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Review

Antivirals and the Potential Benefits of Orally Inhaled Drug Administration in COVID-19 Treatment

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) pandemic has been on the agenda of humanity for more than 2 years. In the meantime, the pandemic has caused economic shutdowns, halt of daily lives and global mobility, overcrowding of the healthcare systems, panic, and worse, more than 6 million deaths. Today, there is still no specific therapy for COVID-19. Research focuses on repurposing of antiviral drugs that are licensed or currently in the research phase, with a known systemic safety profile. However, local safety profile should also be evaluated depending on the new indication, administration route and dosage form. Additionally, various vaccines have been developed. But the causative virus, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has undergone multiple variations, too. The premise that vaccines may suffice to eradicate new and all variants is unreliable, as they are based on earlier versions of the virus. Therefore, a specific medication therapy for COVID-19 is crucial and needed in order to prevent severe complications of the disease. Even though there is no specific drug that inhibits the replication of the disease-causing virus, among the current treatment options, systemic antivirals are the most medically appropriate. As SARS-CoV-2 directly targets the lungs and initiates lung damage, treating COVID-19 with inhalants can offer many advantages over the enteral/parenteral administration. Inhaled drug delivery provides higher drug concentration, specifically in the pulmonary system. This enables the reduction of systemic side effects and produces a rapid clinical response. In this article, the most frequently (systemically) used antiviral compounds are reviewed including Remdesivir, Favipiravir, Molnupiravir, Lopinavir-Ritonavir, Umifenovir, Chloroquine, Hydroxychloroquine and Heparin. A comprehensive literature search was conducted to provide insight into the potential inhaled use of these antiviral drugs and the current studies on inhalation therapy for COVID-19 was presented. A brief evaluation was also made on the use of inhaler devices in the treatment of COVID-19. Inhaled antivirals paired with suitable inhaler devices should be considered for COVID-19 treatment options.

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Introduction

COVID-19 is the third severe respiratory outbreak caused by the coronaviruses in this century, after Severe Acute Respiratory Syndrome (SARS) in 2002 and Middle East Respiratory Syndrome (MERS) in 2006.¹ Distinctly COVID-19 was declared as a pandemic.² SARS-CoV-2, which causes COVID-19 targets lungs and initiates a lung damage leading to death due to respiratory failure. Today, more than 2 years after the beginning of the pandemic, approximately 529 million COVID-19 cases were confirmed, the death toll has exceeded

6 million globally.³ Disease spreading can be reduced using social distancing, face masks, adequate ventilation, general hygiene and travel restrictions but these measures are not generally popular and many countries have lifted them entirely or partly. Therefore, readily accessible self-administered products with good safety and efficacy profiles for early intervention and treatment of SARS-COV-2 infections would be desirable.

Various vaccines have been developed, but resource limitations and economic disparity hinder an even distribution across the world. Moreover, the effectiveness of the vaccines on forthcoming mutations remains unclear and booster doses are likely to be required frequently and their effectiveness and duration of action in the future is unknown. The elderly population, pregnant women, immunocompromised patients and those with chronic disease are especially at a

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higher risk for severe complications of COVID-19, despite being vaccinated. A medication therapy for COVID-19 is of great import to prevent complications of COVID-19 for those subgroups as well as those with no access to vaccines. Plus, there are still patient groups for whom vaccines are yet to be approved.

Although the lungs are the primary target of the virus, no inhaled drug has been approved. Principally, pulmonary administration are highly preferred in lung diseases such as asthma, chronic obstructive pulmonary disease and cystic fibrosis.^{4,5} Inhaled delivery of drugs provides two advantages: an effective treatment with lower doses and minimum side effects.⁶ As COVID-19 can cause acute respiratory distress syndrome (ARDS) and lung damage, targeting the lungs directly promises greater efficacy and various drugs are in clinical trials using inhalers.⁵ This review aims to summarize ongoing antiviral treatments in COVID-19, to discuss possible inhalation approaches, and briefly evaluate inhalation devices.

Antiviral Treatment Approaches in COVID-19

In terms of antiviral therapy, current research focuses on repurposing of antiviral drugs that are licensed or currently in the research phase, with a known systemic safety profile. Despite WHO's statement in an interim guidance⁷ that "Investigational anti-COVID-19 therapeutics should be used only in approved, randomized, controlled trials", several compounds are being tried around the world based on animal models, cell lines or even virtual screening models. This article reviews the most frequently used antivirals, which include Remdesivir, Favipiravir, Molnupiravir, Lopinavir-Ritonavir, Umifenovir, Chloroquine, Hydroxychloroquine and Heparin. These were classified based on their antiviral groupings, along with mechanisms of action and dosage forms (Table 1).^{7–9}

Remdesivir

Remdesivir, an antiviral drug that is an RNA polymerase inhibitor adenosine nucleotide analogue, was developed for treatment of Ebola virus, and was used intravenously to treat the first COVID-19 case in the USA. It is concluded randomized controlled studies are needed to evaluate effectiveness, confidence and robustness of collected data.¹⁰ In a study on compassionate-use of Remdesivir, 53 COVID-19 patients were treated with the drug for 10 days. Although data on viral load were not collected to confirm antiviral effects of Remdesivir, authors observed an improvement in the oxygen-support status of 68% of patients.¹¹ A randomized, double-blind placebo-controlled, multicenter study observed that Remdesivir provide no significant clinical or antiviral effect in severe COVID-19 patients (158 to Remdesivir and

