National Centre for Infectious Diseases

Interim Treatment Guidelines for COVID-19

(Version 1.0, dated 2 April 2020)

ABSTRACT

Background

In December 2019, pneumonia cases caused by a novel coronavirus occurred in Wuhan, Hubei Province. As of 11th February 2020, the World Health Organisation has officially named the disease "COVID-19". In addition, virologists in the coronavirus study group have officially announced the name of the virus to be "SARS-CoV-2". This guideline provides evidence-based recommendations on the therapeutic management of patients with COVID-19 in Singapore.

Methods

Considering the lack of direct evidence for this newly identified COVID-19 infection, published systematic reviews, meta-analyses, cohort studies, case series, animal and *in vitro* studies related to SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) were considered in this guideline as well. Each recommendation was discussed by an expert committee and screened for conflicts of interest.

Results

Several potential treatments for SARS and MERS have been identified in animal and *in vitro* models. Certainty in the evidence was judged to be low as efficacy data from human clinical trials are lacking. On the basis of the limited evidence available for COVID-19, and previous experience with SARS and MERS, interim recommendations for use of antivirals are proposed for the management of COVID-19.

Conclusions

Without randomized controlled trials, determining efficacy is difficult due to patient and treatment variability as well as a lack of appropriate matching controls. We evaluate selected antivirals as potential therapeutic options in the treatment of COVID-19. Further clinical trials are essential to progress antiviral development and prioritise therapies most likely to improve clinical outcomes in COVID-19 patients.

CONTENTS

1. Overview

Early supportive care therapy and monitoring—including oxygen supplementation, organ support and prevention of complications, especially acute respiratory distress syndrome, organ failure and secondary nosocomial infections—remains the cornerstone and most important management strategy for clinical management of COVID-19.

There are still no proven or licensed therapies for any coronavirus (CoV) infection. SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA beta-coronavirus. Similar to SARS-CoV and MERS-CoV, the SARS-CoV-2 encodes non-structural proteins (such as 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase), structural proteins (such as spike glycoprotein) and accessory proteins.[1] The four non-structural proteins are key enzymes in the viral life cycle, and the spike glycoprotein is indispensable for virus-cell receptor interactions during viral entry.[2] Initial analyses of genomic sequences from SARS-CoV-2 indicate that the catalytic sites of the four SARS-CoV-2 enzymes that could represent key antiviral targets are highly conserved, and share a high level of sequence similarity with the corresponding SARS and MERS enzymes.[3] Therefore existing data on MERS and SARS therapies were also evaluated for the treatment of COVID-19.

Most patients with COVID-19 do not require specific antiviral treatment, beyond supportive care. However a subset ~20% may progress to severe pneumonia and about 5% -10% require critical care. This subset of patients who progress to more severe disease may benefit from early treatment with medications with antiviral activity, although robust data in the form of randomised controlled trials (RCT) are still awaited. Immunomodulation (e.g. with IL-6 or JAK inhibitors) has also been proposed to limit the degree of cytokine-mediated pulmonary necroinflammation in later stages of disease (e.g. ARDS, or pre-ARDS) however robust data is still awaited.

Numerous compounds have been tested and showed effectiveness *in vitro* and even in animal experiments, however, translating the findings from these studies into clinical use remains of particular importance especially taking into consideration accessibility and availability of drug, pharmacokinetic properties, pharmacodynamic characteristics and possible side effects at doses used in humans. Most of the studies done in SARS or MERS infected patients were observational and had not been designed to reliably assess the effects of the treatment used. In addition, the timing of the start of antiviral agents is important in most virus infections. Information is needed to identify which patients might most benefit from such treatments and the optimal timing of administration (early in the course of the disease or only at deterioration). Without randomized controlled trials, determining efficacy is difficult due to patient and treatment variability as well as a lack of appropriate matching controls.

Taking into account the above limitations, we discuss selected therapies and propose their role in the treatment of COVID-19.

2. Interim classification for persons at low versus high risk of disease progression (COVID-19)

Low versus High Risk of Disease Progression in COVID-19

Low Risk

- Age <30
- No chronic comorbidities
- Reassuring Clinical Features
  - No dyspnoea
  - Respiratory rate ≤ 20 breaths/min
  - Normal SpO2 %
  - Not requiring oxygen therapy
- Normal Chest X ray
- Reassuring Laboratory results*
  - CRP ≤ 60 mg/L
  - LDH ≤ 550 U/L
  - Lymphocytes ≥ 1x 10^9/L
  - Neutrophils ≤ 3 x 10^9/L

