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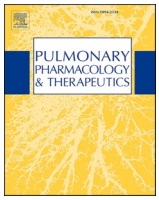

Treatment of respiratory viral infections through inhalation therapeutics: Challenges and opportunities

Nidhi Nainwal

Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Premnagar, Dehradun, Uttarakhand, 248007, India

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ABSTRACT

Respiratory viral infections are the leading cause of death worldwide. The current pandemic of coronavirus infection (COVID-19) challenged human beings for the treatment and prevention of this respiratory viral infection since its outbreak in 2019. Despite advancements in the medical field, scientists were helpless to give timely treatment and protection against this viral infection. Several drugs, whether antiviral or not, were given to the patients to reduce mortality and morbidity rate. Vaccines from various pharmaceutical manufacturers are now available to give immunization against covid-19. Still, coronavirus is continuously affecting people in the form of variants after mutation. Each new variant increases the infection risk and forces scientists to develop some innovative and effective treatments for this infection. The virus uses the host's cell machinery to grow and multiply in numbers. Therefore, scientists are facing challenges to develop antivirals that stop the virus without damaging the host cells too. The production of suitable antivirals or vaccines for the new virus would take several months, allowing the strain to cause severe damage to life. Inhalable formulation facilitates the delivery of medicinal products directly to the respiratory system without causing unwanted side effects associated with systemic absorption. Scientists are focusing on developing an inhaled version of the existing antivirals for the treatment of respiratory infections. This review focused on the inhalable formulations of antiviral agents in various respiratory viral infections including the ongoing covid-19 pandemic and important findings of the clinical studies. We also reviewed repurposed drugs that have been given through inhalation in covid-19 infection.

1. Introduction

Pulmonary disorders are the leading cause of death worldwide. Some of the most common pulmonary diseases are asthma, chronic bronchitis, pulmonary tuberculosis, lung cancer, chronic obstructive pulmonary disorders (COPD), emphysema, pulmonary embolism, pulmonary hypertension, cystic fibrosis, acute respiratory distress syndrome (ARDS), bronchiectasis and viral infections [1,2]. Respiratory virus infections like the common cold caused by rhinovirus, coronavirus, respiratory syncytial virus (RSV), and parainfluenza virus, bronchiolitis caused by RSV, pneumonia caused by coronaviruses, RSV and most influenza viruses, COVID-19, and influenza (flu) etc. affect the upper or lower respiratory tract. Lower respiratory infections are a major problem, with higher mortality and morbidity rate worldwide [3].

In general, treatment of respiratory infection through conventional routes like oral or parenteral is challenging as the microbes reside deep in the airways, where the conventionally administered drug reaches only in a small proportion. In such cases, high doses of drugs are required to reach the minimum inhibitory concentration (MIC) at the infection sites. Unfortunately, systemic administration of drugs at high doses can cause severe side effects. Therefore, delivery of drugs directly to the respiratory tract is an alternative method as it provides a higher concentration of drug at the target site without higher systemic exposure. The ultra-thinness of the alveolar epithelium makes the lungs very permeable for the drugs. The alveolar part of the lung has good vascularization, a large surface area and a direct connection between the pulmonary and systemic circulation [4,5]. Direct delivery of the drug to the lungs increases its efficacy, and local bioavailability and reduces the gastrointestinal tract (GIT) degradation of the drug, and systemic toxicity. In contrast to intravenous injection, inhalation of drugs can provide non-invasive and painless self-administration of drugs directly to the lungs without any assistance from healthcare workers. As per FDA [6,7] inhaled drugs are classified viz. (i) inhaled drug products, administered directly to the lungs for local and/or systemic effect by metered dose inhalers (MDI), dry powder inhalers (DPI) or nebulizers, (ii) nasal drug products administered to the nasal cavity for local and/or

E-mail address: nidhi.nainwal87@gmail.com.

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systemic action [6,7].

Clinically, inhaled drug products are given to the respiratory tract in the form of dry or liquid aerosols. Dry aerosols consist of a powder formulation of drugs, which are deagglomerated and dispersed into fine inhalable particles by a DPI. Liquid aerosol contains fine droplets of solution or suspensions which can be aerosolized as single puffs of a few microliters by MDIs or continuously aerosolized several millilitres of drug products by nebulizers. Among various pulmonary delivery systems, DPIs are more favourable dosage forms because of their better stability and ability to deliver the drug into deep lungs using the patient's respiration [8].

