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COMMENTARY

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Practice considerations on the use of investigational anti-COVID-19 medications: Dosage, administration and monitoring

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Abstract

What is known and Objective: Understanding investigational medications is important. Many older drugs are being investigated for repurposing against COVID-19. We comment on various drugs currently undergoing such trials to optimize their safe use.

Comment: We describe medications used during early COVID-19 outbreaks in South Korea, focusing on practice aspects including the method of drug administration, drug formulation, patient-monitoring for adverse reactions and drug interactions informed by our experience during the 2015 outbreak of Middle East respiratory syndrome (MERS). We comment on hydroxychloroquine, chloroquine, lopinavir/ritonavir with zinc supplement, remdesivir, tocilizumab, ciclesonide, niclosamide and high-dose intravenous immunoglobulin (IVIG).

What is new and conclusion: Effective therapies are urgently needed to manage COVID-19, and existing drugs such as antivirals and antimalarials are under investigation for repurposing to meet this need. This process requires up-to-date drug information to ensure optimum use, particularly safety and efficacy profiles of the medications, until convincing evidence is reported.

KEYWORDS
COVID-19, investigational medication, SARS-CoV-2, severe acute respiratory syndrome

1 | WHAT IS KNOWN AND OBJECTIVE

More than 200 countries have been affected by COVID-19, and 3 110 369 confirmed patients and 226 294 deaths have been reported by the World Health Organization (WHO) as of 30 April 2020.[1,2] The WHO interim guideline recommends symptomatic supportive care and administration of antiviral agents based on the severity of symptoms and risk factors.[3] The Infectious Diseases Society of America (IDSA) has published guidelines on managing patients with COVID-19, but their recommendation is associated with limited clinical trials.[4]

Thus, investigational drugs have been prescribed for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[5] Lopinavir/ritonavir has been presented as an immediate oral (po) therapy for COVID-19. In Korea, lopinavir/ritonavir was the main medication administered during peak outbreaks before the global spread.[6] However, a study by Cao et al[7] challenges this result and cautions the use of this regimen because it lacks effectiveness. Consequently, hydroxychloroquine may be considered the preferred choice; however, its antiviral mechanisms have not been fully investigated and it has even been found to worsen viral infections in animal studies.[8,9] Remdesivir has shown positive results in vitro and in some clinical studies, and other clinical trial results are still expected.[10,11] Here, we describe common investigational medications we have used on our patients, focusing on the practice aspects such as criteria of use, dose adjustments, formulations, adverse reactions and drug interactions to support clinical decision; however, these suggestions should be applied with clinical discretion.

2 | COMMENT

2.1 | Hydroxychloroquine and chloroquine with zinc supplement

2.1.1 | Current evidence updates

Hydroxychloroquine and chloroquine are indicated for the prophylaxis and treatment of malaria.[12,13] Hydroxychloroquine is also a synthetic disease-modifying anti-rheumatic drug used to treat rheumatoid arthritis without significant adverse effects.[10] Both agents have demonstrated good in vitro activity against SARS-CoV-2 and reduce the duration of viral shedding.[8,9] Synergistic viral load reduction was reported following co-treatment with hydroxychloroquine and azithromycin in patients with confirmed COVID-19 in early March of 2020.[14,15] However, no human results have reported the successful treatment of patients with hydroxychloroquine and chloroquine single use. Moreover, chloroquine has been associated with paradoxically harmful effects in the treatment of Chikungunya virus infection in vivo.[16]

2.1.2 | Administration methods

Hydroxychloroquine

Several anecdotal dosing regimens have been used: (a) 400 mg daily for 5 days[17,18]; (b) 400 mg twice daily (bid) on day 1, followed by 400 mg daily for 5 days[19]; (c) 400 mg bid on day 1, followed by 200 mg bid for 4 days[20,21]; (d) 600 mg bid on day 1, followed by 400 mg bid for 6 days[22]; and (e) the US Food and Drug Administration (FDA) has recommended 800 mg on day 1, followed by 400 mg daily for 4-7 days for emergency use authorization (EUA).[13] Published regimens with azithromycin are as follows: (f) 200 mg hydroxychloroquine three times a day (tid) for 10 days with 500 mg azithromycin daily on day 1, followed by 250 mg daily for 4 days[14] and (g) 600 mg hydroxychloroquine daily for 10 days with 500 mg azithromycin daily on day 1, followed by 250 mg daily for 4 days.[15] For patients who cannot swallow or have insufficient gastrointestinal functions, extemporaneous formulations of oral suspensions of 25 mg/mL hydroxychloroquine and 10 mg base/mL chloroquine are available as referenced.[23-25] These formulations are stable when refrigerated for 30 days and should be shaken well before use. Hydroxychloroquine is extensively metabolized by the liver.[26]