High Risk

- Age > 30, particularly >50
- Chronic comorbidities (chronic lung, heart or kidney disease, A1c >7.2%, immunosuppression)
- Concerning clinical features
  - Dyspnoea
  - Respiratory rate > 20 breaths/min
  - Abnormal SpO2 % (<95%)
  - Requiring oxygen therapy
- Chest X ray with pneumonia
- Concerning Laboratory results*
  - CRP ≥ 60 mg/L
  - LDH > 550 U/L
  - Lymphocytes < 1x 10^9/L
  - Neutrophils >3 x 10^9/L
  - Others: Rising Ferritin levels, D-dimer > 1 ug/mL, Elevated troponin

*Certain risk stratification factors may be non-modifiable (e.g. age), whereas others are dynamic (e.g. evolving clinical features, radiology or laboratory results). Repeat labs are recommended at intervals (e.g. 2-3 days) for patients for whom there is concern for clinical deterioration or when there is worsening of disease. Please note that these cut offs are based on aggregate data from Singapore COVID-19 cases and there may be some variability in normal reference ranges between laboratories

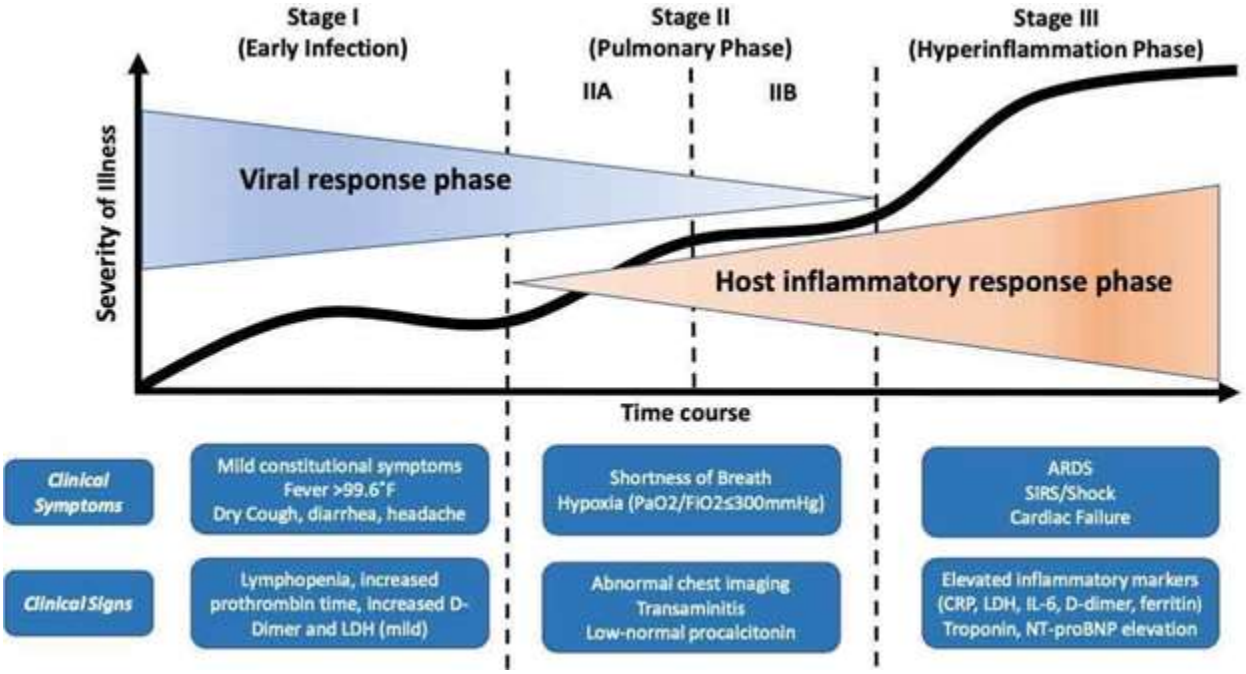
Young et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA 2020; Fan et al. Hematologic parameters in patients with COVID-19 infection. American J of Haematology. Published 4 March 2020; Puah SH et al (ICU data, unpublished)

3. Definition of Severe COVID infection (adapted from Report of WHO-China Joint Mission on Coronavirus Disease 2019)

- Dyspnoea, RR >30 breaths/min, P/F ratio <300, Lung infiltrates >50% of lung fields within 24-48 hours
- Admission to an ICU
- Current receipt of mechanical invasive or non-invasive ventilation
- Current receipt of intravenous vasoactive medications to maintain mean arterial pressure >65 mmHg
- Myocarditis/myocardial dysfunction secondary to SARS-CoV-2

4. Proposed Staging of COVID-19 (Siddiqi)

The staging proposed by Siddiqi et al is a conceptual frame work however bear in mind individual patient's courses may vary and not all patients enter Stage II or III.



From Siddiqi et al, "COVID-19 Illness in Native and Immunosuppressed States", J Heart and Lung Transplantation, 2020.