2. Respiratory viral infections

Viruses are obligate intracellular parasites that are transmitted as inert particles. Outside of a host cell, viruses do not use their energy and hence some scientists do not consider them alive. They only become active after contact with the host cell and use the host cell's energy and tools to make new viruses. To exert their pathogenic effects, they must enter the host body through any of the possible potential routes viz. respiratory tract, gastrointestinal tract, skin, genital tract, or other routes. The skin has a relatively impermeable outer layer of keratin that restricts the entry of viruses into the host body. However, the breaches in skin integrity can allow the virus to enter the host body through the skin. The epithelial lining of the respiratory tract, gastrointestinal tract and urogenital tract does not have keratinized protective layer. Similarly, in the eyes, the protective keratinized layer is replaced by the non-keratinized epithelial lining of the conjunctiva and cornea [9].

In the respiratory tract, the mucociliary blanket of mucus layer from nasal passages to the distal airways in the lungs and the alveolar macrophages are the main protective mechanism. The larger inhaled particles greater than 10 μm in diameter are trapped on the mucociliary blanket and the smaller particles less than 5 μm in diameter are ingested by alveolar macrophages. The virion trapped in the mucus gets swallowed or coughed out. The respiratory system has also innate and adaptive immunity [9]. Despite these protective mechanisms, however, the epithelial surface of the respiratory tract supports the replication of viruses. The virus attaches to the specific receptors on epithelial cells within the mucosa thus cannot get cleared by a mucociliary blanket or phagocytic cells. Viruses that enter the body via the respiratory tract can quickly cause extensive infection and rapid progression of disease with a short incubation period. The virus infection of the host cell mainly involves the incorporation of viral DNA into a host cell, virus replication and release of new viruses. There are six main steps in viral infection viz., attachment, penetration, uncoating, replication, assembly, and release. In the attachment and penetration steps, the virus attaches itself to a host cell, gets entered the cell by endocytosis (naked or enveloped virus) or fusion (enveloped virus) and releases its genetic material there. During uncoating, replication and assembly, the viral DNA or RNA incorporates itself into the host cell's genetic material and induces it to replicate the viral genome. The last stage of virus infection is the release of newly created viruses produced in the host cell. The viruses are released from the infected host cell either by killing the host cell or by budding through the cell membrane without directly killing the cell [10]. To ensure their perpetuation, viruses are then transmitted to other susceptible individuals that is they must be shed with secretions or excretions into the environment, be taken up by another host or a vector, or be passed congenitally from mother to offspring [10,11]. Respiratory viruses are commonly shed in mucus and are expelled from the respiratory tract during coughing or sneezing.

3. Challenges for respiratory infection treatment

An antiviral drug can act by blocking any of the steps a virus uses to infect the host cell. At each step of viral infection, the viral genes interact with various host molecules. The antiviral often acts as the host molecules and interferes with the viral life cycle (Fig. 1) [12]. A common approach to kill the virus is to interfere with the formation of new viral genomes form viral DNA or RNA. DNA viruses use DNA polymerase enzymes for genetic replication and transcribe their mRNA using DNA-dependent RNA polymerase enzymes [11]. Most of the antiviral drugs for respiratory infections act either by blocking viral binding and entry into the host cells, or by preventing the formation of new copies of viral RNA, or by interfering with the production of necessary proteins for viruses or preventing the exit of virus from the host cells [13,14]. Antiviral drugs do not eradicate the viruses directly but stop them from spreading among cells or persons. Depending upon the immunity of the host, when possible, the body mops up the virus already present in the body. Therefore, it is very necessary to start the antiviral treatment early and or when the first symptoms appear, while viruses are low in numbers [13].

Even though viruses cause life-threatening infections and several deaths worldwide, however, there are so few antivirals available for treatment. There are several reasons for this problem. The first reason is viruses are much trickers to target than bacteria. In contrast to bacteria, viral pathogens live inside the host cells and depend on host protein for their functioning and thus do not offer easy targets for the antivirals. There are very few antivirals available in nature, so the researchers must synthesise them. The biggest challenge of antivirals is to ensure that during their action against viruses, the drug does not hurt the hosts as well. The one unfortunate reason is resistance against antivirals. The pathogens make small changes in their genes and proteins that make them unaffected by the drug. The antivirals that were effective previously are no longer effective [13].

