Clinical evidence for the use of antivirals in the treatment of COVID-19

National Centre for Pharmacoeconomics
NCPE Ireland

Medicines Management Programme

COVID-19 Evidence Review Group

27 March 2020
Version 1

Rapid Evidence Review

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Prepared by the COVID -19 Evidence Review Group

Version 1, 27th March 2020

The COVID-19 Evidence Review Group for Medicines was established to support the HSE in managing the significant amount of information on treatments for COVID-19. This COVID-19 Evidence Review Group is comprised of evidence synthesis practitioners from across the National Centre for Pharmacoeconomics (NCPE), Medicines Management Programme (MMP) and the National Medicines Information Centre (NMIC). The group respond to queries raised via the Office of the CCO, National Clinical Programmes and the Department of Health and respond in a timely way with the evidence review supporting the query.

Summary

Chloroquine/Hydroxychloroquine

Clinical evidence	In one clinical study, hydroxychloroquine was initiated in hospitalised patients with confirmed COVID-19 at a dose of 200mg three times daily for ten days. The mean time between onset of symptoms and study inclusion was 4.1 days in the treatment group. Not all patients were symptomatic at the time of treatment initiation. A higher rate of virological cure was observed in the hydroxychloroquine-treated group compared with a control group (1). An abstract of a Chinese study suggested no difference in viral clearance between hydroxychloroquine-treated patients and a control group, though patient numbers and effect sizes in this study are too small to robustly determine a difference in efficacy between treatment groups. Insufficient information is available to critically appraise the quality of the study (2).
International Guidelines	At the time of writing, hydroxychloroquine is more readily accessible than chloroquine in Ireland (3). Hydroxychloroquine is widely recommended in European guidelines for the treatment of patients with COVID-19. Chloroquine is recommended in Chinese guidelines. Guidelines vary in their recommendations to use chloroquine/hydroxychloroquine alone or in combination with other antivirals. Italian and Chinese guidelines recommend combination use and Belgium recommends single-agent use (though this is largely due to uncertainty in the efficacy of other antivirals). These drugs are recommended in mild, moderate and severe disease among the various guidelines. Dose regimens, treatment durations and recommended time of initiation vary across guidelines. Treatment duration varies from 5 days up to 20 days. Use in hospitalised patients is recommended in Belgium, whereas patients with mild symptoms, albeit with risk factors, are recommended treatment in Italy, suggesting a role in primary care (4-7).

Lopinavir-ritonavir

Clinical evidence	Clinical studies, one in a mild/moderate COVID-19 cohort, and one in a more severe cohort failed to demonstrate a benefit from lopinavir-ritonavir (400mg/100mg twice daily for 7-14 days) compared with standard care, or umifenovir (Arbidol®). The median time between illness onset and randomisation was 4.3 days and 13 days in the treatment groups of the

	respective studies. One clinical study found that earlier initiation (within 12 days of symptom-onset) was associated with a greater numerical difference in mortality compared to later initiation. Case reports describe the use of lopinavir-ritonavir from day 10 and from day ≤9 (8-11).
International Guidelines	Guideline recommendations on the role of lopinavir-ritonavir for the treatment of COVID-19 are inconsistent. Belgian guidelines recommend lopinavir-ritonavir only if hydroxychloroquine is contraindicated, while Italian guidelines recommend it as a first-line treatment, in combination with chloroquine or hydroxychloroquine, in patients with mild-moderate disease, and as an alternative to remdesivir in severe/critical disease.. The recommended daily dose is lopinavir/ritonavir 400/100 mg (i.e 2 tablets of 200/50 mg). The treatment duration varies in guidelines, up to 20 days (4-7).

Remdesivir

Clinical evidence	In one reported case, remdesivir was initiated on illness Day 11 following radiographic findings consistent with atypical pneumonia and worsening clinical status. The remdesivir dose is clinical trials is 200 mg as a single dose on day 1, followed by 100 mg once daily for a total duration of 5 to 10 days. Clinical trial protocols require SARS-CoV-2 confirmation within 3 to 8 days, depending on the study(12).
International Guidelines	If access to remedesivir is possible, either through a clinical trial or through an emergency treatment request from Gilead, it is recommended in guidelines for the treatment of patients with severe or critical disease. The duration of treatment varies from 2 to 10 days (8-11).