Summary of Recommendations

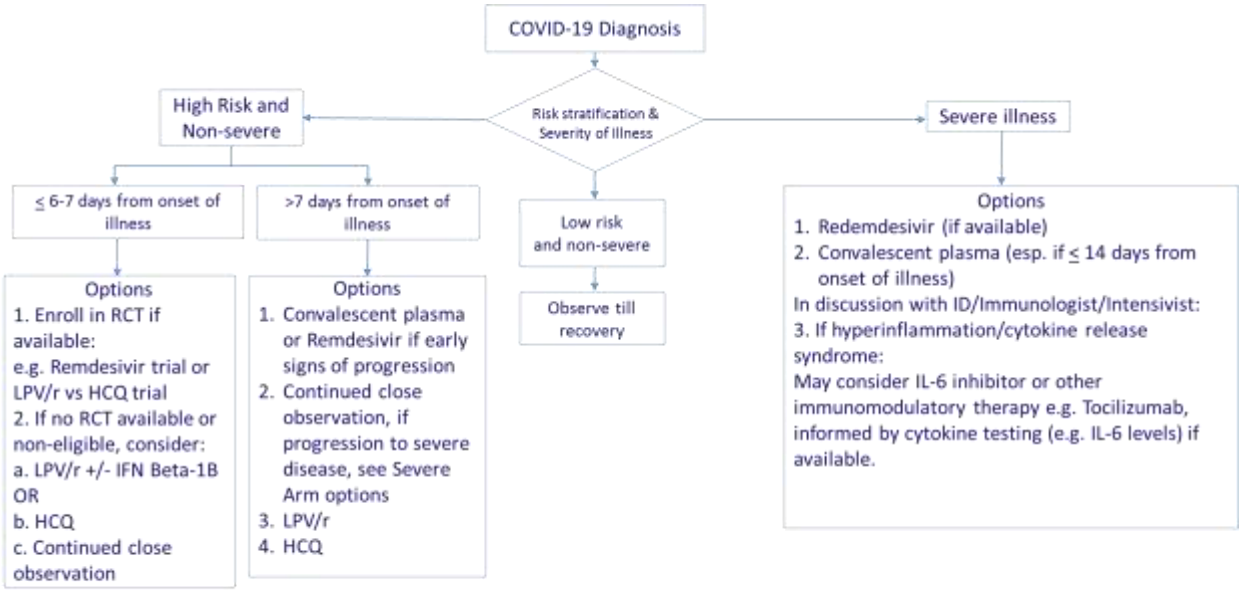
1. Level of Recommendations

The level of recommendations are adapted from the Oxford Centre for Evidence-Based Medicine.

Category	Definition
Levels of evidence	
I	Systematic reviews, meta-analyses, well-designed randomized controlled trials
II	Two groups, non-randomized studies (e.g. cohort, case-control)
III	One-group, non-randomized studies (e.g. before and after, pre-test and post-test)
IV	Descriptive studies that include analysis of outcomes (single-subject design, case series), randomized controlled trials which are not peer reviewed or lacking in rigor
V	Case reports and expert opinion that include narrative literature, reviews and consensus statements
Grades of evidence	
A	Consistent level I studies
B	Consistent level II or III studies or extrapolations from level I studies
C	Level IV studies or extrapolations from level II or III studies
D	Level V evidence or troublingly inconsistent or inconclusive studies at any level
Strength of recommendations	
Strong	Evidence from studies at low risk of bias
Moderate	Evidence from studies at moderate risk of bias
Weak	Evidence from studies at high risk of bias

Most patients with COVID-19 DO NOT require specific antiviral treatment, beyond supportive care. Specific therapy, however, may be considered for patients predicted to progress to severe infection, or who have severe infection.

These interim recommendations and a treatment algorithim were formulated with the currently available evidence with COVID-19 (SARS-CoV-2) and previous data from SARS-CoV and MERS-CoV. (please note that all agents suggested are investigational, or off-label/for compassionate use).



LPV/r = Lopinavir/ritonavir ; HCQ = Hydroxychloroquine, IFN = Interferon

Note that algorithm may be updated/modified pending further clinical trial results and availability of novel therapies

1. **We suggest using remdesivir under a trial/study setting (Level IV, Grade D, Weak) if subjects meet eligibility criteria and a trial is available.**

   In vitro data shows remdesivir exerting potent antiviral activity against SARS-CoV-2; [half-maximal effective concentration (EC50) = 0.77 mcgM, half-cytotoxic concentration (CC50) > 100 mcgM. selective index (SI) > 129.87] (Reference 1). RCT results from China are expected in April 2020. Trial data are awaited but case reports on its use have been reported (Reference 2).