4. Inhaled antiviral agents

Inhaled antiviral agents have been extensively used in the prophylaxis and treatment of respiratory diseases from various viruses. Inhalation of antivirals provides significant pharmacokinetic and pharmacodynamic advantages and reduces the potential toxicity associated with systemic exposure. Aerosolization of drugs provides direct delivery of the antiviral agents to the respiratory tract in a concentration sufficient to remove the pathogenic organism at the site of infection [15,16]. As there is no specific antiviral agent available for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), repurposing of medication is the need of time. It is necessary to conduct clinical investigation of these medications against SARS-CoV-2 infection. Researchers are also trying to deliver the available antiviral agents through the inhalation route. Currently, there are very few inhaled antivirals available on the market. Inhaled ribavirin for RSV and zanamivir for influenza are some approved inhaled medications. In this paper, an up-to-date overview of the treatment of respiratory viral infection in the form of inhaled drug therapies is discussed. This review provides details on the safety, efficacy and development status of aerosolized antiviral compounds that are approved and/or under development stages for the treatment of human respiratory viruses.

4.1. Ribavirin

Ribavirin is a synthetic purine nucleoside analogue with antiviral activity. It has a broad spectrum of activity against both DNA and RNA viruses in vitro and in vivo and is currently used for the treatment of RSV in high-risk infants, viral haemorrhagic fevers, and hepatitis C virus (used together with interferon alfa-2b as in Rebetron® or PEGylated interferon alfa-2b Peg-intron ® or Pegasys®). Ribavirin is a prodrug and is converted to its active 5-monophosphate form, which looks like purine RNA nucleotide. This form interferes with RNA metabolism necessary for viral replication [15]. Systemic administration of ribavirin has shown poor efficacy against naturally occurring influenza infections in humans. This may be because ribavirin concentrates in erythrocytes and is rapidly metabolized by the liver. Aerosol delivery of ribavirin

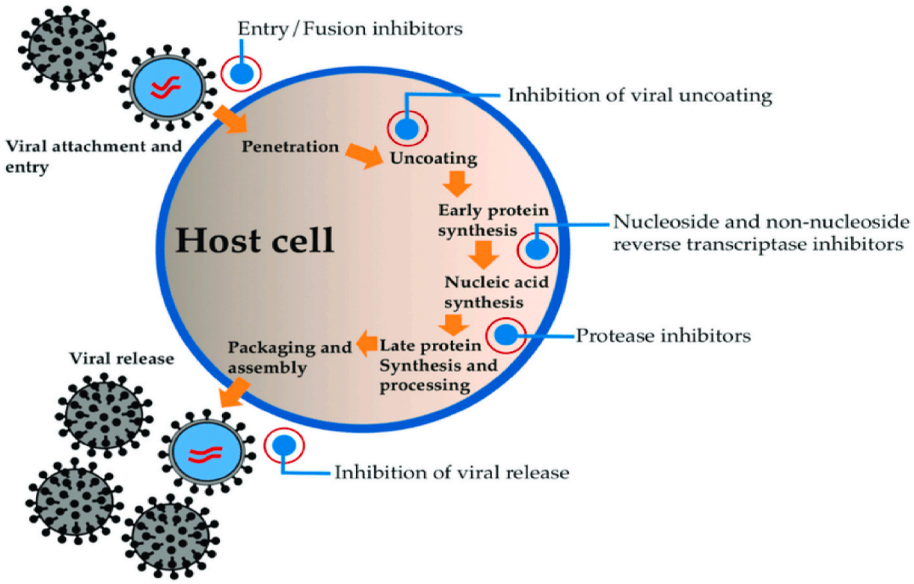

Fig. 1. Major sites of antiviral drugs (Image was reproduced with permission from Molecules, 2020, Reference [12]. Copyright 2020, MDPI).

bypassed these problems. Ribavirin gets phosphorylated into-ribavirin monophosphate by cellular adenosine kinase, followed by conversion to di-and triphosphates by unidentified cellular enzymes. The activation of ribavirin to its phosphate derivatives was examined in uninfected and RSV-infected cells. The enhancement of ribavirin phosphorylation in RSV infected cells was probably because of slight virus induced stimulation of adenosine kinase and other cellular enzymes [17].