79 to placebo), meanwhile it provided an improvement in some clinical parameters.¹² A study from 1062 patients (541 assigned to Remdesivir and 521 to placebo) indicated that those who received Remdesivir had a median recovery time of 10 days, compared with 15 days in the placebo group. All-cause mortality was 11.4% in the Remdesivir group and 15.2% in the placebo. The study supports use of Remdesivir for COVID-19 patients as it may have prevented the progression to more severe respiratory status, and provided a lower incidence of new oxygen use among patients. However, it was stated that treatment with an antiviral drug alone is not likely to suffice due to high likelihood of mortality despite the use of Remdesivir.¹³

The Japanese health authority approved Remdesivir for patients with severe COVID-19 on 7 May 2020 as the first officially authorized drug in the country.¹⁴ On 22 October 2020, FDA approved "New Drug Application (NDA)" for Remdesivir, for adults and pediatric patients (≥ 40 kg and 12 years), and issued an Emergency Use Authorization (EUA) to treat suspected or laboratory-confirmed COVID-19 hospitalized pediatric patients weighing between 3.5 kg and 40 kg, or hospitalized pediatric patients less than 12 years of age and ≥ 3.5 kg.^{15,16} On 19 November 2020, the FDA issued an EUA for the drug Baricitinib, in combination with Remdesivir, for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized adults and pediatric patients ≥ 2 years of age requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).¹⁷ In a double-blind, randomized, placebo-controlled trial based on this approval, the combination of Baricitinib plus Remdesivir was found to shorten the recovery time, and accelerate the improvement of the clinical situation, and decrease death rate and adverse reactions compared with the Remdesivir treatment only.¹⁸

Lopinavir–Ritonavir

Lopinavir–Ritonavir was proposed as a treatment option for COVID-19 on the basis of in vitro activity, preclinical studies and observational studies. Lopinavir is a HIV type 1 aspartate protease inhibitor. Ritonavir is combined with Lopinavir as it increases Lopinavir's plasma half-life via cytochrome P450 inhibition. The efficacy of the oral Lopinavir-Ritonavir combination in patients infected with SARS-CoV-2 was evaluated in a randomized, controlled study. No superiority was found for Lopinavir-Ritonavir combined therapy (99 patients) compared to standard therapy (100 patients).¹⁹ Similarly, no significant time difference in discharge from hospital was observed between both Lopinavir–Ritonavir (374 patients) and usual care (767 patients) groups. Lopinavir–Ritonavir was not associated with reduction in 28-day mortality, hospital stay, or risk of progression to invasive mechanical ventilation or death. The use of Lopinavir

Table 1
Some antiviral drugs for treatment of COVID-19

| Group | Drugs | Mechanism of Action | Clinical Dosing |
|---|---------------------|---|---|
| Inhibitors of viral RNA polymerase/RNA synthesis | Remdesivir | Adenosine nucleotide analogue, prodrug, RdRp ^a inhibitor | Day 1: 200 mg, IV Day 2–10: 100 mg/day, IV |
| | Favipiravir | Guanosine nucleotide analogue, prodrug, RdRp ^a inhibitor | Day 1: 2 × 1600 mg Day 2–7 (or 10): 2 × 600 mg/day, orally |
| | Molnupiravir | N-hydroxycytidine ribonucleoside analogue, prodrug, RdRp ^a inhibitor | Day 1–5: 2 × 800 mg/day, orally |
| Inhibitors of viral protein Synthesis | Lopinavir–Ritonavir | Protease inhibitor | Day 1–10 (or 14): 2 × 400mg/100mg /day, orally |
| | Umifenovir | Fusion inhibitor | Day 1–7 (or 10): 3 × 200 mg, orally |
| Viral entry inhibitors | Chloroquine | Increasing endosomal pH which disrupts virus-cell fusion, as well as interfering with the | Day 1–5 (or 10): 2 × 500 mg/day, orally |
| | Hydroxychloroquine | glycosylation of cellular receptors (ACE-2) ^b of SARS-CoV | Day 1–5: 2 × 200 mg/day, orally |
| | Heparin | Competition with host cell surface glycoproteins or proteoglycans | 5000 IU x 2 /day, subcutaneously |

^a RdRp: RNA-dependent RNA polymerase

^b ACE-2: Angiotensin Converting Enzyme-2

–Ritonavir in patients admitted to hospital with COVID-19 was not supported.²⁰ Many other observational studies also show that use of Lopinavir–Ritonavir provide no significant improvement for COVID-19 patients.^{21–23}

Umifenovir

Umifenovir (Arbidol) is a small indole derivative molecule licensed for the prophylaxis and treatment of influenza and other respiratory viral infections in Russia and China.^{24,25} It is a broad-spectrum antiviral agent against a number of enveloped and non-enveloped viruses, such as Ebola, Hepatitis B and C. For the influenza virus, Umifenovir was shown to increase the stability of the hemagglutinin glycoprotein (HA) and prevent HA from transitioning to a low pH-induced fusogenic state, which inhibits the virus from entering the cell.²⁵

