REVIEW ARTICLE

Pharmacotherapeutics in the Critically Ill COVID-19 Patients

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ABSTRACT

Pharmacotherapeutics are being repurposed and used as off-label at various stages of COVID-19 infection. Clinical trials are being initiated or are ongoing to investigate the effectiveness and safety of these pharmacotherapeutics. This review article outlines the current pharmacotherapeutics and the controversies surrounding their use. The pharmacotherapeutics that were discussed are hydroxychloroquine, favipiravir, lopinavir/ritonavir, remdesivir, interferons, tocilizumab, and steroids. We also discussed the special consideration for pharmacotherapeutics in COVID-19 infection. No pharmacotherapeutics have been found to be effective and approved for the treatment of COVID-19 infection. However, there are clinical trials that have eliminated the possibilities of use of some pharmacotherapeutics while others had shown promising preliminary results of its use.

Keywords: Drug therapy, COVID-19, Critically ill, Steroids, Monoclonal antibody

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INTRODUCTION

World Health Organisastion (WHO) in their latest update on 27th May 2020 regarding clinical management of COVID-19, continue to recommend the following listed pharmacotherapeutics only to be used in the context of clinical trials (1). They listed chloroquine and hydroxychloroquine in combination with azithromycin or without, antivirals, including but not limited to lopinavir/ritonavir, remdesivir, umifenovir, favipiravir, immunomodulators, including but not limited to tocilizumab, interferon-β-1a are not to be administered as treatment or prophylaxis for COVID-19 (1). They also recommended against the routine use of systemic corticosteroids (1). However, several pharmacotherapeutics are being repurposed and used as off-label at various stages of the COVID-19 infection. Some medications are proposed as potential investigational pharmacotherapeutics, many of which are now being or will soon be studied in clinical trials (2). For example, in our neighbouring country Singapore, lopinavir–ritonavir 200 mg/100 mg were prescribed twice daily orally for up to 14 days with or without interferon beta-1b (8 million units every other day for 14 days). In addition to shared decision making and provision of verbal informed consent, this regime is only given to selected patients who required oxygen supplementation or had pneumonia and fulfil the institutions' guidelines (3).

During this COVID-19 pandemic, our institution's Infectious Disease team and pharmacists designed a guideline to treat and manage COVID-19 patients that were admitted in our institution which will need to be revised when more results become available from ongoing clinical trials (see Table I and Table II). Table I shows the suggested pharmacotherapeutics to prescribe according to the severity of COVID-19 infection the patients presented with. This table was updated to be used from 3rd May to 30th June 2020 and currently being revised. Table II is a safety initiative that our institution had taken to assist and alert the prescribers to be cautious when prescribing the pharmacotherapeutics in special conditions and contraindications as these therapies are used off-labelled in the context of COVID 19 management. Table II also serves to guide the prescribers to monitor relevant parameters and common side effects monitoring.

As the efficacy and safety of the pharmacotherapeutics for management of COVID-19 infection continued to be subjected to ongoing trials and certainty of evidence for approval of their use, at the time of writing, we reviewed the current pharmacotherapeutics that are used to manage COVID-19 infected patients and the controversies surrounding their use. The pharmacotherapeutics that will be discussed are hydroxychloroquine, favipiravir,