In 1986, VIRAZOLE® (inhalation solution of Ribavirin 20 mg/ml, USP) was introduced to treat hospitalized infants and young children infected with RSV [18,19]. The inhalation solution is a sterile, lyophilized powder of ribavirin, that is reconstituted with sterile water for injection (20 mg/ml) without any preservative with a pH near 5.5 and can be administered using a face mask, oxygen tank or mechanical ventilator. Small Particle Aerosol Generator (SPAG®-2) is the only tested aerosol generating device for the aerosolization of virazole. The treatment is given using 20 mg/ml virazole solution for 12–18 h daily for 3–7 days, and the average aerosol concentration for a 12-h delivery period would be 190 mcg/L of air [18,19].

Administration of ribavirin in the form of aerosol is effective and safe in both infants and adults in comparison to oral ribavirin, which causes haemolytic anaemia. Administration of aerosolized virazole in combination with other aerosolized medication is prohibited [20]. Inhaled ribavirin long-term therapy for 10 months for parainfluenza 3 was virus found to be feasible, well tolerated, and safe in an infant with severe combined immunodeficiency [21]. Aerosolized ribavirin in combination with parenteral immunoglobulin was found effective in adult blood and bone marrow transplant patient with RSV [22,23]. A once or twice daily nebulizer treatment was developed in the form of MegaRibavirin formulation containing 100 mg of ribavirin per ml for the treatment of influenza in general or in pandemic avian influenza. This formulation was used with an Aerotech II nebulizer in preventing the death of mice suffering from the lethal influenza A virus and allowed short treatment periods with fewer environmental and cost issues [24]. In 1984, the results of a double-blind clinical trial of influenza in college students showed statistically significant reductions in the height and duration of fever, systemic symptoms, and virus shedding after receiving small particle aerosolized ribavirin (2.4 g of ribavirin over 42 h during 68 h of hospitalization). In addition, a more rapid recovery was found in patients suffering from influenza in comparison to the control group [25]. Irrespective of effectiveness, ribavirin use is not approved by FDA in human patients suffering from influenza A and B due to side effects associated with ribavirin like haemolytic anaemia, and significant teratogenic and embryocidal effects [26]. Therefore additional clinical studies are needed to assess the safety and efficacy of aerosolized ribavirin in case of influenza infection [27].

4.2. *Oseltamivir phosphate*

Oseltamivir phosphate (Tamiflu™; Hoffmann-La Roche Ltd, Nutley, NJ, USA) is an oral neuraminidase inhibitor used for the treatment of influenza A and B and the prevention of flu after exposure. Oseltamivir (GS4104) is an ester prodrug which is hydrolysed by hepatic carboxylesterases to its active metabolite oseltamivir carboxylate (OC, GS4071) after oral administration due to hepatic first pass metabolism. It is a sialic acid derivative and has oral bioavailability of more than 80% [28]. Oral treatment with Oseltamivir phosphate (OP) is associated with gastrointestinal complications like nausea, vomiting, diarrhoea, and some central nervous system related adverse effects like vertigo, fatigue, headache, dizziness, and insomnia. Post marketing surveillance has been reported with skin rash, hepatic problems, and thrombocytopenia. Some non-life threatening neurologic and behavioural changes have also been reported, mostly in children from Japan [29].

To avoid the adverse effect related to the oral delivery of OP, some alternative routes must be available. Inhalation route is such an alternative that can deliver the drug directly into the lungs and can reduce the side effects related to the oral delivery of the drug. The necessary metabolic activation of OP can be achieved in the lungs as it is rich in carboxylesterase enzyme [30]. To deliver the drug directly into the lung, Tang et al. [31], prepared a dry powder formulation of liposome encapsulated OP using ovelecithin and cholesterol by active loading technique and spray-drying process. The liposomal OP dry powders showed an average particle size of 3.5 μm. The average fine particle fraction (FPF) of 35.40% indicates the good distribution of OP-DPI in the lung. In comparison to the oral OP solution giving 90% release, OP liposomes gave only 20% initial release in the first 2 h and sustained release for 20 h in PBS (pH 7.4). The result of in vitro metabolism study of OP in rat liver and lung homogenates showed that OP could be transformed into oseltamivir carboxylate (OC) by carboxylesterase enzyme in the rat lung. The Pharmacokinetic studies in rats showed mean residence time (MRT) of 4.652 and 5.608 h in group a, receiving OP solution orally and group b, receiving liposomal OP dry powders respectively. Moreover, group b showed a 1.14-fold higher $AUC_{0\text{-}1}$ and 1.22-fold higher C_{max} in comparison to group a. It was also suggested that in comparison to the oral route, inhalable OP get converted into

oseltamivir carboxylate directly in the lung giving higher C_{max} of the OC [31].

