Rapid Evidence Review

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

Prepared by the COVID-19 Evidence Review Group

Version 2, 4th April 2020

Key changes between version 1 (27th March 2020) and version 2 (4th April 2020): Updated clinical evidence for chloroquine/hydroxychloroquine, inclusion of EMA guidance on the use of chloroquine/hydroxychloroquine, removal of favipiravir study due to withdrawal from the publisher’s website, inclusion of a favipiravir study.

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 | Evidence of efficacy of chloroquine/hydroxychloroquine is inconsistent and limited to two small comparative studies, one abstract, and two case-series (1-5). One randomised, controlled trial including 62 patients treated with standard treatment alone or standard treatment plus hydroxychloroquine 400 mg daily for five days, reported a modest reduction (approximately one day) in time to fever and cough recovery among patients with predominantly mild disease (3). Improvement in pneumonia, assessed by chest CT, occurred in a greater proportion of patients in the hydroxychloroquine group compared with the control group (80.6% vs 54.8%) (3). One non-randomised, controlled study comparing hydroxychloroquine 200mg three times daily for ten days with a control group consisting of patients who refused treatment and patients recruited from other treatment centres, reported a higher rate of virological cure in the hydroxychloroquine-treated group (70% (14/20) vs 12.5% (2/16) negative nasopharyngeal PCR, p=0.001 at day six post-inclusion) (4). An abstract of a Chinese study (n=30) suggested no difference in viral clearance between hydroxychloroquine-treated patients and a control group (2). Two case-series on the use of combination therapy with hydroxychloroquine and azithromycin report conflicting results, though there may be differences in the study populations (1, 5). While some studies have reported positive results, the quality and reliability of studies on the efficacy of chloroquine/hydroxychloroquine were often limited by open-label, non-randomised, uncontrolled study designs, and small patient numbers. Controlled trials in large patient cohorts, ideally randomised and double-blinded, are necessary to provide robust evidence for the systematic use of this chloroquine/hydroxychloroquine for COVID-19 |
| International Guidelines | At the time of writing, hydroxychloroquine is more readily accessible than chloroquine in Ireland (6). 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). Belgian guidance recommends that there is no sufficient evidence about activity of azithromycin and therefore no reason to associate this antibiotic to the |
hydroxychloroquine treatment at this moment. Hydroxychloroquine and chloroquine 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 (7-10).

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### Antiviral dose regimens recommended in international guidelines

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| Chloroquine/ hydroxychloroquine | Belgium (31/03/2020 version 6) | • Chloroquine or hydroxychloroquine monotherapy: first line in patients with confirmed COVID-19  
  - with mild to moderate disease (no O₂ 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%; PaO₂/FiO₂ 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 500mg 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  
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| 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 |
| Belgium (31/03/2020 version 6) | • 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) | Lopinavir/ritonavir 400/100 mg BD | 14 days |
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| 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 (31/03/2020 version 6) | • 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                          |                                                                                   |                                                                                      | 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;
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Background

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 (16, 17). 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. Emerging evidence on other therapeutic candidate antivirals was also reviewed and summarised.

Chloroquine/hydroxychloroquine

Chloroquine and hydroxychloroquine are antimalarial drugs with several pharmacological actions which impart therapeutic efficacy primarily in the treatment of rheumatic disease (18). 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 (18). 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 (6). Effective in vitro inhibition of SARS-CoV-2 has been shown by chloroquine and hydroxychloroquine in pre-clinical studies (19, 20), and a number of sources have identified these drugs as effective treatments for COVID-19 (21, 22). However, while many clinical trials are ongoing, a limited number of completed trials investigating the comparative efficacy of hydroxychloroquine have been published (2-4). Note: a separate Rapid Evidence Review specifically focussing on the efficacy of hydroxychloroquine/azithromycin combination therapy for COVID-19 has been published by the COVID-19 ERG (23).