In a clinical pilot study of COVID-19 patients in Wuhan, Umifenovir treatment was shown to reduce viral load and mortality compared with the control group.²⁶ The antiviral effects and safety of Umifenovir and Lopinavir–Ritonavir in COVID-19 patients were compared in a study, where 50 patients were divided into a Lopinavir–Ritonavir group (34 cases) and a Umifenovir group (16 cases). On the 14th day, no viral load was detected in the Umifenovir group, but the viral load was found in 15 patients (44.1%) treated with Lopinavir–Ritonavir. Patients in the Umifenovir group had a shorter duration of positive RNA test compared with those in the Lopinavir–Ritonavir group. No apparent side effects were found in both groups. The authors concluded that Umifenovir therapy may be superior to Lopinavir–Ritonavir in treating COVID-19.²⁷ In a retrospective cohort study, some of the COVID-19 patients were treated with Lopinavir–Ritonavir combined with oral Umifenovir, while others were treated with oral Lopinavir–Ritonavir only. In the combination group, the rate of conversion of the coronavirus test from positive to negative was “significantly higher” compared to the Lopinavir–Ritonavir only group. A significant improvement in chest tomography has been associated with combined therapy.²⁸ In contrast, a retrospective clinical research study conducted with 134 COVID-19 patients in Shanghai observed that Lopinavir–Ritonavir and Umifenovir did neither relieve symptoms nor accelerate virus clearance after treatment for 5 days.²⁹ Similarly, Li et al.³⁰ reported that Lopinavir–Ritonavir or Umifenovir monotherapy presents “little benefit” for improving the clinical outcome of the patients hospitalized with mild/moderate COVID-19 over supportive care. It is stated that a higher dose is needed to successfully suppress SARS-CoV-2 to achieve an effect comparable with the *in vitro* cytotoxicity tests. But this may not be possible in practice due to the side effects caused by both drugs. In a single-blind randomized controlled trial carried out on a total of 100 patients with COVID-19, patients were randomly assigned to Hydroxychloroquine alone and Hydroxychloroquine plus Umifenovir groups. The administration of both Umifenovir and Hydroxychloroquine has led to an improvement of the hematological parameters. The study introduced Umifenovir as an effective treatment for moderate to severe patients, showing not only a reduced time of CRP (C-reactive protein) normalization, but also a decreased hospitalization stay and mortality compared with those reported for Hydroxychloroquine.³¹ Conversely, another study has shown that additional Umifenovir was not effective in decreasing the duration of SARS-CoV-2 in severe patients and improving the prognosis in non-intensive care unit (non-ICU) patients and mortality.³² A recent retrospective study concluded that Umifenovir did not provide a significant improvement in the treatment of COVID-19 for non-ICU patients and that randomized clinical trials should be performed.³³ In a single-center, randomized, open-label clinical study, the intervention group was given Lopinavir–Ritonavir + Hydroxychloroquine + Interferon- β 1a + Umifenovir. The control group was given the same dose of Lopinavir–

Ritonavir + Hydroxychloroquine + Interferon- β 1a. The results revealed that the addition of Umifenovir did not improve prognosis and mortality in severe and non-ICU COVID-19 patients, and Umifenovir was once again found to be ineffective for COVID-19.³²

Chloroquine and Hydroxychloroquine

Chloroquine (CQ), which belongs to the 4-aminoquinolines group of compounds, has long been used to treat malaria and amebiasis. However, *Plasmodium falciparum* developed widespread resistance to the drug, and with the development of new antimalarials, it has become a choice for the prophylaxis of malaria.^{34,35} Besides its anti-malarial activity, by accumulating in the acidic organelles, CQ exerts both direct antiviral effects on enveloped viruses and decreases activation of several cell types involved in the immune response.³⁶ The antiviral mechanism is achieved by increasing endosomal pH, which disrupts virus-cell fusion. The glycosylation of cellular receptors of SARS-CoV is also disturbed.^{37–39}

A study demonstrated that CQ functioned at both entry, and at post entry stages of SARS-CoV-2 in Vero E6 cells.⁴⁰ However, it was shown that engineered expression of TMPRSS2, a cellular protease that activates SARS-CoV-2 for entry into lung cells, renders SARS-CoV-2 infection of Vero cells insensitive to CQ. Moreover, CQ does not block infection with SARS-CoV-2 in the TMPRSS2-expressing human lung cell line Calu-3. It was concluded that CQ targets a pathway that is not active in lung cells, and thus is unlikely to protect against the spread of SARS-CoV-2 among patients.⁴¹