Antiviral dose regimens recommended in international guidelines

Drug	Guideline (Date published, version)	Patient population	Dosing and frequency	Duration of therapy
Chloroquine/ hydroxychloroquine	**Belgium (19/03/2020 version 4)**	• **Chloroquine or hydroxychloroquine monotherapy: first line in patients with confirmed COVID-19** - with mild to moderate disease (no O_2 requirement/no evidence of pneumonia), and who are in an at-risk group (age > 65 years AND/OR underlying end organ dysfunction (lung, heart, liver,...), diabetes, coronaropathy, chronic obstructive pulmonary disease, arterial hypertension. Recommendation is to stop chloroquine if follow-up at home. - with severe COVID-19 disease who meet at least one of the following criteria (Respiratory rate ≥30/min (adults); ≥40/min (children < 5); Blood oxygen saturation ≤93%; PaO_2/FiO_2 ratio <300; Lung infiltrates >50% of the lung field within 24-48 hours) - with critical disease, via nasogastric tube, when remdesivir is not available in patients who meet at least one of the following criteria (ARDS; sepsis; altered consciousness; multi-organ failure). Switch to remdesivir if it becomes available.	**Chloroquine base: 600mg (10mg/kg) first dose followed by 300mg (5mg/kg) 12 hours later on Day 1 300mg BD on Days 2-5** **OR** **Chloroquine phosphate: 1000mg first dose followed by 500mg 12 hours later on Day 1, 300mg BD on Days 2-5** **OR** **Hydroxychloroquine: 400mg BD on Day 1 200mg BD on Days 2-5**	**5 days**
	Chinese guidelines 7th edition (03/03/2020)	• **Chloroquine phosphate, alpha interferon, lopinavir/ ritonavir, ribavirin and arbidol are listed as potential treatment options. Combinations of >2 antivirals are not recommended. If ribavirin is used, combination with interferon or lopinavir/ritonavir is recommended** - Exact recommendations in these guidelines are unclear, as interpretation is limited by variation in English translations between editions.	**Chloroquine phosphate: 500mg BD for Days 1-2 followed by 500ng QD for Days 3-7 in adults <50kg** **OR** **500mg BD for adults >50kg**	**7 days**
	Italy (NIID, IRCCS 17/03/2020).	• **Chloroquine or hydroxychloroquine in combination with lopinavir/ritonavir** - in patients with stable disease presenting with respiratory and/or systemic symptoms (e.g. MEWS clinical deterioration score <3). • **Chloroquine or hydroxychloroquine in combination with remdesivir (lopinavir/ ritonavir if remdesivir not available) and tocilizumab** - in patients affected by respiratory symptoms, clinically unstable, not in critical conditions (e.g. MEWS clinical deterioration score 3-4) - in critical patients (e.g. MEWS clinical deterioration score >4)	**Chloroquine phosphate: 500mg BD** **OR** **Hydroxychloroquine: 400mg BD on Day 1, 200mg BD thereafter**	**10 days**

Antiviral dose regimens recommended in international guidelines ***continued***

Drug	Guideline (Date published, version)	Patient population	Dosing and frequency	Duration of therapy
	Italy (SIMIT, Lombardia edition 2 13/03/2020)	• **Chloroquine or hydroxychloroquine in combination with lopinavir/ritonavir** - in patients with mild respiratory symptoms, aged > 70 years ± risk factors (diabetes, COPD, heart disease) - in patients with mild respiratory symptoms ± chest x-ray which indicates pneumonia. • **Chloroquine or hydroxychloroquine in combination with remdesivir (discontinue lopinavir/ritonavir)** - in patients who require oxygen therapy or who rapidly deteriorate. - in patients with severe pneumonia, ARDS, or global respiratory insufficiency, haemodynamic failure and need for mechanical ventilation (invasive or not).	**Chloroquine phosphate: 500mg BD** **OR** **Hydroxychloroquine: 200mg BD**	**5- 20 days. Duration determined by clinical evaluation**
Lopinavir-ritonavir	**Belgium (19/03/2020 version 4)**	• **Consider lopinavir/ ritonavir monotherapy if hydroxychloroquine/ chloroquine is contraindicated and within 10 days of symptom onset** - in patients with severe COVID-19 disease who meet at least one of the following criteria (Respiratory rate ≥30/min (adults); ≥40/min (children < 5); Blood oxygen saturation ≤93%; PaO2/FiO2 ratio <300; Lung infiltrates >50% of the lung field within 24-48 hours).	**lopinavir/ ritonavir 400/100 mg BD**	**14 days**
	Chinese guidelines 7th edition (03/03/2020)	• **Chloroquine phosphate, alpha interferon, lopinavir/ ritonavir, ribavirin and arbidol are listed as potential treatment options. Combinations of >2 antivirals are not recommended. If ribavirin is used, combination with interferon or lopinavir/ritonavir is recommended** - Exact recommendations in these guidelines are unclear, as interpretation is limited by variation in English translations between editions.	**Lopinavir/ ritonavir 400/100 mg BD**	**Max 10 days**
	Italy (NIID, IRCCS 17/03/2020).	• **Lopinavir/ ritonavir in combination with chloroquine or hydroxychloroquine** - in stable patients presenting with respiratory and/or systemic symptoms (e.g. MEWS clinical deterioration score <3). If lopinavir/ ritonavir unavailable use darunavir 600mg BD plus ritonavir 100mg BD for 14 days. • **Lopinavir/ ritonavir (if remdesivir not available) in combination with chloroquine or hydroxychloroquine, and tocilizumab** - in patients affected by respiratory symptoms, clinically unstable, not in critical conditions (e.g.: MEWS clinical deterioration score 3-4) - in critical patients (e.g. MEWS clinical deterioration score >4)	**Lopinavir/ ritonavir 400/100 mg BD**	**14 days**

