Controlled Clinical Trial of Intravenous Ribavirin Therapy of Hemorrhagic Fever with Renal Syndrome. Journal of Infectious Diseases 1991; 164(6):1119-1127.
[40] Riner A, Chan-Tack, K; Murray JS; Original Research: Intravenous Ribavirin – Review of the FRA's Emergency Investigational New Drug Database (1997-2008) and Literature Review; Postgraduate Medicine; 121 (3); 5-15

Clinical Pharmacokinetics

Clearance of intravenous Ribavirin is mainly excreted in the urine as unchanged drug and metabolites. Ribavirin is metabolised by reversible phosphorylation and a degradative pathway involving deribosylation and amide hydrolysis to produce an active triazole carboxyacid metabolite[41].

Ribavirin is approximately 28% via the renal route with the remainder through metabolism. There is a long terminal half-life due to phosphorylated ribavirin being sequestered intracellularly. Red blood cells do not degrade phosphorylated ribavirin and thus a proportion of the drug may remain in the system until red blood cells are destroyed.[42] There is a high volume of distribution.

Renal impairment

Data on drug clearance in renal or hepatic impairment is sparse. Patients with impaired renal function should be carefully monitored for signs and symptoms of toxicity, such as haemolytic anaemia.

Renal replacement therapies are unlikely to contribute much to drug clearance due to high volumes of distribution.

Renal Drug Database[41]:
GFR 30 – 50ml/min: 200mg and 400mg on alternative days
GFR 10 -30ml/min: 200mg daily (caution)
GFR less than 10ml/min: 200mg daily

HD: Not dialysed – dose as in <10ml/min
HDF/High flux: Unknown dialysability - dose as in GFR <10ml/min
Continuous arteriovenous/venovenous HD: Unknown dialysability - dose as in GFR 10 – 30ml/min

There are two studies using ribavirin (200–400 mg daily) in combination with interferon in haemodialysis and peritoneal dialysis patients. Anaemia was one of the main problems, resulting in either increased doses of erythropoietin or discontinuation of ribavirin therapy. Most patients were stabilised on a dose of 200 mg daily or 200 mg 3 times a week. A dose of 200 mg daily gave troughs comparable to those in patients with normal renal function taking 1200 mg daily. Patients with impaired renal function should be carefully monitored during therapy with ribavirin for signs and symptoms of toxicity, such as haemolytic anaemia.

Available clinical experience suggests that patients with renal insufficiency and CrCl=50–80 mL/min tolerate the usual dosage regimen of ribavirin.

Individuals with moderate to severe renal insufficiency (CrCl=30–50 mL/min) have tolerated, without reports of complications, a dose regimen with an initial loading dose of 20–25 mg/kg, followed by single daily doses of 10 mg/kg for 9–10 consecutive days.

There is no experience in patients with end-stage renal disease

The manufacturer[43] has guidance using the same doses as the renal drug database above including haemodialysis 200mg daily. They advise using extreme caution and intensive monitoring of haemoglobin concentration with corrective action if needed. If adverse reactions ribavirin should

[41] Ribavirin monograph; Renal drug database; Accessed 14/03/2020
[42] Preston GL, Drusano GL, Glue P, Nash J, Gupta SK. Pharmacokinetics and Absolute Bioavailability of Ribavirin in Healthy Volunteers as Determined by Stable-Isotope Methodology. Antimicrobial Agents and Chemotherapy 1999; 43(10):2451-2456

[43] Ribavirin 200mg Film-Coated Tablets; Aurobindo Pharma- Milpharm Ltd; Last updated 14/10/19; Accessed from medicines.org.uk/emc on 15/03/2020

be held until adverse reactions abate or decrease in severity. If intolerance persists after restarting ribavirin it should be discontinued.

Hepatic impairment

LiverTox[44]: Oral therapy with ribavirin alone is rarely used and has not been associated with serum aminotransferase elevations. As it is often used for hepatitis C treatment increases in ALT are difficult to interpret. Ribavirin can cause dose depended haemolysis of red blood cells which can also indirectly cause a rise in bilirubin. In some patients with severe liver disease this could cause visible jaundice which usually resolves on discontinuation of ribavirin. Haemolysis onset is usually 2-3 weeks after staring therapy.