After a number of subsequent clinical trials in China, it was observed that CQ phosphate were superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, and promoting a virus negative conversion, hence shortening the disease course. An Expert Consensus in China recommended CQ phosphate tablets, 500 mg twice per day for 10 days for patients diagnosed with mild, moderate and severe cases of novel coronavirus pneumonia, if without contraindications to CQ.^{42,43} In a randomized clinical trial of high and low dose CQ in COVID-19 patients, the high-dosage group (i.e., 600 mg CQ twice daily for 10 days) presented greater QTc interval and higher mortality rates (39.0% versus 15.0%) than the low-dosage group (i.e., 450 mg twice daily on day 1 and once daily for 4 days). The higher CQ dosage is not recommended for critically ill patients with COVID-19, particularly when taken concurrently with Azithromycin or/and Oseltamivir due to potentially synergistic cardiac toxic effects.⁴⁴

Hydroxychloroquine (HCQ), a derivative of CQ, was first synthesized in 1946 by introducing a hydroxyl group into CQ and was demonstrated to be 2 to 3 times less toxic than CQ in animals.⁴⁵ HCQ is still widely available to treat autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis.³⁴ Theoretically both agents are similar in their antiviral activity, but there is more clinical data available on the anti-coronaviral activity of CQ than that of HCQ. Of note, CQ is not as widely available as HCQ in some countries.⁴⁶

HCQ ($EC_{50}=0.72 \mu\text{M}$) was more potent than CQ ($EC_{50}=5.47 \mu\text{M}$) in *in vitro* and it was recommended orally in a loading dose of 400 mg twice daily of HCQ sulphate, followed by a maintenance dose of 200 mg given twice daily for 4 days as a recommendation for SARS-CoV-2 infection.⁴⁷ In a randomized clinical trial, after 5 days of HCQ treatment, the symptoms of COVID-19 patients were significantly relieved, the recovery time from cough and fever have shortened.⁴⁸ On the contrary, there are other clinical studies that show HCQ did not improve the clinical status of COVID-19 patients compared with standard care.^{49–52} There are retrospective and randomized clinical studies showing that HCQ was not effective in decreasing viral shedding in subjects with mild to moderate COVID-19 symptoms.⁵³ Similarly, results of another study suggest no important antiviral effect of HCQ in humans infected with SARS-CoV-2. HCQ did not

significantly decrease SARS-CoV-2 oropharyngeal viral load compared to standard care alone.⁵⁴ In addition, it has been reported that the calculated free lung concentrations that would result from proposed dosing regimens are well below the *in vitro* EC₅₀/EC₉₀ values, making the antiviral effect against SARS-CoV-2 unlikely to be achieved with a safe oral dosing.⁵⁵ Moreover, there are studies showing that CQ caused enhanced virus replication in various animal models^{56–58} concluding that, CQ/HCQ would be ineffective, even be harmful in patients.⁵⁹

In an internationally collaborative meta-analysis of randomized trials, treatment with HCQ was associated with increased mortality in COVID-19 patients, and there was no benefit of CQ.⁶⁰ The interim results published by the Solidarity Therapeutics Trial on 15 October 2020, coordinated by the WHO, indicate that Remdesivir, HCQ, Lopinavir-Ritonavir and Interferon regimens appeared to have little or no effect on 28-day mortality or on the hospital course of COVID-19 patients.⁶¹

Favipiravir

Favipiravir is a nucleoside analogue antiviral drug that targets RNA-dependent viral RNA polymerase. It is a selective and potent inhibitor of viral RNA polymerase of influenza, and is effective against all subtypes and strains of influenza viruses. Since it shows antiviral activity against many RNA viruses, Favipiravir is a promising drug for the treatment of many RNA-related infections, and is approved for influenza treatment in Japan.^{62,63}

In a COVID-19 treatment study, Favipiravir was compared with the combination of Lopinavir-Ritonavir. The mean viral clearance time was 4 days in the Favipiravir group (35 patients) and 11 days in the Lopinavir-Ritonavir group (45 patients). Consequently, the recovery rate in chest tomography was reported to be higher in the Favipiravir group.⁶⁴ In another study of 240 COVID-19 patients, either Favipiravir or Umifenovir was given and clinical recovery rates were compared over 7 days, but no significant difference was found between the two.⁶⁵ A randomized controlled open-label trial stated that there was no difference in clinical outcomes between Favipiravir plus inhaled Interferon- β 1b and standard HCQ treatment in adults hospitalized with moderate to severe COVID-19 pneumonia.⁶⁶

A systematic review and meta-analysis of clinical trials on the efficacy of Favipiravir in COVID-19 states that the mortality rate in the Favipiravir group is approximately 30% less than in the control group, but this difference is deemed to be not statistically significant, thus Favipiravir demonstrating no significant beneficial effect in terms of mortality. It is stated that use of antiviral after once the patient has developed symptoms may be too late to be effective, which explains its low efficacy in the clinic.⁶⁷ According to another systematic review and meta-analysis, Favipiravir can promote viral clearance within 7 days and clinical improvement within 14 days, especially in patients with mild-to-moderate COVID-19. The early initiation of treatment with Favipiravir can contribute to positive outcomes for COVID-19.⁶⁸ Another systematic review on the effectiveness of Favipiravir stated that there were no significant difference in fatality rate and the mechanical ventilation requirement between Favipiravir treatment and the standard care in moderate and severe COVID-19 patients.⁶⁹ In a Phase 3 trial entitled as PRESECO (PREventing SEvere COVID-19) evaluating oral antiviral Favipiravir's at home use for mild-to-moderate COVID-19 patients, the preliminary results were reported as not to be yet statistically significant on the primary endpoint of time to sustained clinical recovery.⁷⁰