Antiviral dose regimens recommended in international guidelines *continued*

Drug	Guideline (Date published, version)	Patient population	Dosing and frequency	Duration of therapy
	Italy (SIMIT, Lombardia edition 2 13/03/2020)	• **lopinavir/ ritonavir in combination with chloroquine or hydroxychloroquine** • in patients with mild respiratory symptoms, aged > 70 years ± risk factors (diabetes, COPD, heart disease) • In patients with mild respiratory symptoms ± chest x-ray which indicates pneumonia	**Lopinavir/ ritonavir 400/100 mg BD** **(alternatively, darunavir & ritonavir 800mg/ 100mg QD or darunavir & cobicistat 800/150mg QD)**	**5 - 20 days. Duration determined by clinical evaluation**
Remdesivir	**Belgium (19/03/2020 version 4)**	• **Compassionate use: Remdesivir should be used first line in patients with confirmed COVID-19 with critical disease,** - in patients who meet at least one of the following criteria (ARDS; sepsis; altered consciousness; multi-organ failure).	**200 mg loading dose (IV within 30 minutes) on day 1 100mg OD maintenance dose from Day 2 to Day 10**	**2-10 days**
	Chinese guidelines 7th edition (03/03/2020)	- Not listed	**Not listed**	N/A
	Italy (NIID, IRCCS 17/03/2020).	• **In combination with chloroquine or hydroxychloroquine, and tocilizumab** - in patients affected by respiratory symptoms, clinically unstable, not in critical conditions (e.g.: MEWS clinical deterioration score 3-4) - in combination with chloroquine or hydroxychloroquine and tocilizumab in critical patients (e.g. MEWS clinical deterioration score >4)	**200 mg loading dose (IV within 30 minutes) on day 1 100mg OD maintenance dose from Day 2 to Day 10**	**10 days**
	Italy (SIMIT, Lombardia edition 2 13/03/2020)	• **Remdesivir in combination with chloroquine or hydroxychloroquine** - in patients who require oxygen therapy or who rapidly deteriorate. - in patients with severe pneumonia, ARDS, or global respiratory insufficiency, haemodynamic failure and need for mechanical ventilation (invasive or not).	**200 mg loading dose (IV within 30 minutes) on day 1 100mg OD maintenance dose from Day 2 to Day 10**	**10 days**

ARDS=Acute respiratory distress syndrome; BD=twice daily; *COPD=chronic obstructive pulmonary disease; FiO2=Fraction* of inspired oxygen *PaO2*=partial pressure of arterial oxygen; MEWS=Modified Early Warning Score; QD=once daily;

Rapid Evidence Review

On the basis of preliminary antiviral prioritisation recommendations by the World Health Organisation, a targeted literature search was conducted to identify clinical studies reporting the efficacy of chloroquine/hydroxychloroquine, lopinavir-ritonavir and remdesivir for the treatment of COVID-19 (13, 14). The Evidence Review Group (ERG) conducted a rapid critical appraisal of relevant studies. A landscape analysis of international clinical guidelines was also conducted. Doses, where specified, refer to adult treatment regimens. See Appendix 1 for the Search Strategy.

1. Chloroquine/hydroxychloroquine

Chloroquine and hydroxychloroquine are antimalarial drugs with several pharmacological actions which impart therapeutic efficacy in the treatment of rheumatic disease (15). They share similar chemical structures and mechanisms of action. Hydroxychloroquine (Plaquenil®) is licensed in Ireland for the treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight (15)). It is unlicensed for the treatment of COVID-19. These drugs have been the focus of intense investigation and widespread anecdotal use since the beginning of the COVID-19 outbreak. They have the benefit of (historically) widespread availability, established safety profile in specific patient populations, and low cost. At the time of writing, hydroxychloroquine is more readily accessible than chloroquine in Ireland (3). Effective in vitro inhibition of SARS-CoV-2 has been shown by chloroquine and hydroxychloroquine in pre-clinical studies (16, 17), and a number of sources have these drugs as effective treatments for COVID-19 (18, 19). However, just one clinical trial has been published which reports on the comparative efficacy of hydroxychloroquine versus a control patient group in France (1). A review of this study has been published by the ERG previously (20). An English abstract of a Chinese study reporting the use of hydroxychloroquine in China has also been published (2).

Clinical studies

In an open-label, non-randomised clinical trial, co-ordinated by the IHU Méditerranée Infection in Marseille, the effect of hydroxychloroquine compared with a control group was investigated in 42 hospitalised patients with SARS-CoV-2 infection(1). The mean time between onset of symptoms and study inclusion was 4.1 days in the treatment group. Not all patients were symptomatic at the time of treatment initiation. Twenty-six patients received hydroxychloroquine sulfate 200mg three times daily for ten days, and 16 control patients did not receive hydroxychloroquine. Six hydroxychloroquine-treated patients (23%)

were reported as lost to follow-up (three due to transfer to an intensive care unit, one due to death, one due to nausea and one due to patient decision to discharge from hospital). Among hydroxychloroquine patients, six patients received azithromycin (500mg on day one, followed by 250mg per day for the next four days) to prevent bacterial super-infection. The criteria for selecting patients for combination treatment with hydroxychloroquine-azithromycin were not reported. It was not reported if any of the control patients received azithromycin. Hydroxychloroquine patients were older than control patients (51.2 years vs 37.3 years). Two (10%) of the hydroxychloroquine patients and four (25%) of the control patients were asymptomatic. An intention-to-treat analysis was not undertaken, as the patients who were lost-to-follow-up were not included in the efficacy analyses. The authors reported that 70% (14/20) of the hydroxychloroquine-treated patients were virologically cured compared with 12.5% (2/16) in the control group (p=0.001) at day six post-inclusion. The patients who were lost-to-follow-up were not included in the efficacy analyses. Under the assumption of treatment failure among those who are lost-to-follow-up, 54% (14/26) were virologically cured. All six patients treated with hydroxychloroquine-azithromycin were virologically cured at 6 days however one patient who met the primary outcome of virological clearance at day 6 tested positive again at low titre at day 8. A difference was observed between hydroxychloroquine-treated patients and controls, and between single-drug hydroxychloroquine-treated patients and the hydroxychloroquine-azithromycin - treated patients from day three post-inclusion. The COVID-19 Evidence Review Group calculated the difference between single agent hydroxychloroquine and combination with azithromycin based on the data provided in the paper. There is no significant difference between the groups (Fisher exact test statistic value is 0.1149 and therefore not significant at $p<0.05$) however given the number of patients involved, no statistical significance does not imply no effect. A number of limitations were identified, including the methods used to identify and select patients for each treatment arm, which were not described by the authors. There were also some differences in the baseline characteristics of each treatment arm. Hydroxychloroquine patients were older than control patients (51.2 years vs 37.3 years). Two (10%) of the hydroxychloroquine patients and four (25%) of the control patients were asymptomatic. The authors reported that “Drug effect was significantly higher in patients with symptoms of URTI and LRTI, as compared to asymptomatic patients”, though this data was not provided.