Zinc supplementation may be considered along with chloroquine and hydroxychloroquine based on long-standing research reports that chloroquine is a zinc ionophore and zinc inhibits the coronavirus in vitro.[27,28] Recent clinical trials to evaluate the effects of supplementation with zinc and vitamin C on COVID-19 have also been planned.[29] Although no standard method of zinc supplementation has been established in the treatment of COVID-19, capsules containing 25 mg and 50 mg zinc acetate are available.[30]

Chloroquine

The usual chloroquine dosage for malaria treatment is 1000 mg orally, followed by 500 mg orally after 6-8 hours, and then 500 mg daily for 2 days.[13] In current COVID-19 trials, the doses being tested are (a) chloroquine diphosphate 450 mg bid on day 1, followed by 450 mg daily for 4 days as a low-dose regimen and (b) 600 mg bid for 10 days as a high-dose regimen.[12] In another trial with favipiravir, chloroquine was administered at (c) 500 mg bid on day 1, followed by 500 mg daily on day 2-3, and then 250 mg daily on day 4.[16,31,32] In a THDMS-COVID19 trial, chloroquine (d) 500 or 1000 mg/day was included in study arms added to darunavir with oseltamivir, ritonavir and favipiravir.[33] Under the US FDA EUA, the recommended dose is (e) 1000 mg chloroquine phosphate on day 1, followed by 500 mg daily for 4-7 days of the total treatment.[23] Chloroquine is less potent than hydroxychloroquine in vitro, but it may be used because hydroxychloroquine is unavailable in some countries or the supply is insufficient.[12] Patients with a glomerular filtration rate <10 mL/min need a 50% dose reduction of chloroquine phosphate.[25] Each 200 mg of hydroxychloroquine sulphate is equivalent to 155 mg base, and 500 mg chloroquine phosphate is equivalent to 300 mg base.[12,34]

2.1.3 | Monitoring

The risk of arrhythmia at high cumulative doses necessitates caution in administering chloroquine because of its narrow therapeutic window, especially in patients with QTc >500 ms Furthermore, the electrocardiogram (ECG) may need to be monitored daily in patients with a high risk of cardiovascular disease.

2.2 | Lopinavir/ritonavir

2.2.1 | Current evidence updates

Lopinavir/ritonavir was the main combination treatment used in Korea, and it significantly reduced the viral load.[35] However, it became an alternative option when hydroxychloroquine was contraindicated.[2] Furthermore, Cao et al[7] recommended its administered within 10 days after symptom onset because of the possible benefits of shortening the intensive care unit stay of patients who are treated 12 days before the onset of symptoms. Despite the disappointing results of single use of lopinavir/ritonavir, coadministration with interferon-β1b is currently under evaluation in clinical trials.[36]

2.2.2 | Administration methods

Lopinavir/ritonavir 400/100 mg po bid, the dose for human immunodeficiency virus (HIV) treatment, has been investigated for the treatment of patients with COVID-19.[7] Investigational lopinavir/ritonavir 400/100 mg bid with ribavirin was used for Middle East

respiratory syndrome (MERS),[37] and lopinavir/ritonavir 10/2.5 mg/kg plus favipiravir bid is under investigation in a clinical trial.[33] Thus, a 14-day treatment with these doses is being considered for patients with COVID-19. Patients who are unable to swallow tablets can take an oral solution that is commercially available as lopinavir/ritonavir 80/20 mg/mL.[31] The solution contains ethanol and propylene glycol, and therefore, it is incompatible with polyurethane feeding tubes. Thus, it may be administered using silicone and polyvinyl chloride feeding tubes.[38] Oral solutions should be refrigerated and used within 2 months when stored at room temperature.[38]

2.2.3 | Monitoring

Approximately 14% of the participants were dropped from the trial because of gastrointestinal adverse events (6.8%-19.5%). Migraine (6.3%), hepatic injury (1%-29%), severe cutaneous eruptions and QTc prolongation have also been reported.[38] The potential for multiple drug interactions should be closely monitored because this agent potently inhibits cytochrome P450 (CYP) 3A and P-glycoprotein (Table 1).[38]

2.3 | Remdesivir

2.3.1 | Current evidence updates

In preclinical trials, remdesivir demonstrated significant activity against the SARS-CoV-2 and a high genetic barrier to resistance.[10,11] The manufacturer of remdesivir restricts its supply through the 'expanded access' programme for experimental COVID-19 treatments and 'compassionate use' for pregnant women and children.[39] This agent has shown promising results in vitro and the compassionate use trials showed a generally acceptable efficacy and safety,[6,39,40] but the protocol did not include a comparison group administered the standard of care at participating institutions.[41] Obtaining approval for this indication is highly anticipated based on the positive outcomes with patient in the trials; however, this agent would have very restricted use mainly for the most severely ill patients, as the ongoing trials have many exclusion criteria.