In a recent study [32] an innovative formulation approach is used to develop sustained release DPI of OP by spray drying technique using Hydroxy propyl methyl cellulose (HPMC) and L-leucine. The OP-DPI contains immediate release and sustained release portions. HPMC is used as the rate controlling polymer for the sustained release of drugs. The formulation gave immediate burst release of 49% within 15 min followed by sustained release of drug up to 9 h. OP-DPI showed deposition in the upper respiratory tract as the formulation showed maximum deposition at stage 3 and 1.08 mg fine particle dose (FPD). The formulation was found safe without any sign of inflammation after in vivo toxicological study. As the achieved dose after single inhalation was not high enough to produce the effect, another attempt was made by Shahir Aziz et al. [33], to target a high dose of OP in the lungs. In this study high dose, OP-DPI was formulated using conventional sugar as diluents for inhalation therapy against viral pneumonia. Trehalose micro particulates produced by jet milling were found to be effective in the direct targeting of high dose OP in comparison to lactose, mannitol, and glucose after examination under similar conditions. The MTT (3-(4, 5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium bromide) assay performed using Calu-3 cells derived from bronchial adenocarcinoma, showed the safety of OP-DPI on lung cell [33]. This finding makes inhalation OP treatment more effective and convenient in comparison to the oral route. However, only 2% of OP prodrug get converted into active form pre-systematically, confirming the low benefit of OP nebulization. Therefore, it was suggested that pulmonary administration of OP may not be a good choice to get a high concentration of its active form at the infection site of the lung [34]. Extensive clinical studies are required to explore the application of respiratory administration of OP.

4.3. Zanamivir

Zanamivir is an N-acetylneuraminic acid (sialic acid) transition state analogue that inhibits influenza viral neuraminidase causing subsequent interference with the deaggregation and release of the viral progeny from the infected cell, thereby halting the replication cycle. The poor oral bioavailability of zanamivir of less than 5% makes intranasal and dry powder inhalation delivery a well suited and effective route for its administration [35,36]. Peramivir (Rapivab®), zanamivir (Relenza Tamiflu®), oseltamivir phosphate (Tamiflu®), and baloxavir marboxil (Xofluza®) are the four FDA approved drugs recommended by CDC for influenza treatment. Out of these four drugs, only zanamivir is approved for inhalation use (Relenza®GlaxoSmithKline, Middlesex) [37]. It is approved as aerosol inhalation to treat influenza A and B infection in adults and paediatric patients ≥7 years of age, who have been symptomatic for no more than 2 days. It is also approved in adults and paediatric patients ≥5 years of age for prophylaxis purposes. For treating influenza, zanamivir dose is10 mg twice daily for 5 days with total daily dosing of 20 mg. For prophylaxis purposes, it is10 mg once daily for 10 days. The extent of drug delivery to the lung depends on patient factors such as inspiratory flow. After inhalation of dry powder, approximately 7–21% get deposited in the lower respiratory tract, with the remainder in the oropharynx [38,39].

Relenza is a dry powder of zanamivir which is inhaled into the lungs through the mouth using the breath-activated plastic device (diskhaler ®). The powder is contained in blisters on a rotadisk-a foil disk which is loaded into the diskhaler. In Relenza Rotadisk®, 4 regularly spaced double-foil blisters are present, and each blister contains a powder mixture of 5 mg of zanamivir and 20 mg of lactose (containing milk proteins) [40–42]. Relenza Rotadisk delivered 4 mg of drug from diskhaler at a pressure drop of 3 kPa for 3 s under an in vitro study [35]. Following 10 mg inhalation of zanamivir, the peak serum concentration reached from 17 to 142 ng/ml within 1–2 h and the area under the serum concentration versus time curve ($AUC_{infinity}$) ranged from 111 to 1364 ng h/ml [42].

Neuraminidase inhibitors are associated with viral resistance due to mutation in the neuraminidase gene and/or the hemagglutinin gene of influenza viruses. The H275Y amino acid substitution of the neuraminidase gene is one of the most common mutations associated with a high degree of oseltamivir resistance in the N1 subtype of the influenza virus [43]. No significant zanamivir resistance is detected in seasonal influenza A (H1N1) viruses under the WHO collaborating center surveillance study [44]. The reason could partially be due to different routes of administration for inhalation zanamivir and oral oseltamivir. Proper treatment with zanamivir inhalation has shown a reduction in duration of illness, symptom severity and rate of influenza associated complications. Zanamivir inhalation therapy has been found more effective than oral oseltamivir in terms of reducing the duration of fever as well symptom severity in patients suffering from influenza A or B viruses [45]. The use of oral oseltamivir in combination with inhaled zanamivir has not been found successful in ventilator and extracorporeal membrane oxygenation (ECMO)-treated critically ill patients of pandemic influenza A (H1N1) [46].