Reports of HIV patients taking concomitant Ribavirin with interferon alfa or direct oral antivirals to treat hepatitis C have rarely listed fatty liver with lactic acidosis and hepatic dysfunction. This has not been reported with use of ribavirin on it own.

Patients with advanced cirrhosis and receiving ribavirin in addition to other direct acting viral agents for hepatitis C have resulted in acute hepatic decompensation. If ribavirin can cause hepatic injury then the incidence is very rare.

The manufacture states that as there is no effect of pharmacokinetics in patients with hepatic impairment that there is no dose adjustment required.

Martindale states that ribavirin should be avoided in severe hepatic impairment or decompensated cirrhosis but with no clear reasoning.

Precautions

- Hypomagnesemia, hypocalcemia, anaemia and bradycardia were reported when IV ribavirin was used in SARS patients although this could be multifactorial and related to high doses used.[45]
- Contraindicated in pregnancy, breastfeeding, unstable or uncontrolled heart disease (within 6 months) and in haemoglobinopathies (sickle cell disease ect.)
- Monitor haemoglobin carefully and adjust dose. Most drops in haemoglobin are seen within the first 1-2 weeks of therapy when taking ribavirin orally.[38]
- When given via inhalation cases of worsening lung function, pneumothorax, bacterial pneumonia and cardiovascular events have been reported[34]
- Can worsen gout
- Can worsen psychiatric disorders
- Caution in cardiac diseases
- Caution in adults with dental and ocular disorders
- Caution in adults with haemolysis and anaemia
- Can increase risk of rejection in transplant patients[36]

Drug Interactions

Not many interaction studies have been performed. Check common literature.

[44] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury; Ribavirin; 10/06/2018; Accessed 15/03/2020

[45] Muller et al; Adverse Events Associated with High Dose Ribavirin: Evidence from the Toronto Outbreak of Severe Acute Respiratory Syndrome; Pharmacotherapy; 2007; 27 (4); 494-503

Summary

- **No current evidence for usage in COVID-19 but some unsupported dosing schedules released by China**
- **Some historic usage in the SARS epidemic 2002 with associated doses and adverse reaction information from high IV doses**
- **Lots of monitoring required especially haemoglobin, creatinine, LFTs and electrolytes**
- **Avoid in unstable cardiac disease and haemoglobinopathies**

Darunavir/Cobicistat

Background

Darunavir is an HIV-1 protease inhibitor recommended for combination HAART regimens for both treatment-naive and treatment-experienced patients Cobicistat is a mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates, such as darunavir, where bioavailability is limited and half-life is shortened due to CYP3A-dependent metabolism[46].

Clinical Evidence

Currently no evidence in its usage. A couple of low importance clinical trials underway in China.

Administration and dosage

Presentation: Darunavir + Cobicistat 800mg/150mg tablets, Darunavir 75mg, 150mg, 400mg, 600mg, 800mg tablets, Darunavir 100mg/ml oral suspension, Cobicistat 150mg tablet

Adult dosing:
Darunavir + Cobicistat[47]
800mg/150mg OD for HIV

Darunavir[48]
600mg BD or 800mg OD for HIV

Cobicistat[49]
150mg OD for HIV

Administration via a nasogastric tube: No information on usual sources. Some case reports supporting usage of crushed darunavir tablets down an NG tube[50]. The manufacture of the combined tablet Rezolsta® states that the combined tablet can be cut in half and administered immediately[44].

Clinical Pharmacokinetics

Darunavir:
Absorption with food is 1.7 times higher than without. The type of food is not important
Binds primarily to alpha1-acid glycoprotein and is 95% protein bound
80% cleared in faeces 14% cleared in urine. The terminal elimination half life was 15 hours when combined with ritonavir.

Cobicistat: Cobicistat is 97-98% bound to human plasma proteins. Following oral administration of [^{14}C]-cobicistat, 86% and 8.2% of the dose were recovered in faeces and urine, respectively. It is not readily metabolised. The median terminal plasma half life is 3-4 hours.