Molnupiravir

Molnupiravir, is a prodrug that is metabolized into active antiviral ribonucleoside analogue β -D-N4-hydroxycytidine (NHC). It has

activity against a number of RNA viruses, including SARS-CoV-2, SARS-CoV, MERS-CoV, and seasonal and pandemic influenza viruses. NHC shows its effect on RNA-dependent RNA-polymerase enzyme, which plays a role in viral genome transcription and replication.⁷¹

In a ferret model, Molnupiravir treatment completely blocked transmission to untreated animals. If ferret-based inhibition data of SARS-CoV-2 transmission are predictive for humans, patients with COVID-19 could become non-infectious within 24–36 h after the onset of an oral treatment.⁷² Molnupiravir's antiviral activity was also evaluated in a SARS-CoV-2 hamster infection model combined with Favipiravir. The results indicate that the combined treatment is effective on virus, and reduces the transmission to the uninfected contacts. These findings may form the basis for clinical trial design for combined therapies.⁷³ In an analysis of the results from Phase 1, Phase 2 and Phase 3 clinical trials, Molnupiravir was safe, and caused no major adverse reactions.⁷⁴ According to an interim analysis of a randomized, double-blind, placebo controlled Phase 2/3 study, 7.3% of patients, who received Molnupiravir were hospitalized through Day 29, compared with 14.1% of placebo-treated patients, who were hospitalized or died.^{75,76}

Heparin

Heparin, a well-tolerated anticoagulant pharmaceutical, has been used safely for over 80 years. Alongside anticoagulant and anti-inflammatory properties, it has been known to prevent viral infection, such as SARS-CoV,^{77,78} Zika Virus,⁷⁹ Herpes Simplex Virus,⁸⁰ Influenza⁸¹ and HIV.^{82,83} Furthermore, its anticoagulant potential mainly with low molecular weight heparin (LMWH) is associated with better prognosis in severe COVID-19 patients with sepsis-induced coagulopathy score ≥ 4 or with D-dimer > 6 -fold of upper limit of normal.⁸⁴ The WHO interim guidance recommends LMWHs daily in prophylaxis or subcutaneous unfractionated Heparin twice daily.⁷ Mycroft-West et al.⁸⁵ showed that addition of Heparin (100 μ g/ml) to Vero cells inhibits invasion by SARS-CoV-2 by 70%. Heparin binds to the Spike (S1) protein receptor-binding domain (RBD), inducing a conformational change. Mycroft-West et al. also reported that Enoxaparin, a low-molecular-weight clinical anticoagulant, binds to the S1 RBD protein inducing a conformational change. Heparin is 30-fold-more potent than Enoxaparin.⁸⁵ These findings suggest Heparin as a potent antiviral against SARS-CoV-2.

Potential of Inhaled Antiviral Therapy in COVID-19

SARS-CoV-2 directly targets the lungs and initiates lung damage. Patients usually lose their lives due to respiratory failure.⁸⁶ Although the virus is a respiratory one, the predominant focus has been on those dosage forms that provide systemic effects in the treatment. Unlike systemic dosage forms, inhaled ones can maximize direct delivery to the site of disease without first-pass metabolism, in order to boost the local antiviral activity in the lungs, while minimizing the side effects of systemic drug delivery.⁸⁷ Just at this point, the inhalation route can be considered as the most promising route for the treatment of COVID-19. However, critical drug-attributes should be considered as they are different for inhaled and systemically administered formulations.⁸⁸ There is currently no specific treatment for COVID-19 and some previously licensed antiviral drugs are intended to be repurposed for the treatment. The drug product of **Remdesivir** is administered by intravenous injection and **Heparin** is administered by subcutaneous or intravenous injection. They both are having a systemic effect and can only be administered in the hospital. But most patients are not hospitalized either due to pandemic conditions, or they have no access to an injectable administration of Remdesivir and Heparin. Sun⁸⁹ hypothesized that for Remdesivir to be effective, the drug must be distributed to the lungs and reach sufficient