Zanamivir inhalation powder (Relenza) must only be administered using the proper inhalation device (diskhaler). It should not be made into an extemporaneous solution for administration by nebulization or mechanical ventilation. It has been reported that the patients who received the solution made of zanamivir powder by nebulization or mechanical ventilation suffered fatal cases because the lactose in the formulation obstructed the equipment's functioning [47,48]. The aqueous saline solution of zanamivir that has been used for nebulization in early studies and that is currently under clinical trials for intravenous administration does not contain lactose the presumed reason for ventilator occlusion [49].

In an incidence, off label use of Relenza in the form of nebulized formulation resulted in the death of a mechanically ventilated 25-year-old pregnant woman suffering from severe H1N1 influenza. The reason behind death was the expiratory filter blockade by the lactose present in the Relenza that caused severe hypoxemia (SpO2 dropped to 71–78%) and bilateral pneumothoraxes in the patient [47,48]. Although zanamivir inhalation is safe and effective, alternative routes have also been studied for zanamivir administration. It was found that the use of zanamivir via diskhaler is very difficult, especially in elderly people [50]. In comparison to oral oseltamivir and powder inhaler of laninamivir, delivery of zanamivir correctly from the diskhaler is too tedious with so many steps and requires proper training [51].

4.4. Laninamivir

Laninamivir octanoate (CS-8958) is a neuraminidase inhibitor, that is approved and launched in 2010, only in Japan (Inavir®, Daiichi Sankyo Company Ltd, Tokyo, Japan and biota pharmaceuticals Alpharetta, USA) for the treatment and prevention of influenza A and B virus [52]. It is given in the form of dry powder inhalation as a once-daily dose of 40 mg for adults and 20 mg for children less than 10 years of age [53,54]. It is a sialic acid analogue and has a structure, similar to zanamivir. It is a prodrug that is metabolized in the airways to active laninamivir (R-125489) by intracellular esterases and taken by the epithelial cell lining of the airways. The active form of laninamivir is retained in the airways at a higher concentration than the 50% inhibitory concentration (IC_{50}) against most influenza neuraminidases, for at least 10 days following a single inhalation dose of 40 mg [55]. Laninamivir has limited efflux from epithelial cells that is responsible for its prolonged and high exposure in respiratory tissues. After inhalation, only 15% drug is absorbed systemically [56]. The required dose is inhaled from a single-use disposable TwinCaps® inhaler [57].

The intranasal administration of laninamivir (R-125489) and its prodrug, CS-8958 (laninamivir octanoate) had shown potent inhibitory effects against various influenza viruses, seasonal H1N1, pandemic H1N1, H3 N2, HPAI H5NI viruses and influenza viruses in various in vitro and in vivo studies [58–63]. In the mouse infected model, the

efficacy of single inhalation of CS-8958 was compared with twice daily oseltamivir oral formulation, and once daily zanamivir inhalation for 5 days against pandemic (2009) H1N1 A/California/04/09 virus. A significant reduction in viral titres was found in a single dose of CS-8958 in comparison to oseltamivir and zanamivir [64]. Single inhalation of CS-8958 was found well tolerated in healthy volunteers in a double-blinded randomized placebo-controlled trial I [65]. In further clinical trials, II/III on paediatric and adult patients suffering from influenza during the 2008–2009 influenza season in Japan, single inhalation of CS-8958 was found effective with better patient compliance in comparison to twice daily dosing of orally administered oseltamivir for 5 days [53,54]. In the paediatric patient with influenza, once daily administration of laninamivir octanoate dry powder inhalation was found to be more convenient than twice daily inhalation of zanamivir. No difference was seen in the efficiency and safety between the two drugs [66].