Table I: Treatment and Management Prescribing Guide in COVID-19 Infection

CATEGORY	CASE CLASSIFICATION					MANAGEMENT
	Symptom (Cough/SOB)	Fever	Pneumonia	Oxygen- dependent	Critically ill (Shock/ MOF/ARDS)	
1						Observation
2A	+					Favipiravir 1600mg bd for one day, then 600mg bd for 5-10 days or PO Hydroxychloroquine 400mg bd for one day then 200mg bd for 5-10 days if above contraindicated
2B	+	+				
3A**	+		+			Prone position from this stage onwards Favipiravir 1600mg bd for one day, then 600mg bd for 5-10 days or PO Hydroxychloroquine 400mg bd for one day then 200mg bd for 5-10 days if above contraindicated
3B**	+	+	+			
4A**	+		+	+		Favipiravir 1600mg bd for one day, then 600mg bd for 5-10 days PLUS PO Hydroxychloroquine 400mg bd for one day then 200mg bd for 5-10 days Add IV Dexamethasone 4mg bd if *oxygen 5L or ARDS < 300 paO2/Fio2*. To consider adding Tocilizumab 400mg stat. If persistent fever, 400mg 12 hours later
4B**	+	+	+	+		
5	+	+	+	+	+	Favipiravir 1600mg bd for one day, then 600mg bd for 5-10 days PLUS PO Hydroxychloroquine 400mg bd for a day then 200mg bd for 5-10 days IV Dexamethasone 4mg bd (for ARDS) + IV Tocilizumab 400mg stat If persistent fever/worsening ARDS, IV Tocilizumab 400mg 12 hours later +/- S/C Interferon Beta-1b (250mcg/8MIU) every other day for 7 doses +/- IV Immunoglobulin 0.3 g/kg/od for 5 days + antibiotics

**Risk of clinical progression from 3 to 4: Increasing fever, increasing short of breath (especially exertional dyspnea), tachycardia, reduce absolute lymphocyte count (ALC), increase CRP trend
MOF = Multiorgan failure; ARDS = Acute Respiratory Distress Syndrome

Table II: Summary of Pharmacotherapeutics Prescribing Guide in COVID-19 Infection

Drug	Renal Impairment	Liver Impairment	Pregnancy/Lactation	Monitoring	Contraindications	Common Side Effects
Oral Hydroxychloroquine 200mg (36,37,46,48,49)	Short term use, do not need renal dose adjustment	Use with caution. Consider dose reduction.	Compatible with pregnancy. Low concentration in breast milk	QT prolongation (maintain adequate magnesium and potassium serum levels), renal & liver	QT prolong/ Epilepsy/ Myasthenia gravis/ Retinal pathology	Diarrhoea, nausea, headache, rash,
Oral Favipiravir 200mg (36,47,48,49)	No information about renal dose adjustment Renally cleared. Elimination half-life 2-5.5 hrs. .	No information Mild-moderate liver impairment, AUC increase up to 1.8 times Severe: AUC increase up to 6.8 times	Contraindicated.	Renal panel, liver panel, pregnancy test at initiation, contraceptive methods for men; no sexual intercourse with pregnant women during treatment and for 7 days afterward	Pregnant and lactating women -embryonic deaths and teratogenicity in animals	Diarrhoea, increase uric acid, decrease neutrophil, increase AST, ALT
IV Dexamethasone 4mg/mL (48,49)	Renal/hepatic impairment: dosage has not been studied Geriatric: reduce dose	No dosage adjustment needed	Compatible for pregnant and lactating mothers	-	Active or suspected ocular infections	Hypertension, abnormal vision
Tocilizumab 400mg (40,48,49) IV Infusion over 60 min	Do not need renal dosage adjustment	Liver impairment: Use not recommended	Insufficient data. Fetal risk cannot be ruled out	Liver panel, (4-8 weeks later), latent TB before initiation	Known hypersensitivity to Tocilizumab	Hypertension, Diarrhoea, upper abdominal pain, ALT/ SGPT raised, dizziness, headache, infusion reaction
S/C Interferon Beta-1b (40,48,49)	-	-	Fetal risk cannot be ruled out	Full blood count, liver panel, signs of liver injury, cardiac disease worsening	Hypersensitivity to interferon beta, human albumin, mannitol. Precaution in heart failure	Injection site reaction, rash, decreased lymphocyte count, leukopaenia, myalgia, fever, asthaenia, headache

Not all the medications reviewed in this article are in this table

lopinavir/ritonavir, remdesivir, interferons, tocilizumab, and steroids. We will also discuss the special consideration for pharmacotherapeutics in COVID-19 infection.