2. **If lopinavir/ritonavir use is considered, we recommend its use in early illness (≤12 days) (Level I, Grade B, Moderate).**

   An RCT on lopinavir/ritonavir monotherapy with 199 patients with more severe COVID-19 (overall mortality 22%) showed that time to clinical improvement did not differ between the two groups (median, 16 days), and a mortality rate at 28 days that was numerically lower for lopinavir/ritonavir compared with standard care (19.2% vs 25% , −5.8 percentage points; 95% CI, −17.3 to 5.7). 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, 1.77 to 2.05), but later treatment with lopinavir–ritonavir was not (hazard ratio, 1.30; 95% CI, 0.84 to 1.99) (Reference 3).

3. **We suggest using subcutaneous Interferon beta-1B alone or in combination with lopinavir/ritonavir in early illness (Level V, Grade D, Weak). Given that cytokine storm/hyperinflammation may occur in the second week of illness, we caution use of interferon beyond 7 days, and advise against its use if patient is in the hyperinflammation phase.**

There has been no published RCTs on the use of Interferon beta-1B in COVID-19. Interferon beta-1b with lopinavir/ritonavir has shown improved outcomes in MERS-CoV infection in a non-human primate model (Reference 4). Twelve in vitro studies with data on the antiviral effect of IFN type I have been reported, and all demonstrated an antiviral effect against SARS-CoV (six for IFN-alpha and ten for IFN-beta) (Reference 5).

4. **If contraindications exist to participation in a remdesivir trial, or to the use of lopinavir/ritonavir or interferon, the following may be considered:**
   - **hydroxychloroquine (Level IV, Grade D, Weak), OR**
   - **convalescent plasma (Level V, Grade D, Weak), if available**

   if there are no contraindications.

Hydroxychloroquine

Hydroxychloroquine is less toxic (~40%) than chloroquine in animal data and is widely used in rheumatologic conditions, with in-vitro and in-vivo data for SARS-CoV-2. Recently, a Chinese team showed that chloroquine and hydroxychloroquine inhibit SARS-CoV-2 in vitro with hydroxychloroquine (EC50=0.72%μM) found more potent than chloroquine (EC50=5.47%μM) (Reference 6).

A small study of 20 COVID-19 patients treated with hydroxychloroquine +/- azithromycin by a French group showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. Azithromycin added to hydroxychloroquine (in six of 20 patients) more effectively cleared virus. However because of the nature of the design of the trial (open-label, small numbers), non-randomized, results should be interpreted with caution, and more robust data is needed (Reference 7).

In a non-peer reviewed (pre-print) Chinese, open label, randomised controlled trial which studied 62 patients (31 in each arm) with confirmed but mild COVID-19 (SaO2/SpO2 > 93% or P/F ratio >300) at a dose of 400 mg daily (200 mg BD) of hydroxychloroquine for 5 days with standard treatment (comprising antiviral/antibacterial agents, immunoglobulin with or without corticosteroids) versus standard treatment alone, which had unclear and multiple endpoints found that the hydroxychloroquine group had faster fever resolution (2.2 vs 3.2 days), cough remission time (2.4 vs 3.1), and 4 in the control group progressed to severe illness versus none in the hydroxychloroquine (Reference 8).

In another small Chinese open label randomised controlled study comprising 30 patients (hydroxychloroquine with conventional treatment versus conventional treatment) did not find any difference in viral clearance or radiological progression (Reference 9). The results from these small, and likely underpowered studies with multiple confounders, including concomitant treatments, should be interpreted with caution.

Convalescent Plasma

Several uncontrolled studies have showed a shorter hospital stay and lower mortality in patients treated with convalescent plasma than those who were not treated with convalescent plasma, for SARS-CoV. Caution should be exercised in the use of convalescent plasma given the theoretical risk of exacerbating lung injury secondary to immune-enhancement. Shen et al reported good outcomes with convalescent plasma for five patients with COVID-19, however these was a small case series, and uncontrolled data (Reference 10).

5. **We do not currently recommend the routine use of chloroquine or favipiravir (Ungraded).**

   Good quality, peer-reviewed data lacking with chloroquine and favipiravir, and chloroquine carries more toxicities compared to hydroxychloroquine and was found to be less potent in one Chinese paper (Reference 6).

6. **We do not recommend the routine use of the immunomodulators baricitinib (JAK inhibitors, tocilizumab (IL-6 inhibitor) outside a trial/study setting, although their use may be considered in select patients with cytokine storm/hyperinflammation, and after careful discussion with multi-disciplinary input (rheumatology-allergy-immunology, infectious diseases, intensive care specialists) (Level IV, Grade D, Weak).**