Renal impairment

Darunavir
Renal drug database[51]: dose as in normal renal function. Unlikely to be dialysed
Manufacturer advises no dose change required[52]

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[46] Rezolsta 800mg/150mg film coated tablets; Janssen-Cilag Ltd; Last updated 19/03/2020; Accessed 21/03/2020
[47] Darunavir/Cobicistat monograph; NICE BNF online; Accessed 14/03/2020
[48] Darunavir monograph; NICE BNF online; Accessed 14/03/2020
[49] Cobicistat monongraph; NICE BNF online; Accessed 14/03/2020
[50] Kim, C, Fulco,P, Muzevich, K; Orogastric Administration of Crushed Darunavir Tablets for a Critically ill patient; The Canadian Journal of Hospital Pharmacy; 2014; 67 (1); Pages 39-42
[51] Darunavir monograph; Renal drug database; Accessed 14/03/2020

Cobicistat
Renal drug database[53]: dose as in normal renal function. Unlikely to be dialysed

- Manufacturer advises to use with caution in dialysis patients due to lack of data.
- Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine. For this reason CrCl can be misleading in patients treated with cobicistat. Manufacturer's state it should be avoided with concomitant antiretroviral which require reduction due to renal dysfunctions[54].

Hepatic impairment

Darunavir: Manufacturer contra-indicates usage in severe hepatic impairment (Child-Pugh score C). There is an increase in unbound darunavir in mild to moderate hepatic impairment increasing risk of side effects. Medicine induced hepatitis has been reported – extra LFT monitoring for patients with hepatic conditions[51] Liver Tox reports hepatic injury around 1-8 weeks after starting therapy. Most cases are self-limiting but there have been reports of fatal cases[55].

Cobicistat: No adjustment required in mild to moderate hepatic impairment. No information for severe impairment. Has shown to increase bilirubin and increases in AAT and AST[54]

No information from LiverTox on cobicistat.

Influences on CYP450 metabolism.

Highly protein bound so potentially increased exposure with reduced proteins in liver disease.

Precautions

- Caution in patients over 65 due to limited information
- Contraindicated in patients with severe hepatic impairment and can cause hepatotoxicity
- Not suitable for patients with a sulphonamide allergy as darunavir contains a sulphonamide
- Rarely caused DRESS and Steven-Johnson Syndrome
- Cobicistat can alter creatinine rendering creatinine clearance inaccurate
- Can potentially increase risk of bleeding – caution with haemophiliac patients

Drug interactions

Contraindicated with amiodarone, quinine, ivabradine, ranolazine, domperidone, quetiapine, colchicine, erogot derivatives, dabigatran, ticagrelor[46]
(this list is not exhaustive, always check interactions)

Efficacy reduced by carbamazepine, phenytoin, phenobarbital, rifampicin, lopinavir/ritonavir

Combination not contraindicated but may increase alfentanyl and digoxin blood levels.

Dexamethasone may decrease darunavir and/or cobicistat plasma levels.

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[52] Darunavir 600mg film-coated tablets; Accord-UK Ltd; Last updated 06/09/2019; Accessed from medicines.org.uk/emc on 14/03/2020
[53] Cobicistat monongraph: Renal drug database; Accessed 14/03/2020
[54] Tybost 150mg film coated tablet; Gilead Sciences Ltd; Last updated 17/04/2019; Accessed from medicines.org.uk/emc on 14/03/2020
[55] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury; Darunavir; 01/09/2017; Accessed 14/03/2020

Summary

- **Currently no evidence into its usage in COVID-19**
- **Multiple serious drug interactions possible**
- **Not appropriate for use in severe hepatic disease**
- **Can confuse creatinine calculations due to artificially raised creatinine**

Nitazoxanide

Background

Used in the USA for parasitic infections specifically cryptosporidiosis and giardiasis. It has been in other protozoal and helminth infections, particularly in immunocompromised patients, including those with HIV. It is also being investigated for the treatment of chronic hepatitis C, rotavirus disease and Clostridium difficile colitis[56].

Clinical Evidence

Nitazoxanide has been shown to inhibit SARS-CoV-2 in vitro[35] but there is currently no evidence from clinical trials[57].