HYDROXYCHLOROQUINE

Hydroxychloroquine (HCQ) is known as an antimalarial and antirheumatic therapy and suggested to be used against severe acute respiratory syndrome (SARS) (4). As a weak base, it instigates alkalisation of endosomes, Golgi vesicles and lysosomes leading to interruption of viral entry, post-translational process, and replication. It depicted its role against the early stage of SARS virus infection by preventing the sialic acid biosynthesis and glycosylation of SARS Angiotensin-converting enzyme (ACE) II receptor (4). Hydroxychloroquine has better potency and safety profile in comparison to Chloroquine (4). These preclinical data laid the basis of HCQ use as antiviral. Early reports from China and France studies suggested a promising association of HCQ with faster COVID-19 viral clearance influencing World Health of Organisation (WHO) to embark on SOLIDARITY trial (5,6).

The dosing of HCQ for treatment of COVID-19 infection during initial prescription was based on the Malaria and Systemic Lupus Erythematosus regime leading to a variable dosing regimen from 800mg/day to 1200mg/day as loading dose and 400mg to 600mg per day as maintenance doses (7). A recent multinational registry involving 93,000 patients, HCQ use was associated with thirty percent higher mortality and increased incidences of newly diagnosed ventricular arrhythmia, compared to the control group (8). As a result, these findings had prompted a review of continuing HCQ in other trials. Preliminary analysis of RECOVERY trial showed no benefit on 28-day mortality (25.7% versus 23.5%; hazard ratio 1.11[95% confidence interval 0.98-1.26]; P = 0.10) or hospital stay, comparing 1532 patients receiving HCQ to usual care group of 3232 patients (9). Similarly, WHO ceased SOLIDARITY trial when their preliminary analysis did not show any difference in mortality of hospitalised COVID-19 patients in comparison to standard of care (10). Therefore, as more evidence emerges, the use of HCQ as COVID-19 therapy outside clinical trials should be discouraged.

FAVIPIRAVIR

The prodrug Favipiravir (T-705) is a purine nucleic acid analogue that is ribosylated and phosphorylated intracellularly before forming the active metabolite T-705-RTP (11). The active metabolite competes with purine nucleosides and interferes with viral replication by incorporation into the virus RNA, hence inhibiting the RNA-dependent RNA polymerase of viruses (11). Cai Q et al conducted an open-label, non-randomised trial examining the efficacy of aerosolised interferon in combination with oral Favipiravir prescribed as loading dosing of 3200 mg (1600 mg twice daily) on day-1 and followed by 1200 mg maintenance dose (600 mg twice daily) on day-2 to day-14 versus oral Lopinavir/Ritonavir for treating Covid-19 (12). They found Favipiravir combination therapy cleared the virus faster (median four days versus 11 days; p<0.001) with improvement in chest imaging compared with those receiving Lopinavir/Ritonavir (91.43% versus 62.22%; p = 0.004) (12). However, the study sample was small, not randomised, and furthermore, younger milder diseased patients in the Favipiravir combination arm may affect the outcomes of this study. Chen et al conducted an open-label RCT examining the efficacy of Favipiravir versus Arbidol (ARB) for treating Covid-19 and observed no difference in 7-day clinical recovery rate when comparing between the two groups (13). However, when specific sub-population of non-critical patients without hypertension or diabetes were compared between the groups, the 7-day clinical recovery rate was significantly better among those who received Favipiravir in comparison to those who received ARB (71.43%; 70/98 versus 55.86%; 62/111; p = 0. 02). These impressive findings gave Favipiravir possible prospects as a drug for Covid-19 treatment, especially in the early phase of the disease.