In the post marketing surveillance conducted in Japan in the 2010/2011 influenza season, single inhalation of laninamivir octanoate was found to be effective in more than 90% of patients suffering from influenza A and influenza B virus. It was concluded that if the drug is inhaled correctly, reliable therapeutic effects will be obtained [67]. Biota pharmaceuticals has conducted a phase II randomized, double-blind, placebo-controlled, parallel-arm clinical trial, referred to as IGLOO in 639 adults (aged 18–64 years) with presumed influenza A or B infection to compare the safety and efficacy of two dose levels of 40 mg and 80 mg of inhaled laninamivir octanoate (LANI) dry powder inhaler, with placebo, following delivery of all by a TwinCaps® inhaler. Despite a statistically significant reduction in viral shedding for the patients at both doses compared to placebo on day 3, the median time to alleviation of influenza symptoms was 102.30 h and 103.20 h for 40 mg, and 80 mg LANI in comparison to 104.10 h for placebo. The results showed that the time to alleviation of influenza symptoms that were assessed through Flu-iiQ (Influenza intensity and impact Questionnaire) and diary cards from Day 1–14 didn't reduce in comparison to placebo [52,68,69].

4.5. Interferon (IFN)

Interferons are glycoproteins, that belong to the family of cytokines, which are produced and released by various cells as a result of an inflammatory response to viral infection. Production of interferons can be enhanced by protein engineering and recombination technology at a very low cost [70]. Due to its broad antiviral activity, it is used for prophylaxis of viral infection, specifically viral infection of the respiratory system like rhinovirus, parainfluenza, influenza A and B, adenovirus, and coronavirus. In a series of studies during the early 80s, topical application of interferon to the upper respiratory tract for the prevention of viral acquisition had been demonstrated [71–74]. IFN alpha 2 at a daily dose of 10 million IU, inhibited experimental rhinovirus infection [72]. The same dose treatment showed reduced respiratory illness and viral shedding in the experimental influenza A infections [75]. Although this daily dose of 10 million IU was virologically and clinically effective, it also caused nasal discomfort and mucosal ulceration that leads to the early termination of two field studies [76,77]. Therefore, to find well tolerated, and efficacious dose of IFN, a field test was conducted at twice daily dosing of 1 million IU of IFN alpha 2 for 28 days. This dose was generally well tolerated without any unwanted nasal discomfort and mucosal ulceration. However local irritation on nasal mucosa was still an unwanted side effect that outweighed the clinical effects of IFN alpha 2 [78]. Several studies have confirmed that at this dose intranasal IFN-alpha gave 75–87% protection against rhinovirus infection [79,80].

Intranasal interferon alpha 2 has shown prophylactic efficacy in preventing rhinovirus associated cold. Once daily administration of intranasal interferon at a dose of 5 million units for 7 days prevented rhinovirus infection in the family setting after the index case developed a cold. However, the study failed to prove the efficacy of treatment for other respiratory infections [81]. A preventive approach was studied to reduce the morbidity in children susceptible to respiratory illness using intranasal interferon. The findings concluded that the prophylaxis approach of this kind would not beneficial for respiratory illness in high-risk children [79]. Notably, prophylactic low doses of IFN-α2 of approximately 2×10^6 IU per day are effective in preventing infection when begun 1 week before virus exposure [82].

Aerosolized recombinant interferon-gamma (rIFN- γ) at a dose of 500 μg over 12 days has been found safe and well tolerated in normal humans. Additionally in comparison to the subcutaneous route that produces adverse effects, inhaled rIFN- γ even at higher doses, can be well tolerated [83]. In a phase 1 study, inhaled single doses of 3–100 $\times$ 10^6 INF- β was well tolerated in eight patients suffering from lung cancer without any systemic or local side effects [84]. The major drawbacks of intranasal interferon spray are local nasal irritation and systemic toxicity. The severity of these adverse effects mainly depends on the dose and duration of the administration of intranasal IFN. Very large doses (>10 $\times$ 10^6 IU daily) of INF nasal sprays cause severe systemic toxicity such as transient leukopenia [85]. Recently inhalable formulation of interferon-β-1a (SNG001) completed a phase 3 clinical trial (SPRINTER) in 623 hospitalized Covid-19 patients suffering from SARS-CoV-2. SNG001, a pH neutral nebuliser solution of interferon-β-1a was given via inhalation using ultra device nebuliser at a dose of 15.6 MIU once daily for up to 14 days. Unfortunately, the study failed to show statistically significant benefits for its prespecified endpoints i.e., time to discharge from hospital and recovery. However, there was a reduction in relative risk of progression to severe disease or death within 35 days. This finding provides a strong clinical rationale for additional clinical trials [86,87].