   The JAK and IL-6 inhibitors may have a role in select patients with a cytokine release syndrome but their use (timing) and efficacy is yet to be determined. These agents should not be used in conjunction with interferon beta-1B. Off-label use must be carefully weighed (in terms of risk-benefits). Several guidelines (American, Italian and Chinese, Swiss) have included tocilizumab, for use in patients with COVID-19 and hyperinflammation. Serial monitoring of ferritin, platelet count and inflammatory markers may identify hyperinflammation and calculation of the H score has been suggested to identify patients who may benefit from such therapy. Measurement of cytokines (e.g. IL-6) may be considered to inform decisions on such therapy. Preliminary data (non-peer reviewed) on tocilizumab was reported from a small Chinese study demonstrated that 15 of the 20 patients reduced their oxygen therapy and one patient did not require oxygen therapy following treatment with tocilizumab. The body temperature of all patients returned to normal on the first day after receiving tocilizumab and remained stable then after, with improvement of inflammatory markers e.g. CRP and lymphocytes (Reference 11) . However, the study sample was small and patients received concurrent therapies including lopinavir/ritonavir. Baricitinib is being used in pilot studies in Italy, and in-vitro studies are ongoing, but results are awaited (Eli Lily, personal communication).

7. **We recommend against the routine use of corticosteroids for COVID-19, except in circumstances where its use may be indicated (e.g. refractory shock, documented hypocortisolism) (Level V, Grade D, weak)**

   Steroids have not been conclusively shown to have specific benefits in COVID-19 infection and studies with reported benefits have been uncontrolled, and confounded by concurrent treatments, and have

been known to cause deleterious effects (e.g. bacterial/fungal superinfection) from SARS (2003) data. Steroids will also delay viral clearance, and should be avoided unless there are other reasons for their use such as exacerbation of asthma, COPD and refractory septic shock

8. **No recommendation can be made for the use of other therapies such as mesenchymal stem cell infusion, donor lymphocyte infusions due to the lack of efficacy and safety data (Ungraded)**

9. **We do not recommend chemoprophylaxis for COVID-19, for example, with hydroxychloroquine (Ungraded).**

   There is currently no robust data for chemoprophylaxis for COVID-19. Trials are underway.

Please note that the recommendations above are based on available data, and that updates. Attempts should to be made to conduct randomised clinical trials to validate treatment protocols. Off-label usage of the above drugs outside of a trial should be monitored so as to accrue data real time that could facilitate analysis of treatment outcomes and any adverse events. **Clinical evidence summaries for remdesivir, lopinavir/ritonavir, hydroxychloroquine/chloroquine, favipiravir, IL-6 inhibitors and convalescent plasma are also available from the Ministry of Health-Agency for Care effectiveness at https://www.moh.gov.sg/covid-19/clinical-evidence-summaries .**

References for summary

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Key Drug Summary Table (Note: Therapy should be guided by Infectious Diseases)

Medication	Adult Dose	Notes (Please see full product information leaflet/drug use guide)
Remdesivir	200 mg IV loading, 100 mg IV daily x 5 to 10 days	Only available as part of clinical trial (See Annex A) currently Timing of antiviral initiation may be important, as administration with high viral loads seen after peak viral titer has been found to fail in reducing lung damage despite reducing viral loads. May cause LFT abnormalities/hepatitis.
Lopinavir/ritonavir	400/100 mg BD x 14 days Use syrup if intubated/unable to swallow.	Assess for drug-drug interactions. Main side effect is gastrointestinal intolerance and hepatitis. Monitor LFTs. Duration may be shortened if clinically improved, being discharged, or dose limiting side effects are encountered. May consider monotherapy (in less severe disease) or use in combination with interferon beta-1B, optimally within 1 week of onset of disease.
Interferon Beta-1B	250 microgram (8.0 million IU), contained in 1 ml of the reconstituted solution, to be injected subcutaneously every other day up to 7-14 days (3-7 doses).	If the patient has had significant improvement within 1 week (e.g. normalization of P/F ratios, no need for supplemental oxygen, patient extubated), clinicians may consider a shorter course of therapy (e.g. 3 doses, or 1 week). Consider use in combination with lopinavir/ritonavir. Common side effects: Flu-like symptoms While further data is awaited, benefit of therapy is likely to be derived in starting treatment early (ideally ≤7 days from onset of illness) prior to frank respiratory embarrassment on onset of ARDS. Caution should be exercised in starting interferon in later stages of COVID-19 (e.g. when there is ARDS secondary to the established inflammatory cytokine cascade).
Hydroxychloroquine	400 mg BD x 1 day (loading dose) followed by 200 mg bd for a 4 further days	No routine G6PD evaluation prior to use is required as risk of haemolytic anemia is low. No routine eye checks are needed unless treatment is prolonged. Baseline ECG for QT interval Contra-indications: QTc > 500 msec, Myasthenia gravis Porphyria, Retinal pathology, Epilepsy
Tocilizumab	To discuss with Rheumatology-Allergy-Immunology / Infectious Diseases /Intensive Care Physicians	

SPECIFIC INFORMATION ON LOPINAVIR/RITONAVIR AND INTERFERON BETA-1B

Lopinavir/Ritonavir (Kaletra)