LOPINAVIR/RITONAVIR

Cleavage of polyproteins by two proteases, 3-chymotrypsin-like protease (3CLpro) that is abundant in COVID-19 and papain-like protease (PLpro), determines the reproduction of COVID-19 (14). In the lab, Lopinavir/Ritonavir (LPV/RTV) is shown to inhibit 3CLpro (14). Possibly the reason for it is being suggested to treat COVID-19 infection. Sheahan et al reported that pulmonary function improved with therapeutic LPV/RTV in combination with interferon beta but the combination therapy did not reduce virus replication or severity of the lung pathology (15). An open-label RCT by Cao et al using 14 days of LPV/RTV versus standard of care also showed similar findings with similar time to clinical improvement over 28 days compared to standard of care and no apparent suppressive effects on viral shedding doubting LPV/RTV effectiveness against COVID-19 (16). However, poorly oxygenated critically ill patients (94% or less) were recruited into this study that may reduce the study's ability to detect efficacy. Deng et al, used combination ARB with LPV/RTV versus LPV/RTV alone on positive COVID-19 patients (without invasive ventilation), showed improvement on lung tomography and nasopharyngeal specimens were negative for COVID-19 test by RT-PCR. Thus, indicating LPV/RTV should be given early and not as a sole agent in the treatment of COVID-19 (17). Ivan Fan et al proceeded with comparing combination therapy of LPV/RTV 400mg/100mg twice daily, ribavirin 400mg twice daily, and three doses of interferon beta-1b (8 MIU on alternate days versus monotherapy LPV/RTV 400mg/100mg twice daily that were initiated less than

seven days after symptom onset. They found COVID-19 was cleared shortened faster by five days and shorten hospital stay from 14.5 days to 9 days in the combination group (18). Since maximal viral load is at the time of presentation for COVID-19 infection, it makes sense that a drug which works at inhibiting viral replication should be initiated early where viral load is at its peak.

REMDESIVIR

The prodrug Remdesivir is a nucleotide analogue (19). Two major studies were performed in relation to using Remdesivir (RDV) to treat COVID-19 infected patients. Yeming Wang et al in a multicentred and double-blind trial randomised 2:1 patients with severe COVID-19 in China to either receive intravenous RDV or normal saline placebo for 10 days (19). In this study, the concomitant use of LPV/RVT, corticosteroids, and interferons were allowed (19). Both groups showed similar duration for clinical improvement (median of 21 days in RDV group versus 23 days in the placebo group (HR 1.23; 95% CI, 0.87-1.75) (17). The 28-day mortality was also similar in both groups. However, the investigators stopped the study ahead of time because they realised that their sample size was inadequate to detect clinically beneficial outcomes (19). In addition, the real benefits of RDV administration may be affected by the use of concurrent corticosteroids, LPV/RVT and IFNs.

The other study was a NIH-sponsored international, randomised, double-blind trial of RDV versus placebo (1:1 randomisation ratio) in hospitalised confirmed advanced COVID-19 adult patients with lung involvement (20). Just over a thousand participants were enrolled. Patients were given either RDV (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days (20). This study was also stopped earlier when the study showed a 31% faster recovery time in the RDV group ($P< 0.001$). However, similar mortality rates were detected, 8% in the RDV group versus 11.6% in the placebo group ($p = 0.059$) (20).

INTERFERONS

Interferons (IFNs) are a family of cytokines. Our body naturally produces cytokines when viruses attack our bodies which in turn the viruses try their best to prevent IFNs production. Interferons act like broad-spectrum antivirals and affect at different stages of a virus' lifecycle. It particularly impairs the antiviral adaptive type 1 T-helper cell. In addition, they also activate our immune cells to attack the viruses. However, when IFNs are used late, there may be a possibility it may cause a cytokine storm, but this has not been proven in COVID-19 (21). As for the route of administration, inhaled versus subcutaneous injection, it is still not well understood which technique is associated with a better outcome.

Zhou et al in their study compared patients with moderate illness not requiring oxygen supplementation receiving either inhaled IFN-a2b (5 mU twice daily), ARB (200mg three times a day) or the combination of both broad-spectrum antivirals. Patients who received IFN-a2b treatment was associated with significantly accelerated viral clearance from the respiratory tract and reduced duration of elevated blood levels of the inflammatory markers' interleukin-6 and C-reactive protein (CRP) (21). Interestingly, this study showed viral clearance was faster than therapy with RDV (18, 21). Referring to study by Ivan Fan et al, an improvement was also seen in the IFN group with regards to a suppressed (Interleukin) IL-6 levels and also duration of viral spread being curbed, cytokine responses were diminished, symptoms were relieved, and recoveries of mild to moderate COVID-19 infected patients to successful discharges were improved (18). However, IFNs administration commonly result in side effects such as flu-like symptoms, nausea, fatigue, weight loss, haematological toxicities (cytopaenias), elevated transaminases, and psychiatric problems (depression and suicidal ideation) (21). NIH has so far recommended against the use of interferons for the treatment of COVID-19, except in the context of a clinical trial (21).