Clinical studies of chloroquine/hydroxychloroquine

Two full study reports and one study abstract, reporting the comparative efficacy of hydroxychloroquine for the treatment of COVID-19, were identified (2-4). A randomised, controlled study described the efficacy of hydroxychloroquine plus standard treatment compared with standard treatment alone in 62 patients in China (3). An open-label, non-randomised clinical trial of hydroxychloroquine compared with a control group was conducted in 42 patients in France (4). A third Chinese study, available only as an abstract in English, reported the outcomes of 30 treated with hydroxychloroquine compared with a
control group (2). Two other non-comparative case-series reports on the use of hydroxychloroquine in combination with azithromycin were also identified (1, 5).

Chen Z et al. 30th March 2020

Chen et al reported on a randomized, controlled study conducted at the Renmin Hospital of Wuhan University (Wuhan, China) on March 30th 2020(3). Sixty-two hospitalized patients with COVID-19 who met inclusion criteria were randomised 1:1 to receive standard treatment alone (oxygen therapy, antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids) or standard treatment plus hydroxychloroquine 400 mg daily for five days. Patients with confirmed SARS-CoV-2 were included if they were ≥18 years, had pneumonia on chest CT, and had mild respiratory illness (SaO2/SPO2 ratio > 93% or PaO2/FIO2 ratio > 300 mmHg). Exclusion criteria included severe or critical illness, retinopathy or other retinal diseases, arrhythmias, among others(3).

Clinical characteristics and radiological results were assessed at baseline and 5 days after treatment initiation. The primary endpoint was time to clinical recovery (TTCR), defined as the return of body temperature and cough relief, maintained for more than 72 hours. The mean age of patients was 44.7 years, and 46.8% were male. 22/31 and 17/31 patients had a fever before the intervention in the hydroxychloroquine and control groups, respectively. 22/31 and 15/31 patients had a cough before the intervention in the hydroxychloroquine and control groups, respectively. The times to fever recovery and cough recovery were approximately one day shorter in the hydroxychloroquine group (fever: 2.2 (SD 0.4) days vs 3.2 days (SD 1.3), p=0.0008; cough: 2.0 (SD 0.2) days vs 3.1 (SD 1.5) days, p=0.0016). Four patients, all in the control group progressed to severe illness. Improvement in pneumonia, assessed by chest CT, occurred in 25/31 patients (80.6%) in the hydroxychloroquine group compared with 17/31 (54.8%) in the control group (3).

This study is limited to patients with mild COVID-19 disease, and has a very short (five-day) follow-up. Limited details of standard-care received by patients were provided e.g. the nature of other antivirals or antibiotics which may have been received. Nevertheless, the study demonstrated encouraging findings on the potential clinical benefits of hydroxychloroquine on mild COVID-19 disease(3).

Gautret et al. 20th March 2020

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(4). 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. Sixteen untreated patients from another centre and cases refusing the protocol were included as negative controls. These 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 number of limitations were identified. Patients were not randomised to treatment and the methods used to identify and select patients for each treatment arm were not described by the authors. This is a particular concern for the control group which included patients who refused the treatment or who were treated in other centres. This study is therefore at high risk of selection bias. 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. Further the exclusion of six patients as lost to follow up, given the known outcome introduces considerable bias in the determination of response.

*Chen J et al. 06th March 2020*

An English abstract of a Chinese study reporting the use of hydroxychloroquine in China was published on 6th 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 of 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).