Administration and dosage

Presentation: 500mg tablets (unlicensed in the UK), 100mg/5ml oral suspension (unlicensed in the UK)

Nitazoxanide tablets and oral suspension are not bioequivalent. Bioavailability of the oral suspension is 70% relative of that of the tablet.[58]

Adult dose:
500mg 12 hourly for 3 days – Giardias/Cryptosporidim[59] doses up to 10 days used experimentally for Clostridium difficile and up to 36 weeks in chronic hepatitis C[60].

Clinical Pharmacokinetics

Nitazoxanide is absorbed from the GI tract and the extent of absorption is enhanced if given with food. Nitazoxanide was found to deacetylate extremely rapidly to tizoxonide in plasma (half-life about 6 minutes at 37 degrees)[61] and a peak is seen 1 to 4 hours after an oral dose. Tizoxonide is more than 99% bound to plasma proteins. Elimination of the total dose of nitazoxnide occurred both in urine (31.5%) and faeces (66.2%).

Renal impairment

"The pharmacokinetics of nitazoxanide in patients with compromised renal or hepatic function have not been studied. Therefore, nitazoxanide must be administered with caution to patients with hepatic and biliary disease, to patients with renal disease and to patients with combined renal and hepatic disease"[58].

As it is so highly protein bound it is unlikely to be removed by dialysis.

Hepatic impairment

Long term use doesn't seem to cause liver damage[62]

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[56] Nitazoxanide monograph; Martindale: The complete drug reference; Medicines Complete; Accessed 21/02/2020
[57] Li, G and De Clercq, E; Therapeutic options for the 2019 novel coronavirus (2019-nCoV); Nature Reviews Drug Discovery; 2020; 19; 149-150
[58] Nitazoxanide monograph: AHFS Drug Information; Medicines Complete: Accessed 21/02/2020
[59] Alinia (nitazoxanide) Tablets; Romark Pharmaceuticals (Tampa Florida); June 2005; Accessed through FDA < https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021818lbl.pdf> Accessed on 15/03/2020
[60] Rossingnol, JF et al; Improved virologic response in chronic hepatitis C genotype 4 treated with nitazoxanide, peginterferon and ribavirin; Gastroenterology; 2009; 136 (3); 856-862
[61] Broekhuysen, J; Nitazoxanide: pharmacokinetics and metabolism in man; International Journal of Clinical Pharmacology and Therapeutics; 2000; 38 (8); Page 387 - 394
[62] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury; Nitazoxanide; 04/02/2014 Accessed on 14/03/2020

Side Effects

Generally side effects seem to be mild; abdominal pain, nausea, diarrhoea, vomiting and headache. Less commonly reported adverse effects include; anorexia, fever, flatulence, pruritis and dizziness. Rarely reported side effects include spontaneous bone fracture and discoloration or urine and eyes. Increased creatinine and liver enzyme values noted.

Precautions

- Pregnancy
- Renal and Hepatic impairment

Drug interactions

The metabolic product tizoxonide is 99% bound to plasma proteins so there is a theoretical interaction with other highly protein bound drugs ie. Warfarin, phenytoin

In vitro there are no effects on the P450 enzymes so other interactions are not expected

Summary

- **Nitazoxanide has been shown to inhibit SARS-CoV-2 in vitro but no clinical trial results have been published yet.**
- **Good safety profile**
- **Not readily available in the UK**

Favipiravir (Avigan®)

Background

Favipiravir is an experimental drug with action against RNA viruses developed by Toyama Chemical of Japan. It is reserved for novel or re-emerging influenza when other anti-influenza medications are ineffective or not effective[63]. The manufacturer publication states that "Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is an antiviral drug that selectively inhibits the RNA-dependent RNA polymerase of influenza virus. It is phosphoribosylated by cellular enzymes to its active form, favipiravir-ribofuranosyl-5′-triphosphate (RTP). Its antiviral effect is attenuated by the addition of purine nucleic acids, indicating the viral RNA polymerase mistakenly recognizes favipiravir-RTP as a purine nucleotide"[64].

Clinical Evidence

Currently there are numerous clinical trials in China testing the safety and efficacy of Favipiravir in COVID-19 patients. On 18/03/2020 a Chinese Sci-Tech official announced that following a clinical trial in Shenzhen favipiravir has shown to be effective against SARS-CoV-2 but as of 22/03/2020 a credible source or paper could not be identified on PubMed® or through internet searches.