TOCILIZUMAB

Tocilizumab (TCZ) is a recombinant anti-IL-6 monoclonal antibody that is synthetically in incorporated mouse antihuman IL-6 antibody into human protein, thus making TCZ less antigenic when administered in human (22). It acts by competitively blocking the pro-inflammatory cytokine, namely IL-6. This inhibition will prevent dimerisation of the second receptor of IL-6, which is identified as gp130. As a result, no signalling transmission of IL-6 cytokine into cells without this formation of high-affinity IL-6/gp130 complexes. The effect of TCZ is very specific to IL-6 and do not involve other cytokine receptor family that utilises gp130 (23).

TCZ has a role in addressing the cytokine release syndrome phenomenon, which is attributed by overproduction of IL-6 (24,25). Interleukin-6 release is triggered by host defence response against tissue injury and infection (26). It has a protective role in destroying infective agent and cells healing; however, excessive production via dysregulated mechanism could lead to life-threatening organ failure (27). TCZ at a dose of 8mg/kg demonstrated a sustained reduction in bio-inflammatory markers compared to the lower dose of 4mg/kg (25). The immune mechanism that orchestrated acute morbidity and mortality in Covid-19 infection could be attributed by activation of aberrant pathogenic T-lymphocytes along with the formation of inflammatory monocytes that bears high expression for IL-6 (26). Initiation of TCZ is based on the presence of hyper-inflammation indicators via biochemical parameters such as high CRP, ferritin level, worsening

lymphopenia and hypofibrinogenaemia along with the combination of clinical findings of shock, hypoxia, acute heart and liver failure as well as acute kidney injury (23,28). An initial spike in IL-6 level was reported after treatment with TCZ which is caused by the accumulation of IL-6 in the serum before it is gradually cleared, and improvement of the inflammatory process is observed (29). Absence of fever, reduction in oxygen requirement, absorption of consolidation evidence via lung tomography, normalisation of leukopenia and CRP level were recorded on the fifth day of TCZ prescription (30). The recommended dose is 400mg with 100mls of 0.9% normal saline dilution given at one-hour infusion rate. The maximum single dose should not exceed 800mg, and an extra dose of TCZ is advisable after 12 hours from the first dose of administration (31). Those received TCZ within the first four days of admission showed improvement in survival rate (32). A major dose-dependent adverse event was reported in patients with long term therapy of TCZ which include secondary bacterial infections, and therefore it is not recommended for patients with untreated active infections such as tuberculosis (31, 33).

STEROIDS

Glucocorticosteroid (GCS) has both anti-inflammatory and immunosuppressive effects (34). They exert their effects via membrane-associated receptors on the intracellular signalling pathways (34). They can inhibit genes responsible for the synthesis of pro-inflammatory proteins, including cytokines, chemokines, adhesion molecules and inflammatory enzymes as well as stimulate genes encoding anti-inflammatory mediators, such as interleukin-10, nuclear factor-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) inhibitors and interleukin-1-receptor antagonists (34). With these effects, both signs and symptoms of lung inflammation improved by reducing the plasma extravasation leading to improvement of the overall pulmonary gas exchange and ventilation-perfusion mismatch (34). Nevertheless, according to Surviving Sepsis Campaign (SCC) Guideline on the management of critically ill adults with COVID-19, routine administration of corticosteroids (CS) is not recommended (35). The panel discourage routine use of systemic CS in respiratory failure without acute respiratory distress syndrome (ARDS) but suggested to use systemic CS when critically ill COVID-19 patients presents with ARDS and using lower doses and shorter treatment courses (35).