Gautret et al. 27th March 2020

A second report by Gautret et al, expanded the initial case series of six patients treated with hydroxychloroquine-azithromycin to 80 patients (1). Patients with confirmed COVID-19 were admitted to the University Hospital Institute Méditerranée Infection in Marseille, France (24). Patients with no contraindications were offered combination therapy with hydroxychloroquine sulphate 200mg three times daily for ten days plus azithromycin 500mg on day 1 followed by 250mg per day for the next four days. Ceftriaxone (a broad spectrum antibiotic) was added in patients with pneumonia and NEWS score≥5. ECGs were performed on each patient before treatment and two days after treatment began. Hydroxychloroquine-azithromycin treatment was either not started or discontinued after two days on the basis of QTc risk-benefit assessment, and other abnormalities on ECG. Eighty patients who received combination hydroxychloroquine-azithromycin treatment for at least three days and who were followed-up for at least six days were included in the analysis. The median age of patients was 52.5 years; 52.5% were male; 57.5% had at least one chronic condition known to be a risk factor for severe COVID-19. The mean duration between the onset of symptoms and hospitalisation was five days (range 1-17 days). 53.8% and 41.2% of patients presented with LRTI with URTI respectively. Four patients were asymptomatic. 92% of patients had a low NEWS score (0-4), suggesting a mild disease. 53.8% of patients had LDCT compatible with pneumonia within 72 hours of admission. The mean PCR Ct value was 23.4. The mean time between the onset of symptoms and the initiation of treatment was 4.9 days. Treatment was stopped on day 4 in one patient because of the risk of a potential drug interaction. Viral load tested by qPCR was negative in 83% of patients on day 7 and 93% at day 8. Most patients (65/80, 81.3%) were discharged from the authors’ unit with a favourable outcome at the time of writing. The mean time from treatment initiation to discharge was 4.1 days (SD 2.2). Three patients were transferred to the ICU, including one death. Adverse events were described as rare and minor, occurring on seven occasions (unclear if these are seven events, or seven patients) including nausea/vomiting, diarrhoea and blurred vision.
This study is limited by the lack of a control arm, which is required to demonstrate whether
the observed clinical outcomes were a result of hydroxychloroquine-azithromycin
combination therapy, single-agent hydroxychloroquine or azithromycin therapy, supportive
care or the natural progression of the disease. The study numbers are very small, given the
heterogeneous nature of the disease course. The study does not provide information on the
status of all patients who were initiated on hydroxychloroquine-azithromycin treatment,
only those who received at least three days of treatment or who were followed up for at
least six days. It is possible that those patients who discontinued treatment early may have
had more severe disease, necessitating a change in treatment.

*Molina et al. 28th March 2020*

A prospective study of 11 consecutive patients admitted to a French Hospital (APHP-Saint
Louis Hospital) who received hydroxychloroquine (600 mg/d for 10 days) and azithromycin
(500 mg Day 1 and 250 mg days 2 to 5) were followed up for virological and clinical
outcomes (5). The mean age was 58.7 years and eight patients had significant comorbidities
associated with poor outcomes. At the time of treatment initiation, 10/11 had fever and
received nasal oxygen therapy. Within five days, one patient died, two were transferred to
the ICU, and treatment with hydroxychloroquine and azithromycin was discontinued after
four days because of QT prolongation in one patient (5). Repeated nasopharyngeal swabs
were still positive for SARS-CoV2 RNA in 8/10 surviving patients at days 5 to 6 after
treatment initiation (5).

As described above for the Gautret et al study, the Molina et al study is limited by the lack
of a control arm, which is required to demonstrate whether the observed clinical outcomes
were a result of hyd/az combination therapy, single-agent hydroxychloroquine or
azithromycin therapy, supportive care or the natural progression of the disease. The study
numbers are very small, given the heterogeneous nature of the disease course.

### Summary of clinical evidence on chloroquine/hydroxychloroquine

Evidence of efficacy of chloroquine/hydroxychloroquine is inconsistent and limited to two
small comparative studies, one abstract, and two case-series (1-5). One randomised,
controlled trial including 62 patients treated with standard treatment alone or standard
treatment plus hydroxychloroquine 400 mg daily for five days, reported a modest reduction
(approximately one day) in time to fever and cough recovery among patients with
predominantly mild disease (3). Improvement in pneumonia, assessed by chest CT, occurred
in a greater proportion of patients in the hydroxychloroquine group compared with the
control group (80.6% vs 54.8%) (3). One non-randomised, controlled study comparing
hydroxychloroquine 200mg three times daily for ten days with a control group consisting of
patients who refused treatment and patients recruited from other treatment centres,
reported a higher rate of virological cure in the hydroxychloroquine-treated group (70% (14/20) vs 12.5% (2/16) negative nasopharyngeal PCR, p=0.001 at day six post-inclusion) (4). An abstract of a Chinese study (n=30) suggested no difference in viral clearance between hydroxychloroquine-treated patients and a control group (2). Two case-series on the use of combination therapy with hydroxychloroquine and azithromycin report conflicting results, though there may be differences in the study populations (1, 5). While some studies have reported positive results, the quality and reliability of studies on the efficacy of chloroquine/hydroxychloroquine were often limited by open-label, non-randomised, uncontrolled study designs, and small patient numbers. Controlled trials in large patient cohorts, ideally randomised and double-blinded, are necessary to provide robust evidence for the systematic use of this chloroquine/hydroxychloroquine for COVID-19.