concentration level. However, based on available data in humans and animals, it is unlikely that so called 'sufficient concentrations' to kill SARS-CoV-2 in the human lung can be achieved with an intravenous dose of Remdesivir (100–200 mg). The author stated that direct pulmonary administration of Remdesivir can provide a higher drug concentration in the lung, and also reduce systemic toxicity in patients. Since COVID-19 patients often have lymphopenia in addition to lung damage, inhibition of the virus in lymphocytes, lymph nodes, spleen, blood vessels, and other organs is indeed necessary, as well as inhibition of SARS-CoV-2 in the lung. Sun states that an intravenous Remdesivir is also necessary in combination with the pulmonary route with an adjustment of the intravenous dose.⁸⁹ **Favipiravir, Molnupiravir, Lopinavir-Ritonavir, Umifenovir, CQ and HCQ** are administered in oral tablet or capsule forms. However, some patient subgroups (i.e. intubated or pediatric ones) are unable to take antivirals in oral forms. Therefore, Lopinavir-Ritonavir tablets are crushed in hospitals and given to those patients as "reformulated on-site" in liquid form, a common pandemic practice.^{90,91} But, the alteration of this formulation causes the formation of unstable crystal structure leading to approximately 50% loss in bioavailability.⁹² The alteration process of formulation puts an extra burden on healthcare professionals in the hospital. Wang and Chen⁹³ reported that the reason why Lopinavir could not be beneficial in COVID-19 patients may be due to the insufficient concentration level of oral Lopinavir in the lungs to inhibit SARS-CoV-2 replication. They base their hypothesis on a tissue distribution study of orally administered Lopinavir-Ritonavir in rats by Kumar et al.⁹⁴ This study revealed that the concentration of oral Lopinavir in lung tissue remains relatively low. In a biodistribution study of [¹⁸F] Favipiravir in mice, lungs were the 'lowest accumulation' site of the antiviral agent, whereas the highest accumulation was seen in kidney, liver and stomach.⁹⁵ Theoretically however, an antiviral used in the treatment of COVID-19 should accumulate primarily in the lungs. Data on COVID-19 treatment so far suggest that antiviral agents may not provide an effective concentration in the lungs, demolishing the promise for a definitive antiviral accumulation in the lungs when administered systemically.

Due to these limitations of the conventional drug therapy, it can be considered the inhalation therapy may provide a superior alternative with greater benefits in COVID-19. In support of this hypothesis, various inhalation studies have already been carried out. Sahakijjarn et al. produced high-potency Remdesivir dry powder formulations for inhalation, using the thin film freezing technique, to maximize delivery to the lungs. It has been stated that the formulations were suitable to treat patients with COVID-19 on an outpatient basis and earlier in the disease course.⁹⁶ Vartak et al. developed a nebulized and scalable nanoliposomes of Remdesivir against COVID-19. The nanoliposomes have an optimal particle size, effective aerosol characteristic, high drug entrapment efficiency, minimal mammalian cell toxicities and prolonged drug release.⁹⁷ Vermillion et al. investigated the pharmacokinetics and efficacy of Remdesivir administered by inhalation in African green monkeys to make Remdesivir more convenient for non-hospitalized patients. Relative to an intravenous administration at 10 mg/kg, an about 20-fold lower dose administered by inhalation produced comparable concentrations of the pharmacologically active form in lower respiratory tract tissues. Inhaled Remdesivir resulted in lower systemic exposures as compared with intravenous route. The efficacy study with repeated dosing of inhaled Remdesivir demonstrated reductions in viral replication in bronchoalveolar lavage fluid and respiratory tract tissues compared with placebo.⁹⁸ Albariqi et al. successfully prepared an inhalable HCQ crystalline powder for potential treatment of COVID-19.⁹⁹ Tai et al. showed that an inhalable form of liposomal HCQ had desirable pharmacokinetics in a rat model. It was shown that inhalable liposomal HCQ can be delivered directly to the lungs for COVID-19 pulmonary treatment with less frequent dosing and at a relatively lower dose.

For delivery, a disposable closed-loop system, which minimizes the spreading of aerosols and reduces contamination risk, was developed and connected to a nebulizer.¹⁰⁰

Currently, there are several clinical trials on the inhalation treatment of COVID-19. One of them is a Phase 1 study of inhaled aerosolized HCQ that has been administered via the Aerogen nebulizer. It has been reported that administering aerosolized HCQ at a lower dose than the oral dose may rapidly achieve a respiratory tract concentration that would suffice to inhibit SARS-CoV-2.^{101,102} Another Phase 1 study has been performed with inhaled dry powder HCQ that has been administered via Cyclops dry powder inhaler. The rationale of the study was that HCQ administered as dry powder via inhalation in SARS-CoV-2 could be safer than oral HCQ, hence allowing for higher and more effective pulmonary concentrations without dose-induced toxic effects.^{103,104} Further phase studies are required for inhaled aerosolized or dry powder HCQ. An ongoing study aims at developing new "Ready-to-Use" inhalable forms of HCQ that can be used directly through nebulization or using dry powder inhalers for the COVID-19 viral infection.¹⁰⁵ Another clinical trial characterized the impact of inhaled Remdesivir on viral load in participants with early stage COVID-19, but the study was halted by the company conducting it, due to "unsatisfactory lung deposition".¹⁰⁶ Another ongoing study weighs inhaled nanoparticle formulation of Remdesivir in terms of its safety, tolerability and pharmacokinetics on healthy subjects.¹⁰⁷