Lopinavir is licensed as a human immunodeficiency virus 1 (HIV-1) protease inhibitor that is co-formulated with ritonavir to increase lopinavir half-life through the inhibition of cytochrome P450. Lopinavir/ritonavir (LPV/r) are hypothesized to exhibit anti-CoV activity by inhibit the 3-chymotrypsin-like protease of SARS and MERS,[2] which is a key enzyme in CoV polyprotein processing. LPV and/or LPV/r have anti-CoV activity *in vitro*, as well as in MERS-CoV-infected non-human primates and in non-randomised trials of SARS patients.[4-8]

Summary of evidence

SARS

A previous study on the sequential changes in viral load and disease progression of SARS suggested that there was an initial viral replicative phase that led to a maximal viral load at around day 10. Thereafter, the disease progressed to ARDS and severe end-organ damage in some patients.[9] Using the strategy to reduce the peak viral load by an effective antiviral agent, a retrospective matched cohort study showed that the addition of LPV/r as an initial treatment (median, 5.5 days after symptom onset) for patients newly diagnosed to have SARS was associated with a reduction in overall death rate (2.3%) and intubation rate (0%) compared with that in a matched cohort who received standard treatment of ribavirin (15.6% and 11.0% respectively, $p<0.05$), and a lower rate of use of methylprednisolone at a lower mean dose.[4] However, when LPV/r was given as rescue therapy later in the course of illness (median, 18 days after symptom onset) when patients had worsening oxygen saturation, shortness of breath, and relevant radiological findings, and were judged to have failed pulse steroid treatment, there was no difference in overall death rate and rates of oxygen desaturation and intubation compared with the matched cohort.[4]

Another retrospective matched cohort study found that the adverse clinical outcome (acute respiratory distress syndrome or death) was significantly lower when LPV/r was added to the treatment regimen compared to the controls (2.4% v 28.8%, $p<0.001$) at day 21 after the onset of symptoms. In addition, the LPV/r group had a progressive decrease in the viral load, an early rise in the lymphocyte count, a reduction in the cumulative dose of pulsed methylprednisolone, and fewer episodes of nosocomial infections.[5] In the subgroup analysis, patients who received LPV/r as the initial treatment seemed to run a milder disease course and had a reduction in the viral load. Their need for rescue pulse methylprednisolone for severe respiratory deterioration was therefore reduced. The authors hypothesized that LPV/r might have improved the outcome either by a direct effect on the viral load or by an indirect steroid sparing effect because of a reduction in immunopathological damage.[5]

MERS

Although the antiviral activity of LPV against MERS-CoV has been reported in Vero cells, other studies report complete inactivity.[6, 10] Another *in vitro* study reports that LPV/r has inferior *in vitro* antiviral activity compared to remdesivir and interferon beta.[11] In mice, therapeutic LPV/r and interferon beta combination improved pulmonary function, but failed to reduce viral replication or severe lung pathology.[11] Common marmosets that were treated with LPV/r or interferon beta-1b had better clinical scores, less weight reduction, less pulmonary infiltrates, and improved pathological findings. Furthermore, necropsied lung and extrapulmonary tissues from the treated group had lower mean viral loads.[7] The combination of both LPV/r and interferon beta-1b is being tested in a randomized control trial in Saudi Arabia among patients

with MERS.[12] Apart from this, experience in humans till date is limited to two case reports of successfully treating MERS-infected patients with LPV/r, ribavirin and interferon.[13, 14]

COVID-19

There are no reported *in vitro* studies of LPV/r on SARS-CoV-2. Four patients with COVID-19 were given LPV/r combined with Chinese medicine treatment. After treatment, three patients showed significant improvement in pneumonia associated symptoms, two of whom were confirmed to be COVID-19 negative and discharged, and one of whom was negative for the virus at the first test.[15] Locally, five patients were treated with LPV/r within 1 to 3 days of desaturation, but evidence of clinical benefit was equivocal.[16] While defervescence occurred within 1 to 3 days of LPV/r initiation, it was unable to prevent progressive disease in 2 patients. Decline in viral load as indicated by the cycle threshold value from nasopharyngeal swabs also appeared similar between those treated and not treated with LPV/r.

A randomized, controlled, open-label trial of 199 hospitalized COVID-19 adult patients with more severe disease (overall mortality rate 22%, patients who were eligible: oxygen saturation <=94% or less on room air or PaO2 < 300 mm Hg) were randomized to receive lopinavir/ritonavir 400 mg/100 mg PO BD for 14 days added to standard care (n=99) or standard care alone (n=100). Time to clinical improvement did not differ between both groups, except on a modified intention to treat analysis, which excluded 3 persons with early death (15 vs 16 days, p <0.05) The mortality rate at 28 days was numerically lower for lopinavir/ritonavir compared with standard care (19.2% vs 25%) but did not reach statistical significance. Limitations of this trial include late recruitment and more severe illness: the median interval time between symptom onset and randomization was 13 days (IQR, 11 to 16 days), and also combination therapy was not studied. In an intention-to-treat analysis, 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, 1.77 to 2.05), but later treatment with lopinavir–ritonavir was not (hazard ratio, 1.30; 95% CI, 0.84 to 1.99). Lopinavir/ritonavir may thus still have a role in early disease and in combination with other antivirals[17].