International guideline recommendations on chloroquine/hydroxychloroquine

**Belgium (31st March 2020).** Interim Clinical Guidance for Patients Suspected of/Confirmed with COVID-19 in Belgium 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 remdesivir is unavailable) in patients with critical disease. If used, hydroxychloroquine should be started at suspicion/diagnosis(22). 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. Belgian guidance recommends that there is no sufficient evidence about activity of azithromycin and therefore no reason to associate this antibiotic to the hydroxychloroquine treatment at this moment (22).

**Italy (SIMIT, Lombardia) (13th March 2020).** The Italian Society of Infectious and Tropical Diseases Handbook of care of people with COVID-19 recommends chloroquine or hydroxychloroquine in combination with lopinavir-ritonavir (or darunavir-ritonavir, or darunavir-cobicistat), or remdesivir, 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(9).

**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 remdesivir 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 (25). 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 (25).

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 (26).

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(7).

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. (27) 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(16). The WHO has recently launched the WHO-Solidarity trial, a multi-centre, adaptive, randomised, open-label, controlled clinical trial to evaluate the clinical efficacy and safety of four treatment options against standard of care for COVID-19. The treatment options in the trial are remdesivir; lopinavir-ritonavir; lopinavir-ritonavir with interferon beta-1a; and chloroquine or hydroxychloroquine. As of March 27 2020, over 70 countries have already confirmed they will contribute to the trial, with many others in the process of joining.

European Medicines Agency (EMA). The EMA has recommended that:

- For COVID-19, chloroquine and hydroxychloroquine should preferably be used in the context of clinical trials. Outside clinical trials, they can be used in accordance with national established protocols.
- Chloroquine and hydroxychloroquine should continue to be used in chronic conditions. In order to prevent unnecessary strain on supply chains, patients should only receive
their usual supply of medicines. Healthcare professionals should not write prescriptions that cover more than the usual duration (28).

**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). Belgian guidance recommends that there is no sufficient evidence about activity of azithromycin and therefore no reason to associate this antibiotic to the hydroxychloroquine treatment at this moment. Hydroxychloroquine and chloroquine 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 (7-10).

**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). (29) Lopinavir-ritonavir has been shown to have in vitro activity against SARS-CoV-1. (30-32). Limited clinical data has also been reported for lopinavir-ritonavir, combined with ribavirin and interferon alfa, in MERS (33). Lopinavir-ritonavir in combination with interferon-beta 1b is currently under investigation for the treatment of MERS-CoV (34). The potential for benefit from lopinavir–ritonavir treatment in COVID-19 has been well documented (35).

**Clinical studies of lopinavir-ritonavir**

To date, while observational cohort studies have reported the use of lopinavir-ritonavir (36, 37), the clinical evidence for comparative 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 (11-14)

*Caö et al. 18th March 2020*

Caö 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 (11). 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 (38).

**Li et al 23rd March 2020**

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) (14). 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 ((39) 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.

Han et al 19th February 2020

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 dyspnœa, poor diet, and lethargy reported quick improvement of the clinical symptoms (12). 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 (12).

Lim et al 13th February 2020

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 (13). 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 (13). Subsequent commentary has suggested that the pattern of viral titres suggests that the natural course of the disease may be a more likely driver of improvement in this case (40).

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 nine (7-10).