An English abstract of a Chinese study reporting the use of hydroxychloroquine in China was published on 06th March 2020 (2). Thirty treatment-naïve patients with confirmed COVID-19 were randomised 1:1 to hydroxychloroquine 400mg daily for five days, or a control group. The disease status of the patients at enrolment was not reported, though it is assumed that they were not severe. The primary endpoint was negative conversion rate of COVID-19 nucleic acid in respiratory pharyngeal swab after seven days. On day 7, COVID-19 nucleic acid of throat swabs was negative in 13 (86.7%) cases in the HCQ group and 14 (93.3%) cases in the control group ($P>0.05$). Similarly, no differences were observed

between the treatment groups in median time for body temperature normalization median duration from hospitalization to virus nucleic acid negative conservation. A lower proportion go patients had radiological progression shown on CT (5 cases (33.3%) of the HCQ group and 7 cases (46.7%) of the control group). Patient numbers and effect sizes in this study are too small to robustly determine a difference in efficacy between treatment groups. Insufficient information is available to critically appraise the quality of the study (2).

Summary of clinical evidence on chloroquine/hydroxychloroquine

In one clinical study, hydroxychloroquine was initiated in hospitalised patients with confirmed COVID-19 at a dose of 200mg three times daily for ten days. The mean time between onset of symptoms and study inclusion was 4.1 days in the treatment group. Not all patients were symptomatic at the time of treatment initiation. A higher rate of virological cure was observed in the hydroxychloroquine-treated group compared with a control group(1). An abstract of a Chinese study suggested no difference in viral clearance between hydroxychloroquine-treated patients and a control group, though patient numbers and effect sizes in this study are too small to robustly determine a difference in efficacy between treatment groups. Insufficient information is available to critically appraise the quality of the study (2)

International guideline recommendations on chloroquine/hydroxychloroquine

Belgium (19th March 2020). Interim Clinical Guidance for Patients Suspected of/Confirmed with COVID-19 in Belgium (19 March 2020) strongly recommend that the use of hydroxychloroquine in suspected/confirmed COVID-19 be restricted to hospitalised patients. Recommendations are stratified for patients depending on whether COVID-19 is suspected or confirmed, and the severity of disease. Hydroxychloroquine is recommended as a first-line treatment in high risk patients with mild to moderate disease, and in patients with severe disease. It is recommended as a second-line treatment option (if remedesivir is unavailable) in patients with critical disease. If used, hydroxychloroquine should be started at suspicion/diagnosis(19). The recommended dose of hydroxychloroquine is 400mg initially, followed by 400mg 12 hours later, followed by 200mg twice daily up to day 5. If hydroxychloroquine is unavailable, chloroquine base may be considered at a dose of 600mg initially, followed by 300mg 12 hours later, followed by 300mg twice daily up to day 5.

Italy (SIMIT, Lombardia) (13th March 2020). The Italian Society of Infectious and Tropical Diseases (SIMIT Lombardy, 13 March 2020) Handbook of care of people with COVID-19 recommends chloroquine or hydroxychloroquine in combination with lopinavir-ritonavir (or darunavir-ritonavir, or darunavir-cobicistat), or remedesivir, depending on the severity of the disease. The recommended dose is 200mg twice daily. Treatment is recommended for a duration of 5-20 days, with timing to be determined according to clinical evolution.

Treatment with chloroquine or hydroxychloroquine alone is recommended if lopinavir-ritonavir is contraindicated(6).

Italy (NIID, IRCCS) (17th March 2020). The National Institute for the Infectious Diseases "L. Spallanzani" IRCCS, Rome, Italy, Recommendations for COVID-19 Clinical Management, recommends chloroquine or hydroxychloroquine in combination with lopinavir-ritonavir (or darunavir-ritonavir, or darunavir-cobicistat) for mild/moderate disease, and in combination with remedesivir and tocilizumab for severe/critical disease. Treatment is recommended for a duration of 10 days. A G6PD deficiency test is recommended before chloroquine and hydroxychloroquine administration (21). The recommended dose of hydroxychloroquine is 400mg initially, followed by 400mg 12 hours later, followed by 200mg twice daily up to day 10. The recommended dose of chloroquine is 500mg twice daily up to day 10 (21).

Spain (19th March 2020). The Recommendations of the Spanish Society of Hospital Pharmacy do not include chloroquine or hydroxychloroquine among specific antiviral treatments. Hydroxychloroquine is referred to among other agents with limited evidence, at a dose of 400mg twice daily on day 1 followed by 200mg twice daily up to day 5 (22).

China (19th February 2020). The Chinese Preventive Medicines Association (Tentative Sixth Edition) includes chloroquine phosphate among trial drugs which may be used for COVID-19, without specifying specific treatments for different levels of severity. The recommended dose is 500mg twice daily. The course of treatment with trial drugs should be ≤10 days(4).