Administration and dosage

Preparations: Tablets manufactured on demand for influenza

Adult doses: orally 1.6 grams BD on day 1 followed by 0.6 gram BD for days 2 to 5[63]

Clinical Pharmacokinetics

A study in non human primates using intravenous favipiravir showed complex non-linear kinetic profile. There was a larger increase in drug concentration between the first and second doses. The authors of the study believe this is because favipiravir inhibits aldehyde oxidase which is the main enzyme used in the drug elimination. The half-life is around 2-6hours[65].

Renal and Hepatic impairment

No current information available

Side Effects

- Anorexia[64]

Precautions

- Pregnant and breast feeding (some information that it may be teratogenic
- Higher doses have been associated with anaemia and hepatic disorders in primates[62]

Drug interactions

No other information available

Summary

- **Experimental treatment with currently no reported clinical trials**
- **Early information emerging from trials in China seem promising**
- **No public information regarding precautions, renal and hepatic effects or side effects**

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[63] Favipiravir monograph; Martindale: The complete drug reference; Accessed from medicines complete; Accessed on 22/03/2020

[64] Furuta, Y et al; Favipiravir (T-705), a novel viral RNA polymerase inhibitor; Antiviral research; 2013; 100 (2); 446-454

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Remdesivir

Background

This is an unlicensed experimental drug which is made by Gilead sciences.

Remdesivir, is a prodrug that metabolizes into its active form GS-441524, an adenine nucleotide analogue that potently inhibits the SARS, MERS and SARS CoV-2 RNA dependent RNA polymerases (preliminary in vitro data on the latter). It therefore reduces viral replication[66]. Mutations are expected to emerge in the polymerase gene but currently are of unknown impact.

Clinical Evidence

There are in vitro and in vivo data in mice (RDV and IFNb superior to lopinavir/ritonavir in MERS) and macaques suggesting efficacy in MERS and SARS –CoV-2. There are two clinical trials (NCT04252664, 2/5/20; NCT04257656, 2/6/20) currently recruiting two patient populations in China; those with severe disease and those with mild/moderate disease. Two doses are in trial. Results are expected end of April. A US NIH led trial just started.[67]

Administration and dosage

Indication for usage:

- SARS CoV-2 confirmed by PCR
- Request within 8 days of PCR positive result
- Patient requiring mechanical ventilation
- Ideally no inotropic/vasopressor support

IV preparation in a stable lyophilized formulation that does not require cold chain for transport and storage. Intravenous infusion for 30 minutes. No special training or equipment is required for the drug administration.

The remdesivir dosing regimen for adult and adolescent (≥ 40 kg) patients is as follows: single remdesivir 200 mg IV loading dose (infused over 30 min) on Day 1 of treatment followed by 9 to 13 once daily 100 mg IV (infused over 30 min) maintenance doses. The recommended Remdesivir dosing duration is a total of 10 days, but dosing may be continued for an additional 4 days at 100 mg IV once daily if SARS-CoV-2 remains detectable at day 10 of treatment[68].

For pediatric patients with body weight < 40 kg, a body weight-based dosing regimen of one loading dose of remdesivir 5 mg/kg IV (infused over 30 min) on Day 1 followed by 9 to 13 once daily remdesivir 2.5 mg/kg IV (infused over 30 min) maintenance doses will be administered. Use of this weight-based regimen is expected to maintain remdesivir exposure that is comparable to that observed in adults.

Daily monitoring or renal (creatinine and BUN) and liver (ALT, AST) functions should be performed.