Many clinical studies on the inhalation of Heparin and LMWH were conducted before the pandemic.^{108–120} According to van Haren et al., there is a strong scientific and biological basis to test the nebulized Heparin as a therapy for COVID-19 pneumonia and ARDS. Besides, delivering Heparin via inhalation to the upper airways, the main entry point of the virus, may provide a prophylaxis.¹²¹ And it should not be a surprise that there are some completed and ongoing clinical studies on the use of nebulized Heparin and LMWH in COVID-19,^{122–129} which investigate therapeutic effects of Heparin and LMWH on symptom management of COVID-19-induced inflammation, and on vascular pulmonary thrombosis. In one of the ongoing meta-trial, it was aimed to investigate that whether the administration of nebulized Heparin to the hospitalized COVID-19 patients would reduce intubation rates and the risk of death.¹³⁰ At the end of the study, it was concluded that inhaled nebulized Heparin was safe in hospitalized COVID-19 patients and urgent randomized studies are needed to evaluate the efficacy.¹³¹ Our study group has recently completed a clinical Phase 2b trial that proposes inhaled LMWH given via soft-mist inhaler significantly improves hypoxemia in COVID-19 patients. Soft-mist inhaled LMWH was well-tolerated and markedly decreased the need for the oxygen treatment (vs. reservoir masks, high-flow oxygen therapy) at the end of the 10-day treatment.¹³² However, randomized studies with larger patient groups are needed to support this study.

Evaluation of Inhaler Devices for Antiviral Therapy in COVID-19

Pressurized metered-dose inhalers (pMDIs) are the most popular delivery systems in the pulmonary field.¹³³ The main action of pMDIs is the activation of the device and the synchronization of the patient's breathing, where aerosol formation occurs with the help of a propellant gas.¹³⁴ The key components here include a container, propellants, actuator, formulation and metering valve. Initially developed using chlorofluorocarbon propellants, this system has been modified over the years due to environmental concerns regarding the irreversible damage to the atmospheric ozone layer. Current devices include hydrofluoroalkanes as an environmentally safe alternative.¹³⁵ pMDIs are highly unlikely for a target group with a decreased breathing capacity, like COVID-19 patients, to perform adequately; an action even normal patients find challenging. Moreover pMDIs tend to leave

a “cold feeling” during administration and induce bronchospasm in some patients.¹³⁵ Although these disadvantages may leave pMDIs an undesirable option, especially for the severe COVID-19 patients, there are newly developed pMDIs which has spacers and valved holding chambers suitable especially for children.⁸⁸ Under the right supervision in hospital settings, the pMDI plus spacer may be similarly effective as nebulizers.¹³⁶ In addition, pMDIs reduces the risk of aerosol generating particles compared with nebulizers. But this advantage resulted in high demand for pMDIs and caused a shortage.¹³⁷ For ambulatory patients with mild COVID-19 symptoms, pMDIs may be advantageous over nebulizers as they are portable and transmission risk is lower comparing to nebulizers due to the closed system in the pMDIs. However, it is not possible to use for mechanically ventilated patients. Modern dry powder inhalers (DPIs) were developed as an alternative to pMDIs.¹³⁸ Regarding the mechanism of DPIs; the micronised drug is weakly bound to a carrier (e.g., α -lactose monohydrate) which prevents aggregation and provides sufficient flowability in powder form.¹³⁹ Patients are typically encouraged to breathe forcefully and deeply when using a DPI¹⁴⁰; but severe COVID-19 patients may find this action to be difficult to perform and inadequate dose uptake could be seen. DPIs can be suitable for mild-to-moderate COVID-19 patients who does not have breathing difficulties. Although DPIs are eco-friendly devices, one of the reasons pMDIs are still frequently prescribed is their low cost compared to DPIs.¹⁴¹ Albeit, they are easier to carry and thought to cause less risk of transmission compared to nebulizers, as with pMDIs, it is not possible to use DPIs in mechanically ventilated patients with severe symptoms. In addition, in the early days of the pandemic, developing dry powder formulations for COVID-19 could not be considered as an urgent therapy in hospitals as it would take more time than formulating nebulizers containing liquid dosage forms.

Nebulizers are one of the common devices for delivery of drug formulations to the lungs. They produce aerosol droplets from solutions or suspensions of liquid or solid particles. Although administration of higher doses is possible, longer administration times disfavors nebulizers in comparison to pMDIs and DPIs.¹⁴² Generally, nebulizers can be classified into three groups: jet nebulizers, ultrasonic nebulizers and vibrating mesh nebulizers.¹⁴³

Jet nebulizers are the earliest nebulizer technology. The mechanism of jet nebulizers is the flowing of a gas stream from a compressor through a capillary tube with a high speed in which the fluid is drawn up to be atomized through the capillary tube. Contact of large aerosol droplets with the baffle inside the nebulizer prevents production of large droplets. Atomization force may cause unwanted changes in formulation. In the case of ultrasonic nebulizers, instead of compressed air gas, high frequency vibrating piezoelectric crystals produce sound waves which in return form liquid droplets. Ultrasonic nebulizers cause heat formation and result in degradation of heat sensitive substances. Also, ultrasonic nebulizers are less efficient in nebulization of suspension and viscous liquid due to the decreased aerosolization force and are far more expensive compared to jet nebulizers. Lastly, vibrating mesh is a relatively new nebulizer technology. It also uses piezoelectric crystals to force liquids extrusion through vibrating mesh. They can reach deep areas of the lung with shortened time compared to jet nebulizers.^{144,145}

During nebulization, the leakage of formulation aerosols into the air by the patient's breathing pattern causes undesired drug loss. It is noteworthy to underline that in the case of COVID-19, the risk of contamination increases via nebulization.^{146–149} Current guidelines warn against the use of nebulizers.¹⁵⁰ As nebulized drug may induce cough in patient, the caregiver thus may face an increased risk of virus contamination.¹⁵¹ However, there is no conclusive evidence regarding transmission of SARS-CoV-2 via nebulizers and these statements remain as a debate. Despite the disadvantages, nebulization is

the easiest and fastest way to administer inhaled treatment to unconscious patients with severe symptoms.