2.3.2 | Administration methods

Remdesivir was tested at a dosage of 200 mg intravenously once on day 1, followed by 100 mg daily for 5-10 days or until respiratory symptoms improve.[42] The lyophilized solid containing 100 mg preservative-free remdesivir needs to be reconstituted with sterile water for injection and diluted with intravenous infusion fluids to a concentration of 100 mg/20 mL remdesivir.[43] No special training or equipment is required for drug administration.

2.3.3 | Monitoring

One case of cardiac arrest and hypotension was reported during the trial (n = 673) in patients with Ebola viral infection.[44] Nausea, vomiting, gastroparesis and haematochezia with increased liver enzyme levels were reported by three patients during its compassionate use to treat COVID-19.[41] If possible, daily monitoring of renal and liver functions should be performed.[45]

2.4 | Tocilizumab

2.4.1 | Current evidence updates

A retrospective, observational study (n = 21) administered 400 mg tocilizumab, an interleukin (IL)-6 blocker, intravenously once to patients who had respiratory failure, shock or organ failure.[46] Although three patients received a subsequent dose, the benefit is unknown.[43] However, the potential benefit in decreasing mortality was evident as no deaths were reported out of 21 patients.[4]

2.4.2 | Administration methods

Other dosages used in trials are 8 mg/kg (maximum, 800 mg/dose) intravenously every 12 hours (q12h) or one 200 mg intravenous dose (up to two doses). Subcutaneous tocilizumab at two 162 mg doses followed by two more doses after 12 hours has been used in combination with hydroxychloroquine (400 mg q12h followed by 200 mg q12h orally for total of 7 days) and azithromycin (500 mg daily orally for 3 days).[47] It is stable at room temperature for 24 hours protected from light.[48]

2.4.3 | Monitoring

All patients should be monitored for signs and symptoms of infection before, during, and after treatment. Cases of severe liver damage and intestinal perforation have been reported.[4,46,48] Although beneficial outcomes were observed in most patients, this should be interpreted cautiously as all patients in the study received routine treatment for 1 week and then tocilizumab was administered as an additional agent. The risk of neutropenia should be monitored.

2.5 | Other medications

2.5.1 | Ciclesonide

Ciclesonide is an inhaled corticosteroid for the treatment of asthma, which has been a potential candidate for repurposing in the treatment of patients with MERS or COVID-19.[49] The dosage used in a current trial was 320 mcg q12h for 14 days.[50] Ironically,

TABLE 1 Examples of Lopinavir/ritonavir's Drug Interactions[38]

Lopinavir (A)/ritonavir (B)	Avoid combination (X)	Need therapy change or monitoring (X)
Increased the serum concentration of 'X'		
'A/B' (strong CYP3A4 Inhibitor) may increase the serum concentration of 'X'	Ado-trastuzumab emtansine, avanafil, ticagrelor, budesonide(systemic), dasatinib, delamanid, domperidone, dronedarone, everolimus, lovastatin, lercanidipine, salmeterol, tamsulosin, terfenadine	amlodipine, aripiprazole, budesonide (oral, nasal, topical), clozapine, corticosteroids, CYP3A4 substrates, evogliptin, fentanyl, imatinib, lacosamide, mirtazapine, oxycodone, pranlukast, thiotepa, trazodone
'A/B' (strong CYP3A4 and P-glycoprotein inhibitor) may increase the serum concentration of 'X'	rivaroxaban	apixaban
'A/B' (P-glycoprotein/ABCB1 inhibitor) may increase the serum concentration of 'X'	pazopanib, topotecan	afatinib, betrixaban, celiprolol, colchicine, doxorubicine, edoxaban, rifaximin, venetoclax
'A/B' (protease inhibitors) may increase the serum concentration of 'X' or decrease the metabolism of 'X'	alfuzocin, midazolam, lovastatin, simeprevir, simvastatin	atorvastatin, rosuvastatin, sildenafil, TCAs, CCBs, tacrolimus(topical)
'A/B' (protease inhibitor) may enhance the adverse/toxic effects of 'X'		cyclophosphamide, temsilolimus
'A' may enhance the QTc-prolonging effect of 'X'	amiodarone, quinidine	methadone
'A' may increase the serum concentration of 'X'	antihepaciviral combination products, voxilaprevir	rifabutine, bedaquilline, elvitegravir, itraconazole, vincristine, vinblastine
'B' may increase the serum concentration of 'X' or may enhance the adverse effects	amiodarone, metronidazole, flecainide, glecaprevir/pibrentasvir, propafenone	cyclosporin, digoxin, itraconazole, ketoconazole, linagliptin, prednisolone, quetiapine, tadalafil, zolpidem
Decreased the serum concentration of 'X'		
'A/B' (protease inhibitors) may decrease the serum concentration of 'X'		abacavir, estrogen derivatives, valproate products, tacrolimus, zidovudine
'A' may decrease the serum concentration of 'X'	darunavir, quinine, voriconazole	didanosine, progestines, warfarin
'B' may decrease the serum concentration of 'X'	quinine, voriconazole	canagliflozin, deferoxamine, methadone, olanzapine, theophylline derivatives, warfarin, clopidogrel, thyroid products
Increased the serum concentration of 'A/B'		
'X' may increase the serum concentration of 'A'		ketoconazole
'X' may enhance the QTc-prolonging effect of 'A'	clarithromycin	
Decreased the serum concentration of 'A/B'		
'X' may decrease the serum concentration of 'A/B' (CYP3A4 Substrate)		orlistat, sarilumab, siltuximab, tocilizumab
'X' may decrease the serum concentration of 'A'	fosamprevir	fosphenytoin, phenytoin, nelfinavir, carbamazepine, efavirenz, phenobarbital