Clinical Pharmacokinetics

Preclinical pharmacokinetic profile in non-human primates and other relevant animal species indicating high and persistent levels of pharmacologically active nucleoside triphosphate metabolite in peripheral blood mononuclear cells (PBMCs); this measurement is used as a surrogate for drug levels in cells relevant for Ebola virus infection, supporting once daily administration. The same dose is in trials in COVID-19

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[66] Gordon, C et al; The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus; The Journal of Biological chemistry; 2020

[67] Ko, W et al; Arguments in favour of remdesivir for treating SARS-CoV-2 infections; International Journal of Antimicrobial Agents; 2020

[68] Al-Tawfiq, J et al; Remdesivir as a possible therapeutic option for the COVID-19; Travel Medicine and Infectious Disease; Mar 2020

Tissue distribution studies in non-human primates indicate effective penetration and distribution of remdesivir into immune privileged sites (genital tract, eye, and to some extent brain). Relatively high levels of remdesivir metabolites were also detected in human semen following single and repeated administration of remdesivir, suggesting potential for antiviral effect in human genital tract. Good penetration in lung tissue is expected.

In one adaptive clinical trial protocol it states that in vitro remdesivir is a substrate of CYP3A4. This could mean drug-drug interactions but the same protocol states that in vivo that drugs that effect CYP enzymes are not expected to effect remdesivir drug levels as its metabolism is likely to be mediated by hydrolase activity. Gilead (the manufacturer) feels that there is no reason to believe that a significant interaction exists between CYP3A4 inhibitors and Remdesivir[69].

Renal and Hepatic impairment

There are no clinical safety or pharmacokinetic (PK) data available for remdesivir in patients with renal and/or hepatic impairment. Given the benefit:risk ratio in patients with COVID19 no dose modification is recommended at the present time for patients with renal and/or hepatic impairment. However patients with significant renal and liver impairment might be excluded in the current compassionate programme.

Side Effects

Remdesivir has been used in the recent Ebola outbreak in a clinical trial; it was discontinued early as the arm of the trial using monoclonal antibodies showed superior efficacy early in the trial. Safety data are available from preclinical and clinical (phaseI,II) data in Ebola trials and preclinical and limited anecdotal clinical data (no trial data yet) in coronaviruses (MERs/SARS-CoV-2).

Clinical safety profile from > 100 human subjects dosed with intravenous remdesivir supports the clinical dosing regimen recommended for the treatment of Ebola. Single and repeated doses of remdesivir were safely administered in Phase 1 studies in healthy human subjects, PREVAIL IV study in male Ebola virus disease (EVD) survivors, as well as during compassionate use for the treatment and post exposure prophylaxis of Ebola infection.

Single dose of remdesivir IV infusion from 3 to 225 mg was well tolerated with no dose limiting toxicity observed. No treatment emergent AEs were observed in more than 1 subject per arm. No evidence of renal or liver toxicity was observed. All AEs were Grade 1 or 2. Multiple-dose IV administration of remdesivir 150 mg once-daily for 7 or 14 days was generally well tolerated. No subjects had a Grade 3 or 4 treatment- emergent laboratory abnormality during the study. Reversible Grade 1 or 2 ALT or AST elevations were observed in several subjects without abnormalities in total bilirubin, alkaline phosphatase (ALP), or albumin. There was no abnormality or clinically significant change in international normalized ratio (INR) in any subjects. Remdesivir did not show any effects on renal function in the multiple-dose study.

To date, remdesivir has been administered on an expanded compassionate access basis to patients with Ebola infection. The treated cases included a 39-year- old female diagnosed with recrudescent Ebola in the UK, meningitis and a neonatal patient with acute Ebola infection in the 2014-2016 outbreak, as well as ongoing treatment of confirmed Ebola infection cases in the ongoing outbreak in Eastern DRC treated under MEURI protocol.

Remdesivir has been administered to two adult subjects following a high-risk exposure to Ebola or Sudan virus in laboratory settings. A five-day course of remdesivir post-exposure prophylaxis at 100 mg once- daily was well tolerated without any treatment- associated safety observations or

[69] McCreary, E and Pogue, J; COVID-19 Treatment: A review of Early and Emerging Options; Infectious Diseases Society of America; 2020

laboratory abnormalities. Both subjects remained PCR negative for viral RNA following the remdesivir treatment[70].

There are no clinical safety or pharmacokinetic (PK) data available for remdesivir in patients with renal and/or hepatic impairment. Given the benefit:risk ratio in patients with COVID19 no dose modification is recommended at the present time for patients with renal and/or hepatic impairment. However patients with significant renal and liver impairment might be excluded in the current compassionate programme.