World Health Organisation (WHO). World Health Organisation Interim Guidance on the Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected (13 March 2020), advises that there is no current evidence to recommend any specific anti-COVID-19 treatment for patients with confirmed COVID-19. (23) World Health Organisation Informal consultation on the potential role of chloroquine in the clinical management of COVID 19 infection (13 March 2020) agreed that there is equipoise for the inclusion of chloroquine in clinical trials and to proceed with the evaluation of chloroquine in COVID 19 patients(13)

Summary of guideline recommendations on chloroquine/hydroxychloroquine:
Hydroxychloroquine is widely recommended in European guidelines for the treatment of patients with COVID-19. Chloroquine is recommended in Chinese guidelines. Guidelines vary in their recommendations to use chloroquine/hydroxychloroquine alone or in combination with other antivirals. Italian and Chinese guidelines recommend combination use and Belgium recommends single-agent use (though this is largely due to uncertainty in the efficacy of other antivirals). These drugs are recommended in mild, moderate and severe disease among the various guidelines. Dose regimens, treatment durations and

recommended time of initiation vary across guidelines. Treatment duration varies from 5 days up to 20 days. Use in hospitalised patients is recommended in Belgium, whereas patients with mild symptoms, albeit with risk factors, are recommended treatment in Italy, suggesting a role in primary care (4-7).

2. Lopinavir-ritonavir

Lopinavir-ritonavir is an antiretroviral fixed drug combination (HIV protease inhibitors), currently licensed in Ireland for the treatment of human immunodeficiency virus (HIV-1). (24) Lopinavir-ritonavir has been shown to have in vitro activity against SARS-CoV-1. (25-27). Limited clinical data has also been reported for Lopinavir-ritonavir, combined with ribavirin and interferon alfa, in MERS (28). Lopinavir-ritonavir in combination with interferon-beta 1b is currently under investigation for the treatment of MERS-CoV (29). The potential for benefit from lopinavir–ritonavir treatment in COVID-19 has been well documented(30). However to date, while observational cohort studies have reported its use (31, 32), the clinical evidence for efficacy is limited to two open-label randomised, controlled studies (both of which failed to demonstrate a benefit for lopinavir–ritonavir) and observational case reports (8-11)

Clinical studies

Cao et al reported results of a randomised, controlled, open-label trial involving hospitalised adult patients with confirmed SARS-CoV-2 infection with an oxygen saturation (Sao2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) of less than 300 mm Hg. 199 patients were randomised 1:1 to either lopinavir 400mg–ritonavir 100mg twice a day for 14 days, in addition to standard care, or standard care alone (8). The primary end point was the time to clinical improvement defined as the time from randomisation to either an improvement of two points on a seven-category ordinal scale (previously used for an influenza clinical trial conducted by the authors and recommended by the WHO) or discharge from the hospital. The median age of the total cohort was 58.0 years and 60.3% were male. The median time between illness onset and randomisation was 13 days in the treatment group. There were no meaningful between-group differences in baseline characteristics. No difference in the time to clinical improvement was observed between Lopinavir–ritonavir and standard care (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI], 0.90 to 1.72). Mortality was also similar between the treatment groups (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI, −17.3 to 5.7). A post-hoc analysis revealed a greater numerical difference in mortality between treatment groups, in favour of Lopinavir–ritonavir, among patients treated within 12 days after the symptom-onset than among those treated later. Numerical differences in favour of Lopinavir–ritonavir were observed in a number of secondary outcomes, including a shorter stay in the intensive care unit (6 days vs. 11 days;

difference, −5 days; 95% CI, −9 to 0), but these were not significant. Lopinavir–ritonavir treatment was stopped early in 13 patients (13.8%) because of adverse events. Gastrointestinal adverse events in particular were more common in lopinavir–ritonavir group than in the standard-care group. The open-label design of this trial is a limitation as it may lead to performance-bias and detection-bias for subjective outcomes. The applicability of this trial to all patients with COVID-19 is uncertain, particularly as the overall mortality (22.1%) in the trial was higher than was been observed elsewhere(33) .

Li et al reported results of the ELACOI (The Efficacy of Lopinavir Plus Ritonavir and Arbidol Against Novel Coronavirus Infection) study (ClinicalTrials.gov Identifier: NCT04252885) (11). Forty-four patients with mild/moderate COVID-19 were randomised 2:2:1 to lopinavir 400mg–ritonavir 100mg twice a day monotherapy for 7-14 days (n=21), Arbidol® (umifenovir) 200mg three times daily) for 7-14 days (n=16), or no antiviral treatment (n=7). Umifenovir is a haemagglutinin inhibitor antiviral used in China and Russia, with reported efficacy against influenza viruses ((34) The ELACOI study intended to enrol 125 patients but the local recruitment pool was rapidly exhausted as the epidemic was coming under control. The study was blind to participants, those physicians and radiologists who reviewed the data and radiological images, but open-label to clinicians who recruited patients and research staff. The primary outcome was the time of positive-to-negative conversion of SARS-CoV-2 nucleic acid from initiating treatment to day 21, with the enrolment day as the first day of treatment. There were some differences between the study populations in mean age, proportion with underlying chronic diseases. The time from onset to treatment was 4.1 to 5.6 days across the treatment groups. The mean time to positive-to-negative conversion of SARS-CoV-2 nucleic acid during the 21-day follow-up period was significantly different between the treatment groups: 8.5 (IQR, 3-13) in the lopinavir-ritonavir group, 7 (IQR, 3-10.5) in the arbidol group and 4 (IQR, 3-10.5) in the control group (P =0.751). During the follow-up period, 5 (23.8%) patients in the LPV/r group experienced adverse events, compared with no apparent adverse events in the arbidol or control group. More patients treated with LPV/r progressed from mild/moderate to severe/critical status than other two groups. The study was limited by the sample size which was not adequately powered to detect significant differences between treatment groups.