**International guideline recommendations on lopinavir-ritonavir**

**Belgium (31st March 2020).** Interim Clinical Guidance for Patients Suspected of/Confirmed with COVID-19 in Belgium 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) (22).

**Italy (SIMIT, Lombardia) (13th March 2020).** Italian Society of Infectious and Tropical Diseases 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 (9).

**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 remdesivir (if unavailable), in combination with chloroquine or hydroxychloroquine and tocilizumab in severe/critical disease. Treatment is recommended for a duration of 14 days (9).

**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 (26).

**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(7).
**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. (27) The WHO-Solidarity trial includes lopinavir-ritonavir; and lopinavir-ritonavir with interferon beta-1a as treatment options, as described above.

<table>
<thead>
<tr>
<th>Summary of guideline recommendations on lopinavir-ritonavir:</th>
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| 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 (7-10).

**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 (19, 41, 42). An extensive clinical safety database exists from its investigational use in Phase I, II and II trials for the Ebola virus and MEURI (17).

Remdesivir, as an unlicensed investigational therapy, is only available through compassionate use or via a clinical trial from the pharmaceutical company Gilead Sciences.

**Clinical Studies on remdesivir**

Evidence of remdesivir efficacy is limited to one case report from the United States.

*Holshue et al. 05th March 2020*

In one case report describing a 35-year old man in Washington, intravenous remdesivir (dose not reported) was initiated on illness Day 11 (15). 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 patient’s clinical condition improved. At the last point of follow-up, the patient was asymptomatic aside from cough which was decreasing in severity.

A number of randomized controlled trials of remdesivir for COVID-19 are also underway in the US, China and France (43-45) to determine the safety and efficacy of remdesivir as a
potential treatment at various stages of 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 (46) The timing of treatment may differ 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 studies conducted in China.

| 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(15). |

**International guideline recommendations on remdesivir**

**Belgium (31st March 2020).** Interim Clinical Guidance for Patients Suspected of/Confirmed with COVID-19 in Belgium recommends that remdesivir should be used in critical disease for 2 to 10 days(22).

**Italy (SIMIT, Lombardia) (13th March 2020).** Italian Society of Infectious and Tropical Diseases 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(9).

**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 remdesivir in combination with chloroquine or hydroxychloroquine, and tocilizumab for severe and critical disease. Treatment is recommended for a duration of 10 days (9).

**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 (26).

**China (19th February 2020).** The Chinese Preventive Medicines Association (Tentative Sixth Edition) does not refer to remdesivir (7).

**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. (27) 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 (17). The WHO-Solidarity trial includes remdesivir as a treatment option, as described above.

<table>
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<th>Summary of guideline recommendations on remdesivir:</th>
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<td>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 (11-14).</td>
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**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.

**Favipiravir**

An open-label study by Cai et al comparing favipiravir to lopinavir-ritonavir, previously included in Version 1 of this Rapid Evidence Review, was withdrawn from the publisher’s website at the request of the author(s) and/or the editor (47). The study has therefore been removed from this review.