Precautions

According to GMC guidance, patient/family consent should be sought for unlicensed drugs.

There are two formulations that Gilead are releasing as part of their compassionate use programme – Both were originally developed as investigational medicinal products for use in their Ebloa, SARS, MERS and Covid-19 studies. We will need to pre-warn nurses that both are labelled as GS-5734, and do not have an expiry date on the packaging.

- The primary formulation in clinical trials use currently is the dry powder vial, exactly as described in the WHO paper – 150 mg vials of lyophilised powder for reconstitution
- The second is a product that was used early in early studies, which requires storage in a freezer at <-20 degC – Again these are 150 mg vials, but in solution

Drug interactions

No information currently

Summary

- **Gilead will not release this drug unless the patient is mechanically ventilated. Slightly unclear unlikely to release drug if the patient is on inotropes or vasopressors**
- **Most of the available drug in the compassionate use program is currently going to Italy at the time of writing**
- **No data on pharmacokinetics eg renal failure/haemofiltration is available at the time of writing**

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Corticosteroid Therapy

Background

The use of corticosteroid therapy in the management of adult respiratory distress syndrome (ARDS) and acute lung injury (ALI) has been the subject of much controversy for many years. This controversy extends to the use of corticosteroids in the management of COVID-19 patients. The use of corticosteroids in refractory shock is common place within critical care units and is a weak recommendation of the surviving sepsis guideline for COVID-19 patients. The dose should be low and for the shortest period possible. The surviving sepsis guideline does not recommend routine use of steroids as there is some evidence that it can increase viral shedding, however, in very sick patients with ARDS low dose corticosteroids for the shortest period possible is recommended[71]. In other publications including the WHO interim guidance advises to avoid steroids in most cases.

Clinical Evidence

The clinical data for use of corticosteroids in SARS-CoV-1 (2002) infections are mixed. Multiple analyses show no impact on outcomes, one report demonstrates decreased mortality in critically ill patients, and others have documented worse outcomes for patients receiving steroids, including increased time to viral clearance or an increase in the composite endpoint of ICU admission or death.

A paper in the Lancet[72] and interim guidance by the WHO[73] discourages use of steroids in most COVID-19 patients. This stance has resulted from study outcomes of steroid use in the SARS and MERS outbreaks where the risks of using steroids didn't outweigh the benefits and even though most studies were not robust evidence those done to completion showed an increase in harm with steroid usage. As there is not enough evidence for clinical benefit these authors advise that steroids should be avoided. The WHO states that in the case of sepsis then steroids may be considered by clinicians for patients whom adequate fluids and vasopressor therapy do not restore hemodynamic stability. The risk of administering steroids include potential prolonged shedding of the coronavirus which has been observed in MERS-CoV patients although this did not effect the mortality rate[74]. The WHO is prioritising clinical trials investigating steroid use as more data is needed.

The updated surviving sepsis guidelines for COVID-19 patients states that as there is no direct evidence of use of steroids in COVID-19 they suggest low dose steroids for patients with refractory shock over no steroid treatment. This is a weak recommendation based on low evidence. The guidance suggests not using steroids routinely in ARDS but as COVID-19 has been associated with cytokine storm which is reminiscent of secondary hemophagocytic lymphohistiocytosis (HLH). Some authors suggest using steroids in patients with a high likelihood of HLH. As there is not enough evidence the surviving sepsis has a weak recommendation (suggestion) in the sickest patients with ARDS.

Summary

- **The WHO advises that corticosteroids should not be routinely used to treat acute lung injury or adult respiratory distress syndrome in critically ill patients with suspected or proven COVID-19 infection outside of clinical trials.**

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[73] The World Health Organisation; Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected; 13/03/2020/ Accessed 24/03/2020
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- **Surviving Sepsis guidelines state that 'Low dose' corticosteroid therapy for refractory shock states should be used cautiously at the lowest dose and shortest duration possible and in accordance with the Surviving Sepsis Campaign guidelines and also in the sickest patients with ARDS[71].**

- **The evidence in COVID-19 is not currently available and the available guidelines are controversial and conflicting. The clinician should use their best judgement in the situation and monitor the patient for side effects of steroid usage of the decision is made to use them.**

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