One case report of a 47-year old man treated with lopinavir-ritonavir in Wuhu, China, describes the use of lopinavir-ritonavir 800/200 mg daily *(ERG note: this is higher than the licensed dose for this treatment, and higher than is recommended in international COVID-19 treatment guidelines)* dose than the following hospital transfer due to acute exacerbation of clinical symptoms including expiratory dyspnoea, poor diet, and lethargy reported quick improvement of the clinical symptoms (9). The exact timing of treatment was not reported but it is assumed to be at least nine days post symptom-onset, given the reported date of hospital transfer. Treatment also included methylprednisolone, recombinant human interferon alfa-2b, ambroxol hydrochloride and moxifloxacin hydrochloride (9).

Another case report of a 54-year old man in Korea, described the use of lopinavir-ritonavir 400mg-100mg twice daily from day ten of illness (10). No serious respiratory symptoms were reported. β-coronavirus viral load started to decrease on the day after treatment initiation and no detectable or little coronavirus titres were observed from day 17 of illness. Other treatments over the course of the patient follow-up included ceftriaxone, tazobactam, levofloxacin, azithromycin, and peramivir. The authors acknowledged that that the decreased load of SARS-CoV-2 resulted could have resulted from the natural course of the healing process rather than administration of lopinavir/ritonavir, or both (10).

Summary of clinical evidence on lopinavir-ritonavir:
Clinical studies, one in a mild/moderate COVID-19 cohort, and one in a more severe cohort failed to demonstrate a benefit from lopinavir-ritonavir (400mg/100mg twice daily for 7-14 days) compared with standard care, or umifenovir (Arbidol®).The median time between illness onset and randomisation was 4.3 days and 13 days in the treatment groups of the respective studies. One clinical study found that earlier initiation (within 12 days of symptom-onset) was associated with a greater numerical difference in mortality compared to later initiation. Case reports describe the use of lopinavir-ritonavir from day ten and from day ≤nine(4-7).

International guideline recommendations on lopinavir-ritonavir

Belgium (19th March 2020). Interim Clinical Guidance for Patients Suspected of/Confirmed with COVID-19 in Belgium (19 March 2020) recommends that lopinavir/ritonavir can be considered a second choice for severe disease, when hydroxychloroquine is contraindicated, but only if this treatment could be administered early in the course of the disease (within 10 days after symptoms onset) (19).

Italy (SIMIT, Lombardia) (13th March 2020). Italian Society of Infectious and Tropical Diseases (SIMIT Lombardy, 13 March 2020) Handbook of care of people with COVID-19 recommends lopinavir-ritonavir (or darunavir-ritonavir, or darunavir-cobicistat) in combination with chloroquine or hydroxychloroquine, for high-risk patients with mild disease, and for severe disease if remdesivir is unavailable. Treatment is recommended for a duration of 5-20 days, with timing to be determined according to clinical evolution (6).

Italy (NIID, IRCCS) (17th March 2020). The National Institute for the Infectious Diseases "L. Spallanzani" IRCCS, Rome, Italy, Recommendations for COVID-19 Clinical Management, recommend lopinavir-ritonavir (or darunavir-ritonavir, or darunavir-cobicistat) in combination with chloroquine or hydroxychloroquine, for mild/moderate patients, and as an alternative to remedesivir (if unavailable), in combination with chloroquine or

hydroxychloroquine and tocilizumab in severe/critical disease. Treatment is recommended for a duration of 14 days (6).

Spain (19th March 2020). The Recommendations of the Spanish Society of Hospital Pharmacy include lopinavir-ritonavir alone, and in combination with either interferon beta-1b (subcutaneous injection) or interferon afa-2b (nebulised), among specific antiviral treatments. Specific recommendations on which patients may be eligible for treatment are not provided. Treatment is recommended for a duration of 14 days for lopinavir-ritonavir +/- interferon-beta-1b. If combined with interferon-alfa-2b, the interferon component of therapy is recommended for a duration of 5-7 days (22).

China (19th February 2020). The Chinese Preventive Medicines Association (Tentative Sixth Edition) includes lopinavir/ritonavir among trial drugs which may be used for COVID-19, without specifying specific treatments for different levels of severity. The course of treatment with trial drugs should be ≤10 days(4).

World Health Organisation (WHO). World Health Organisation Interim Guidance on the Clinical management of severe acute respiratory infection when novel coronavirus infection is suspected (13 March 2020), advises that there is no current evidence to recommend any specific anti-COVID-19 treatment for patients with confirmed COVID-19. (23)

Summary of guideline recommendations on lopinavir-ritonavir:
Guideline recommendations on the role of lopinavir-ritonavir for the treatment of COVID-19 are inconsistent, with Belgium recommending it only if hydroxychloroquine is contraindicated, and Italian guidelines recommending it as a first-line treatment, in combination with chloroquine or hydroxychloroquine, in patients with mild-moderate disease, and as an alternative to remdesivir in severe/critical disease. The recommended daily dose is lopinavir/ritonavir 400/100 mg (i.e 2 tablets of 200/50 mg). The treatment duration varies in guidelines, up to 20 days(4-7).

3. Remdesivir

Remdesivir is an investigational broad-spectrum antiviral drug which has shown to effectively inhibit SARS-CoV-2 in vitro and in MERS and SARS-CoV-1 animal models (16, 35, 36). An extensive clinical safety database exists from its investigational use in Phase I, II and II trials for the Ebola virus and MEURI (14).