Benefits

Usage of LPV/r is not routinely recommended for all patients with COVID-19, but its use may be considered, in combination with interferon beta-1b or alone, for patients who have or who are anticipated to develop severe pulmonary disease, and who are in early phase of illness (<=7 days from onset).

Harms

Diarrhoea, nausea, and asthenia are the most frequently reported reactions in patients receiving LPV/r therapy.[18] Elevated total cholesterol, triglyceride and hepatic enzyme levels have also been reported.[17] Symptoms and laboratory tests returned to normal after LPV/r therapy was ceased. In the local study done on COVID-19 patients, four of the 5 patients treated with LPV/r developed nausea, vomiting, and/or diarrhea, and 3 developed abnormal liver function test results.[16]

LPV/r is recommended to be used with caution in patients with Hemophilia A or B, hepatic impairment or underlying hepatic disease, as well as patients with underlying structural heart disease, preexisting conduction system abnormalities, ischemic heart disease or cardiomyopathies.[19]

Additional Considerations

There are a number of clinically important drug interactions that have been reported with LPV/r use, necessitating dosage adjustments of interacting drugs and/or LPV/r, and several other drugs are which contraindicated with concomitant LPV/r. We strongly recommend to consult a drug interaction database (such as www.covid19-druginteractions.org) or a pharmacist.

LPV/r has the potential to interact with certain drugs (such as flecainide, propafenone, midazolam, and triazolam) that are highly dependent on CYP3A or CYP2D6 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Co-administration with LPV/r is also not recommended for drugs (such as rifampicin) that may substantially reduce LPV plasma concentrations, or drugs whose plasma concentrations elevated by LPV/r may lead to serious adverse reactions (such as simvastatin and lovastatin). To reduce the risk of their toxicity when co-administered with LPV/r, the recommended actions include: (i) monitoring of the drug plasma concentration; (ii) the use of alternative agents; (iii) dosage adjustments.[20]

Kaletra tablets are to be swallowed whole, not to be chewed or crushed. Exposure of lopinavir can be reduced by 45% when the tablet is crushed.[19] The syrup formulation of LPV/r contains propylene glycol (15.3%) and alcohol (42% v/v) and is not recommended for use with polyurethane feeding tubes due to incompatibility and also should not be given to pregnant women, or co-administered with drugs capable of producing disulfiram-like reactions (e.g. metronidazole).[19]

Conclusions

With limited experience from *in vitro*, animal and human studies, LPV/r alone or in combination may be considered as a potential treatment option for COVID-19. The randomised controlled trial on LPV/r alone showed a possible positive effect on a modified intention to treat analysis, but was limited by recruitment of patients later in disease course with more severe illness, and did not study its efficacy in combination with other antivirals.

Interferon beta-1b

Interferon beta-1b is a cytokine that is licensed for use in the treatment of relapsing multiple sclerosis. It is a type I interferon, and is a signalling protein made and released by host cells in response to the presence of several viruses, that help regulate the activity of the immune system.

The host innate interferon response is crucial for the control of viral replication after infection. Although CoVs are able to suppress the interferon response for immune evasion, they remain susceptible to interferon treatment *in vitro*. The interferon response can be augmented by the administration of recombinant interferons or interferon inducers.[2] Antiviral effects of type I interferons have been demonstrated in monkey (Vero; Vero-E6), fetal rhesus monkey kidney (fRhK-4) and human (Caco2, CL14, and HPEK) cell lines.[21]

Various combinations of interferon alfa or interferon beta used alone or with other antivirals have been used to treat patients with SARS or MERS.

Summary of evidence

SARS

In an uncontrolled open-label study of 22 SARS patients, the interferon alfacon-1 treatment group had a shorter time to 50% resolution of lung radiographic abnormalities, had better oxygen saturation, resolved their need for supplemental oxygen more rapidly, had less of an increase in creatine kinase levels, and showed a trend toward more rapid resolution of lactate dehydrogenase levels compared with the group receiving corticosteroids alone.[22]

Although interferon beta was shown to be superior to interferon alpha or interferon gamma in *in vitro* study of the SARS-CoV,[23-27] there are no studies using interferon beta on SARS patients.