Favipiravir 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 Ebola virus disease (48, 49). In an in vitro study, inhibition of SARS-CoV-2 infection in Vero E6 cells was not as effective with favipiravir as it was for remdesivir or chloroquine (19). Chen et al reported on a prospective,
multicentre, open-labelled, randomized study assessing the clinical efficacy and safety of favipiravir versus arbidol as treatment for COVID-19 (50). Two hundred and thirty six patients aged ≥18 years with COVID-19 pneumonia, within 12 days of initial symptoms were randomised 1:1 (116:120) to routine treatment plus favipiravir (1600mg twice daily on day one, 600mg twice daily from day two onwards), or routine treatment plus arbidol 200mg three times daily, for a duration of 7-10 days. Exclusion criteria included severe patients whose expected survival time was expected to be less than 48 hours, among others. The primary outcome was the clinical recovery rate at 7 days or the end of treatment, defined as continuous (>72 hours) recovery of body temperature, respiratory rate, oxygen saturation and cough relief after treatment. Results were stratified for moderate patients with COVID-19, severe patients with COVID-19, COVID-19 patients with hypertension and/or diabetes. The authors did not include subgroup analysis in the statistical plan, and it is therefore unlikely that the study was powered to detect a difference between subgroups. 46.6% of patients were male, 70% of patients were aged ≥65 years, 33% had hypertension and 19% had diabetes. 89% of patients had severe COVID-19, with slightly more patients in the arbidol group having severe COVID-19 compared with the favipiravir group (93% vs 89%). No significant difference in basic characteristics was observed between the two groups. There was a notable difference in the proportion of patients receiving other concomitant antivirals, which may have included ribavirin, chloroquine and/or interferon (24.32% in the arbidol group vs 11.22% in the favipiravir group, p=0.0045). The clinical recovery rate was 51.67% (62/120) in the arbidol group and 61.21% (71/116) in the favipiravir group after a 7 day's antiviral treatment (non-significant difference 9.54%, 95% CI: -3.05% to 2.2%, P=0.1396). The difference in recovery rate was more pronounced for patients with moderate disease compared to severe disease (15.6% vs 5.6% difference between treatment groups). There was minimal difference in clinical recovery rate between the two treatment groups in patients with hypertension and/or diabetes. For patients with moderate disease, and for patients with hypertension and/or diabetes, the time of fever reduction and cough relief (present in 58% and 59% of all patients with moderate disease, respectively, and in 38% and 62% of all patients with hypertension and/or diabetes, respectively) was reported to be significantly shorter in the favipiravir group than in the arbidol group (mean time not reported, p<0.0001). No statistically significant differences in auxiliary oxygen therapy or non-invasive mechanical ventilation were observed between the two treatment groups, though numerical differences favoured favipiravir. There was an imbalance in the severity of COVID-19 between the treatment groups with the arbidol group having slightly more patients with severe disease. This study was limited by its open-label design, lack of power for subgroup analysis, imbalances in the treatment group in disease severity and in the proportion of patients receiving other concomitant antivirals, with the arbidol group having slightly more patients with severe disease, and also more patients receiving other antivirals. While the stratified analysis based on severity is unaffected by the severity imbalance, the impact of concomitant antiviral therapy on clinical outcomes is unknown. The ERG is not aware that favipiravir is readily available for use in Ireland.
**Ribavirin**
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 (7). 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 (17).

**Danoprevir**
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) (51). Eligible patients had demonstrated respiratory symptoms and imaging-confirmed pneumonia. After 4 to 12 days’ treatment, all eleven patients enrolled were discharged from hospital (51). The ERG is not aware that danoprevir is readily available for use in Ireland.

**Other treatments with possible anti-viral activity**

**Interferons**
Interferon-alpha and –beta are type I interferons, made and released by host cells in response to the presence of several viruses, that help regulate the activity of the immune system. Interferons are included in ongoing COVID-19 clinical trials, primarily as part of combination therapy targeting both virus replication and the host’s inflammatory response. Interferon-beta 1a and interferon-beta 1b are licensed in Ireland for the treatment of multiple sclerosis. Interferon-alpha 2b is licensed in Ireland for the treatment of chronic hepatitis B and C and various haematological malignancies. Both interferon-alpha and –beta have shown effective in vitro inhibition of SARS-CoV-1 replication, with interferon-beta showing the greatest potency (52). Clinical improvements have been observed in vivo with interferon-beta in MERS-CoV (53). The MIRACLE study in Saudi Arabia is assessing the combination of interferon-beta 1b with lopinavir-ritonavir for the treatment of MERS-CoV (34). A randomised, double-blind, placebo-controlled trial of interferon-beta-1a 10 mcg once daily for six days for the treatment of ARDS in 301 adults with moderate to severe ARDS, did not show improvement in death or ventilator-free days over 28 days (54). 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 (7).
Meplazumab

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 (55). 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. Seventeen 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 (56). No adverse effect was found in meplazumab-treated patients. The ERG is not aware that meplazumab is readily available for use in Ireland.
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 3rd April 2020**

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References


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45. www.clinicaltrialsregister.eu.