Clinical Studies

In one case report describing a 35-year old man in Washington, intravenous remdesivir (dose not reported) was initiated on illness Day 11 (12). The patient was already on

supplemental oxygen, vancomycin and cefepime and was initiated on remdesivir following radiographic findings consistent with atypical pneumonia and worsening clinical status. On illness Day 12, the patients's clinical condition improved. At the last point of follow-up, the patient was asymptomatic aside from cough which was decreasing in severity. Remdesivir, as an unlicensed investigational therapy, is only available through compassionate use from the pharmaceutical company Gilead Sciences. A number of randomized controlled trials of remdesivir for COVID-19 are also underway in the US, China and France (37-39) to determine the safety and efficacy of remdesivir as a potential treatment at various stages if the illness i.e. patients with mild/moderate, moderate and severe disease. The dose in clinical trials is 200 mg as a single dose on day 1, followed by 100 mg once daily for a total duration of 5 to 10 days. Access to remdesivir outside of a clinical trial is only possible on the basis of an emergency treatment request, when enrollment in a clinical trial is not feasible. At the time of writing (25th March), new compassionate use requests were not being accepted due to overwhelming demand, with the exception of requests for pregnant women and children, with severe manifestations of COVID-19 (40) The timing of treatment may vary between studies, depending on the inclusion criteria described in the preliminary clinical trial protocols, which vary between studies. Protocols require confirmation of SARS-CoV-2 ≤4 days before randomization or <72 hours before randomization in the US/international studies, and ≤8 days or ≤12 days since illness onset in the China studies.

Summary of clinical evidence on remdesivir:
In one reported case, remdesivir was initiated on illness Day 11 following radiographic findings consistent with atypical pneumonia and worsening clinical status. The remdesivir dose is clinical trials is 200 mg as a single dose on day 1, followed by 100 mg once daily for a total duration of 5 to 10 days. Clinical trial protocols require SARS-CoV-2 confirmation within 3 to 8 days, depending on the study(12)..

International guideline recommendations on remdesivir

Belgium (19th March 2020). Interim Clinical Guidance for Patients Suspected of/Confirmed with COVID-19 in Belgium (19 March 2020) recommends that remdesivir should be used in critical disease for 2 to 10 days(19).

Italy (SIMIT, Lombardia) (13th March 2020). Italian Society of Infectious and Tropical Diseases (SIMIT Lombardy, 13 March 2020) Handbook of care of people with COVID-19 recommends remdesivir for patients in need of oxygen therapy or with severe symptoms in combination with chloroquine or hydroxychloroquine. Treatment with remdesivir is recommended for a duration of 10 days(6).

Italy (NIID, IRCCS) (17th March 2020). The National Institute for the Infectious Diseases "L. Spallanzani" IRCCS, Rome, Italy, Recommendations for COVID-19 Clinical Management,

recommend remzdesivir in combination with chloroquine or hydroxychloroquine, and tocilizumab for severe and critical disease. Treatment is recommended for a duration of 10 days (6).

Spain (19th March 2020). The Recommendations of the Spanish Society of Hospital Pharmacy include remdesivir among specific antiviral treatments. Specific recommendations on which patients may be eligible for treatment are not provided. Treatment is recommended for a duration of 10 days (22).

China (19th February 2020). The Chinese Preventive Medicines Association (Tentative Sixth Edition) does not refer to remdesivir (4).

World Health Organisation (WHO). World Health Organisation Interim Guidance on the Clinical management of severe acute respiratory infection when novel coronavirus infection is suspected (13 March 2020), advises that there is no current evidence to recommend any specific anti-COVID-19 treatment for patients with confirmed COVID-19. (23) However, the WHO R&D blueprint Informal Consultation of prioritization of candidate therapeutic agents for use in novel coronavirus 2019 infection (24 Jan 2020) identified remdesivir as the most promising candidate therapeutic based on the broad antiviral spectrum, the in vitro and in-vivo data for coronavirus and the extensive clinical safety database (14).

Summary of guideline recommendations on remdesivir:
If access to remdesivir is possible, either through a clinical trial or through an emergency treatment request from Gilead, it is recommended in guidelines for the treatment of patients with severe or critical disease. The duration of treatment varies from 2 to 10 days (8-11).

4. Other antivirals

A number of other drugs are being developed/repurposed as potential therapeutic candidates for COVID-19. The following section is a descriptive summary of new and emerging data which has not been subjected to a rapid critical appraisal. This list is not exhaustive and will be updated periodically by the ERG.

Ribavirin is licensed for the treatment of hepatitis C virus, and is included in Chinese COVID-19 treatment guidelines, preferably in combination with interferon or lopinavir-ritonavir (4). The WHO considered that ribavirin does not appear like a candidate worth further investigating, based on the available evidence. This was based on experience with its evaluation in SARS in Canada in 2003 which may have resulted in higher mortality than in other countries. Toxicity risks, such as reduced haemoglobin concentration, were also considered undesirable in patients with respiratory disorders (14).

Interferon-alpha 2b is licensed in Ireland for the treatment of chronic hepatitis B and C and various haematological malignancies. *Interferon-beta 1b* is licensed in Ireland for the treatment of multiple sclerosis. Interferon-alpha is included in Chinese COVID-19 treatment guidelines (5 million units (or equivalent), nebulised inhalation, twice daily) preferably in combination with ribavirin or lopinavir-ritonavir (4). In vitro data suggest that IFN α might have inhibitory effects against SARS-CoV-1 (41).The MIRACLE study in Saudi Arabia is assessing the combination of interferon-beta with lopinavir-ritonavir for the treatment of MERS-CoV (29).

Danoprevir (Ganovo®) (a HCV protease (NS3/4A) inhibitor approved and marketed in China since 2018 for chronic hepatitis C virus), boosted by ritonavir was shown to be safe and well-tolerated in a small non-comparative study (n=11) of "moderate" COVID-19 patients at the Nineth Hospital of Nanchang, China (ClinicalTrials.gov Identifier: NCT04291729) (42). Eligible patients had demonstrated respiratory symptoms and imaging-confirmed pneumonia. After 4 to 12 days' treatment, all eleven patients enrolled were discharged from hospital (42). The ERG is not aware that danoprevir is readily available for use in Ireland.