Abbreviations: CCB, calcium channel blocker; CYP3A4, cytochrome P450 3A4; QTc, corrected QT Interval; TCA, tricyclic antidepressants.

systemic corticosteroids are contraindicated in severe pneumonia caused by viruses such as MERS-CoV and SARS-CoV because they suppress the innate immune system, resulting in increased viral replication. This recommendation is the same as that of the IDSA COVID-19 guidelines except for acute respiratory distress syndrome. There are claims of decreased immunosuppressive effects of this agent with presumably fewer systematic effects because of the administration route.[50] The need for compliance to the recommended administration technique for this medication should be emphasized, if it becomes available for use based on trial results.

2.5.2 | Niclosamide

Another medication undergoing repurposing investigations for SARS-CoV-2 is niclosamide, an oral anthelmintic drug used worldwide at a single dose of 2 g/d. Niclosamide exerts anti-MERS activity, inhibits SARS-CoV replication and abolishes viral antigen synthesis in vitro,[51,52] and therefore, is considered a possible treatment option. However, it is cytotoxic and has low absorption including low oral bioavailability (10%) and although efforts have been made to formulate derivatives to overcome these obstacles, its extensive clinical development as an antiviral agent may still be hindered. An

interventional trial has been registered to evaluate the use of chloroquine with or without azithromycin, faviprevir, nitazoxanide or ivermectin for the treatment of patients with COVID-19 in a real-life setting, but recruitment has not commenced as of 14 April 2020.[53]

2.5.3 | High-dose intravenous immunoglobulin (IVIG)

The co-administration of high-dose intravenous immunoglobulin (IVIG) at 25 g/d for 5 days (body weight, 66 kg) with moxifloxacin was reported in a case series study.[54] Although no trials are currently recruiting, the IVIG doses used in protocols are in the range of 0.2-0.5 g kg^{-1} day^{-1} and the use of this agent is expected to be limited to patients in severe or critical conditions.[55]

Other medications that are currently undergoing clinical trials with the associated dosages are baricitinib (4 mg/d orally) in combination with lopinavir/ritonavir (250 mg orally bid)[56]; favipiravir (1600 mg bid on day 1, followed by 600 mg bid from day 2-7) with tocilizumab[57]; arbidol (200mg orally three times), oseltamivir (75 mg orally bid) and lopinavir/ritonavir(500 mg orally bid)[58]; and sarilumab (400 mg intravenously) with azithromycin and hydroxychloroquine.[59]

3 | WHAT IS NEW AND CONCLUSION

The National Medical Center in Korea has played a pivotal role in managing infectious diseases since the MERS outbreak in 2015 and now serves as the headquarters for COVID-19 treatment operations.[60] At the beginning of the current outbreak of COVID-19 in January 2020, the guidelines we adopted for treating patients infected with SARS-CoV-2 were established based on the previous experience with the MERS outbreak, although clinical outcomes still need to be evaluated.[61] We hope that this paper will help clinicians understand, prioritize and monitor the drugs being used until results of clinical trials are available.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

SJR designed, conceptualized and wrote the original draft, and reviewed and supervised the paper; JEK designed, wrote the original draft and edited and reviewed the paper; SJR was responsible for funding acquisition.

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