MERS

In vitro studies showed superiority of interferon beta compared to interferon alpha-2b, interferon-gamma, interferon universal type 1 and interferon alpha-2a in reducing MERS-CoV replication.[10, 28] A recent study published showed that interferon beta demonstrated superior antiviral acitivity to LPV/r in vitro, and the antiviral activity of LPV/r and interferon beta combination on MERS-CoV is dominated by interferon beta when LPV/r is used at clinically relevant concentrations.[11] In mice, therapeutic LPV/r and interferon beta improves pulmonary function but does not reduce virus replication or severe lung pathology.[11] A study done in common marmosets showed that interferon beta-1b improvements in clinical outcomes.[7]

In a cohort study of 51 patients, the use of interferon beta demonstrated improved survival in patients treated with interferon beta in the univariable analysis, but the multivariable analysis which included a marker of severity of illness did not show an association between treatment with interferon beta and survival and could have been because interferon beta was given to less severely ill patients.[29]

Since interferon beta was shown to be the most potent against MERS-CoV *in vitro*, it was selected to use in the randomised control trial (MIRACLE trial) in combination with LPV/r to determine if this combination improves clinical outcomes in MERS-CoV patients.[12]

COVID-19

No studies published yet.

Benefits

Usage of interferon beta is not routinely recommended for all patients with COVID-19, but its use may be considered, in combination with LPV/r or alone, for patients who have or who are anticipated to develop severe pulmonary disease, and who are in early phase of illness (<=7 days from onset).

Dosage: Subcutaneous interferon beta-1b 250 microgram (8.0 million IU), contained in 1 ml of the reconstituted solution, to be injected <u>every other day</u> for 14 days (7 doses).

Harms

As the dosage regimen recommended does not have a dose titration step at the start of treatment, close monitoring is required.

Injection site reactions occurred frequently after administration of interferon beta. Flu-like symptoms have been seen. Rarely, monocloncal gammopathy patients treated with interferon beta-1b may develop systemic capillary leak syndrome.[30] Other uncommon side effects include hypersensitivity, pancreatitis, depression, cytopenia, cardiomyopathy, and liver and thyroid dysfunction.[30]

Additional Considerations

Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when interferon beta is administered in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance (e.g. anti-epileptics). Additional caution should be exercised with any co-medication which has an effect on the haematopoietic system. No interaction studies with anti-epileptics have been carried out.

Interferon beta should be used with caution in patients with bone marrow suppression, cardiovascular disease, seizure disorder, hepatic impairment, thyroid dysfunction, severe renal failure, history of depression. It is contraindicated for use in pregnancy, patients with current severe depression and/or suicidal ideation, patients with decompensated liver disease.

Conclusions

With limited experience from *in vitro*, animal and human studies, interferon beta-1b alone or in combination may be considered as a potential treatment option for COVID-19. Results from ongoing randomised controlled trials have been initiated to test its efficacy.

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Annex A: Remdesivir Trials: Workflow for referral

Background

1. There is no established treatment for COVID-19, though various therapeutic options are under investigation. Remdesivir (GS-5734) has shown in-vitro activity against SARS-CoV-2[1] and has been used on a compassionate-use basis in the treatment of COVID-19 in patients[2].

2. Randomised controlled clinical trials are underway to evaluate the therapeutic use of Remdesivir in COVID-19. There are 3 clinical trials currently underway in NCID, (a) Gilead (Moderate), (b) Gilead (Severe), and (c) NIH.

Workflow for Referrals to Clinical Trial

1. Check that patient fulfils criteria in the following table:

Gilead (Moderate)	Gilead (Severe)	NIH
1st SARS-CoV-2 PCR positive in last 96 hours	1st SARS-CoV-2 PCR positive in last 96 hours	Any SARS-CoV-2 PCR positive in last 72 hours (i.e., can be repeated to confirm eligibility if last PCR >72 hours prior)
Pneumonia, as defined by CXR opacities	Pneumonia, as defined by CXR opacities	Pneumonia, as defined by: (i) CXR/CT opacities, OR (ii) Crepitations and SpO2 ≤94% on room air, OR (iii) Requiring supplemental O2
SpO2 >94% on room air	SpO2 ≤94% on room air, or requiring supplemental O2	Any SpO2
Not intubated	Not intubated	Intubated or not intubated
Fever ≥37.8°C	Fever ≥37.8°C	No requirement for fever
CrCl >50	CrCl >50	CrCl >50
ALT/AST <5x ULN	ALT/AST <5x ULN	ALT/AST <5x ULN
33% chance of obtaining placebo (2 treatment arms, 1 placebo arm)	0% chance of obtaining placebo (2 treatment arms)	50% chance of obtaining placebo (1 treatment arm, 1 placebo arm)

2. Discontinue any other experimental treatment for COVID-19 (including lopinavir-ritonavir [Kaletra], interferon-beta, hydroxychloroquine, or chloroquine). Patients have to be off any of these medications for >24 hours before starting Remdesivir. If team is considering referral to clinical trial team, avoid starting other experimental treatment.

3. Patients will need baseline FBC, Cr, LFTs (including AST), and random glucose within 24 hours prior starting treatment.

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