Meplazumab is an anti-CD147 humanized IgG2 monoclonal antibody, which has shown to be effective in vitro inhibition of SARS-CoV-2 replication and virus-induced cytopathic effect in Vero E6 cells (43). An open-label, concurrent controlled trial at Tangdu Hospital of Fourth Military Medical University in Xi'an, China, evaluated whether meplazumab, as add-on therapy, improves patients with COVID-19 pneumonia. Eligible patients were described as having "common, severe or critical COVID-19 pneumonia", and received add-on administered 10 mg meplazumab intravenously at days 1, 2, and 5. The primary study endpoint was the virological clearance (i.e. negative conservation rate and time to negative) using qRT-PCR in nasopharyngeal swabs samples. (ClinicalTrials.gov Identifier: NCT04275245) Patients hospitalized in the same period were observed as concurrent control. The clinicaltrials.gov listing for this trial described it as a single centre, single-arm trial. 17 patients were allocated to meplazumab and 11 hospitalized patients who met the inclusion criteria and with no exclusion criteria signs were collected as concurrent control in the same period. All patients received recommended therapy according to local guidelines, including antivirals. Improvements among the meplazumab group in terms of time to virological clearance, time-to-discharge, time to virological clearance and inflammatory markers were reported (44). No adverse effect was found in meplazumab-treated patients. The ERG is not aware that meplazumab is readily available for use in Ireland.

Favipravir is an RNA-dependent RNA polymerase (RdRp) inhibitor approved for the treatment of influenza in China and Japan, and previously identified by the WHO as a promising candidate for testing in patients with Ebova virus disease (45, 46). In an in vitro study, inhibition of SARSCoV-2 infection in Vero E6 cells was not as effective with favipravir

as it was for remdesivir or chloroquine (16).Favipravir was compared to lopinavir and ritonavir in an open label control study for the treatment of COVID-19 in a study conducted in China (47). Patients with duration of disease onset of less than seven days were eligible for inclusion. Patients in a severe clinical condition were excluded. Fifty six patients with laboratory confirmed COVID-19 from 20th January to 14th February 2020 were screened, of which 35 were eligible for the favipravir arm of the study. A total of 91 patients with confirmed COVID-19 patients who had started treatment with lopinavir/ritonavir between 24th and 30th January were screened; 45 were eligible for the control arm of the study. The dose of favipravir was 1600mg twice daily on day 1 and 600mg twice daily on days 2-14. The dose of lopinavir-ritonavir was 400mg/100mg twice daily. Treatment was continued until viral clearance or until 14 days had passed. All patients also received interferonα 60μg twice daily by aerosol inhalation as well as usual standard care such as anti-pyretics, oxygen, rehydration, antiemetics and analgesics. Viral clearance (using qPCR) and improvement rate of chest computed tomography (CT) at day 14 after treatment were the efficacy outcomes; measurements were taken at days 4,8 and 14. No significant difference between groups was noted at days 4 and 8 but a significant difference (after adjusting for potential confounders) was noted at day 14 on improvement rates of chest CT changes (91.4% versus 62.2%, 32/35 versus 28/45 (p=0.004). The median time of viral clearance for favipravir patients was 4 days (IQR 2.5 to 9) and in the lopinavir and ritonavir group 11 days (IQR 8 to 13) (P<0.001). Fewer adverse reactions were reported in the favipravir arm compared to the control arm (total number of adverse reactions; 4 vs 25). The open-label, retrospective control design of this trial is a limitation as it may lead to performance-bias and detection-bias for subjective outcomes (47). The ERG is not aware that favipravir is readily available for use in Ireland.

Appendix 1

A targeted literature review was conducted to inform the Rapid Evidence Review based on a search strategy developed by the Information Specialist at the National Centre for Pharmacoeconomics. A typical hierarchy of evidence was considered in the search, from highest to lowest:

- Systematic Literature Reviews and meta-analyses
- Randomized Controlled Trials
- Observational studies
- Published expert opinion

The landscape Review of International Clinical Guidelines identified up-to-date guidelines predominantly from other European countries and also China, the initial epicentre of the COVID-19 pandemic. Clinical trial registers in the EU, US and China were searched for evidence of ongoing or completed clinical trials.

Search strategy 26th March 2020

Source	Search	No. of hits
Pubmed	2019-nCoV OR 2019nCoV OR COVID-19 OR SARS-CoV-2 OR ((wuhan AND coronavirus) AND 2019/12[PDAT]:2030[PDAT])	
	AND ("Chloroquine"[Mesh]) OR "Hydroxychloroquine"[Mesh]	6
	AND "Lopinavir"[Mesh] OR "lopinavir-ritonavir drug combination" [Supplementary Concept]	8
	AND "remdesivir" [Supplementary Concept]	5
LitCovid	chloroquine or hydroxychloroquine	19
	lopinavir	22
	remdesivir	15
Google Scholar:	COVID-19 coronavirus OR "coronavirus pneumonia" OR “COVID-19” OR “2019 novel coronavirus infection” OR “2019-nCoV” AND	
	"chloroquine" OR "hydroxychloroquine"	362
	"lopinavir" or "lopinavir-ritonavir"	384
	"remdesivir"	390
ClinicalTrials.gov	COVID-19 (synonyms 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2)	
	AND chloroquine or hydroxychloroquine	11
	AND lopinavir	18
	AND remdesivir	8
clinicaltrialsregister.eu	COVID-19	12
ChinaXiv.org	Title:(coronavirus) OR Title:(COVID) (limit:2020)	14

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