A retrospective study on patients with COVID-19 pneumonia presented with ARDS and received methylprednisolone was associated with a lower risk of mortality (36). However, this study was limited by unadjusted confounding factors (36). Recently RECOVERY trial released their preliminary pre-published report on a randomised, controlled, open-label study on the use of Dexamethasone in patients hospitalised with COVID-19 infection (37). They detected reduction of 28-day mortality among those requiring invasive mechanical ventilation or oxygen at randomisation but not among those did not require respiratory support with a signal of harm. However, cautions should be taken when interpreting this preliminary report as it has not undergone peer review (37). Therefore, given this disease complexity, genetic variability and individual susceptibility, the use of CS needs to be rationalised before using considering its individual risks and benefits (36).

SPECIAL CONSIDERATION FOR PHARMACOTHERAPEUTICS IN COVID-19 INFECTION

Many of the repurposed therapeutic options carry cardiotoxicity risk (38). Thus, its use needs to be weighed of risk and benefit when about 33% of COVID-19 infected patients may suffer cardiac injury. Hydroxychloroquine is known for its direct arrhythmic effect, while LPV/RTV, Favipiravir and RDV are associated with QT interval prolongation. Therefore, while the efficacy of these agents is yet to be ascertained, it is advisable to avoid or withhold therapy in patients with QT interval more than 500ms or has underlying heart disease. When prescribing combination therapies, one needs to be cautious combining these proarrhythmic drugs such as azithromycin or moxifloxacin or potassium or magnesium reducing drugs. Frequent electrocardiogram (ECG) or telemetry monitoring is necessary at baseline and from the second to fourth dose of HCQ to increase the safety of its use.

In patients with known Glucose-6-phosphate dehydrogenase (G6PD) deficiency, the risk for haemolysis is low when HCQ is used (39). Therefore, HCQ can be initiated without delay while performing G6PD screening (39). Liver injuries were reported in 18-56% COVID-19 patients with the prevalence is increased with infection severity (40). Furthermore, liver injuries in COVID-19 patients may also be the result of adverse drug reaction, especially with the use of LPV/RTV (41). Interferon-beta also caused a mild increase in serum aminotransferase counts which possibly is dose-related and should be avoided in jaundiced patients. It is recommended to withhold TCZ and RDV if Alanine transferase is 3 to 5 times above normal range (42) Conversely, hepatotoxicity reports were rare with HCQ, and related information was limited for Favipiravir and RDV (42). Nevertheless, drug interactions that may enhance potential of toxicity, should be considered as many of the pharmacotherapeutics are metabolised in the liver and shared the common Cytochrome P450 pathway.

More than one-third of COVID-19 infected patients developed acute kidney injury (43). It is unknown if the current therapeutics discussed in this article

imposed further nephrotoxicity. Nonetheless, no renal dose adjustments are required for LPV/RTV and with short term use of HCQ. Patients suffering severe renal impairment are excluded in the current trials of newer antivirals involving Favipiravir. RDV injection formulation contains cyclodextrin, therefore, glomerular filtration rate less than 30mL/min prevent its use (44).

The use of HCQ, LPV/RTV and TCZ do not require dose adjustments in obese patients (45-47). Availability of safety data among pregnant patients with COVID-19 infection are understandably scarce and mainly extrapolated from experience in other diseases. Hydroxychloroquine and LPV/RTV have been the therapeutic choice in pregnant women without a marked increase in congenital malformation (48). In contrast, Favipiravir is teratogenic, as shown in animal studies and contraindicated in pregnant patients (49). Safety of RDV, TCZ and IFN beta is uncertain due to insufficient data.

CONCLUSION

With a better understanding of the COVID-19 infection, many medications are being used, especially off label in the effort to treat this infection and reduce its sequelae. Despite the pandemic, clinical trials are being conducted to investigate potential therapies for COVID-19 in ensuring safe and best outcomes. Currently, no pharmacotherapeutics clearly has shown being effective. However, a few clinical trials have eliminated the possibilities of some like the use of hydroxychloroquine, while others have shown promising preliminary results as in the use of remdesivir and steroids.

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