In soft-mist inhalers, the drug is dissolved in a solution, so it is relatively less affected by moisture than dry powders, hence more suitable for use in humid ambient conditions. Its relatively low speed and long spray time facilitates a reproducible inhalation of the aerosol.^{152–154} Most distinctively, soft-mist inhalers are active systems that do not require propellant gas. The energy required for aerosol generation comes from a mechanical force, and is independent of the patient's respiratory capacity. The versatile design of soft-mist inhalers may reduce airborne particulate contamination by allowing the patient to breathe through the mouth and exhale through the nose, which is a critical factor in COVID-19.

Soft mist inhalers are more optimal in terms of increased drug accumulation in the lungs. Clinical studies conducted in volunteers using radiolabeled drug particles and gamma scintigraphy, indicate that drug aerosols administered with Respimat[®], a soft mist inhaler, had a higher accumulation in lung with a mean (range) of 51%, particularly in peripheral lung tissues.^{155,156} Also, a recent study by our research team has shown that fine particle fraction was 44.4% with Pulmospray[®], which is a specially designed soft mist inhaler.¹³² A key advantage of soft-mist inhalers is its easy administration. The drug is administered in soluble form with a specific volume produced from a single-use dosage form or multidose, and provide the opportunity of repeated administration with various ranges of doses^{157,158}. The single-use dosage form can be advantageous in COVID-19 patients in terms of reducing the risk of contamination. In addition, being liquid dosage forms that do not contain propellant and can be easily carried makes it possible to use them in all patients with mild or severe COVID-19.

Formulation and device suitability can be evaluated according to the characteristics of the devices and the above-mentioned antiviral agents. When evaluated in terms of solubility, all active substances except Molnupiravir and Heparin show low solubility in water. Molnupiravir and Heparin formulations can be prepared for use in nebulizers, pMDIs and soft mist inhalers as their solubility in water is 39.7 mg/mL and 50 mg/mL respectively. For other antiviral agents, various solubility enhancing formulation strategies can be developed and solution forms of these active substances can be prepared. Cyclodextrins can be used as solubilizing agent for the formulation of poorly soluble active ingredients. The formulation of Remdesivir, which is currently available in the market as intravenous, was prepared using cyclodextrins due to the solubility problem of the active substance.¹⁵⁹ Although their use in the lungs has not been approved by the FDA yet, EMA's report states that cyclodextrins are safe for nasal and pulmonary use.^{160,161} Therefore, as solubility enhancers, cyclodextrins can be used in the preparation of above-mentioned antivirals in solution formulation. In addition, the preparation of dry powder formulations and pMDI formulations with co-solvent is a suitable option for these agents that have solubility problems.

Several reports for inhaled HCQ stated that doses ranging from 2 to 4 mg twice daily to 20 mg once daily can be effective in treating COVID-19 symptoms.^{162–164} Oral dose of HCQ for COVID-19 ranging from 200 mg to 800 mg.¹⁶⁵ Considering that the dose of the drug is so low when administered as pulmonary, treatment can be achieved at very low doses with similar calculations for other antiviral agents.

Conclusion

The primary target of SARS-CoV-2 is the lungs. However, the medical approaches form a contradiction in terms of systemic administration of drugs for the treatment of COVID-19. Here, inhalation is a superior administration route in terms of inhibition of airborne viruses in the lungs. Hence, it is able to achieve higher lung accumulation of the drug and elimination of the side effects. Preclinical and

clinical studies conclude that inhalation technology offers a promising and effective route in COVID-19 treatment that should be taken into consideration. Development of inhaler forms of antiviral drugs, some of which are currently used for COVID-19 treatment, will be more effective in the lungs and safer than conventional dosage forms. As for inhaler devices, apart from their features the potential environmental effect should also be considered while prescribing. It should be kept in mind that the effects of such a widespread disease are bound to leave behind serious ecological waste. Although it is true that a disposable product would cause ecological concerns, there is a serious issue of sanitizing reusable devices such as nebulizers. Overall, for the treatment of COVID-19 the health professions should consider the suitability of the specific device for the patient and associated risks. Although each device has a separate practical advantage, soft mist inhalers might be a suitable choice for pandemic conditions. Further clinical studies are necessary to determine the future of soft mist inhaler technology in the treatment protocols.

Author Contributions

GS wrote the original draft and contributed to editing of the review and the literature research. NB, AE, MC contributed equally to the literature research and writing of the review. OAD and SS contributed to writing and editing of the review and the literature research. AYP conceptualized, designed and supervised the review. All authors have read and agreed to the published version of the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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