4.6. Cidofovir

Cidofovir is a nucleotide analogue with in vitro and in vivo activity against human cytomegalovirus infection. This drug has been approved by US food and drug administration for the treatment of HIV-positive patients suffering from cytomegalovirus and had off label use for recurrent respiratory papillomatosis therapy [88]. The conventional approach of cidofovir delivery has some issues like poor absorption with the oral route and localized fibrosis with parenteral administration. In addition, the drug also causes serious nephrotoxicity [89]. It was suggested that as an alternative approach, delivery of cidofovir directly into the lungs would be beneficial [90]. In herpesvirus uninfected cells cidofovir get phosphorylated into its active form cidofovir diphosphate by cellular enzymes. Cidofovir diphosphate forms an adduct with choline that has a long intracellular half-life of several days [91,92]. It means delivery of a single low dose of drug directly to the lung could provide week longer protection and could avoid the high dose related nephrotoxicity [92].

Inhaled cidofovir (NanoFOVIR™) was a preclinical program of Nanotherapeutics funded by the National Institute of Allergy and Infectious Disease in 2009 for 5 years [93]. The purpose was to develop inhaled dry powder of injectable cidofovir for the treatment of variola major infection causing smallpox or for the post-exposure prophylaxis. The results of preliminary studies on the rabbit pox virus infecting rabbits, using a 5 mg/kg dose of inhaled NanoFOVIR™ suggested better systemic bioavailability in comparison to IV cidofovir at 1 mg/kg dose. The drug was retained in the lungs for up to 8 h, providing a higher concentration of drug in the lungs. The results provided data that can be used in future for the therapeutic evaluation using aerosolized monkeypox in nonhuman primates. This program is not active now as there were difficulties related to the device used for the inhalation. It was supposed that the nebulized inhaled liquid version of cidofovir would be a better fit [88]. Previously, inhaled cidofovir has been found highly efficacious against various pox models, giving long term effects and prolong retention in the lungs [94]. In comparison to the subcutaneous cidofovir (HPMPC, Vistide®), an inhaled formulation of cidofovir resulted in better survival in Balb/C mice [95]. Inhaled cidofovir

appeared to be effective as adjuvant therapy for recurrent respiratory papillomatosis in a 4-month-old boy. However, clinical trials are required to further investigate the safety and efficacy of inhaled Cidofovir [96].

4.7. DAS181

The influenza virus gets bound to the sialic acid receptor on the respiratory epithelial cell of the host to cause infection in humans [97]. DAS181 (Fludase; NexBio, Inc now known as Ansun Biopharma, Inc.,) is a novel compound that acts as a viral receptor inactivator [98]. It is different from neuraminidase inhibitor as it selectively cleaves off the sialic acid receptor on the respiratory epithelium, and thus prevents binding of the influenza virus to the sialic acid receptor [99]. It is administered as a dry powder through an inhaler [100]. Intranasal administration of DAS 181 was found effective in the prophylaxis and treatment of all influenza strains including, oseltamivir resistant seasonal influenza stains containing H274Y mutation in various preclinical studies [29]. It displayed a potent effect against the deadly H5N1 strain of avian influenza in preclinical studies [101]. Currently, a randomised phase III study is ongoing to evaluate the efficacy and safety of DAS181 to treat lower respiratory tract parainfluenza infection in immunocompromised patients. It also contains a sub study to evaluate the effectiveness of DAS181 on patients with severe covid-19. The estimated study completion date is December 31, 2023 [102].

To increase the effectiveness and duration of lung deposition of DAS181 formulations (DAS181-F03 and DAS181-F04), two phase I double -blind, randomized, placebo controlled single dose and multiple dose escalation studies with three cohorts were performed in healthy adults [99]. In the first trial, the cohort inhaled a single dose of 20 mg of DAS181-F03 powder or placebo (lactose monohydrate) for one day (one day cohort) or daily for ten days (ten-day cohort) [103]. In the second trial, the cohort inhaled 20 mg of DAS181-F04 powder or placebo daily for 3 days (three-day cohort) [104]. DAS181-F03 and DAS181-F04 formulations differed only in the excipient as DAS181-F03 did not contain MgSO4. The trial examined the safety, tolerability, pharmacokinetic and immunogenicity of larger particles of 10 μ DAS181 powder at a higher dose of 20 mg per day. It was suggested that the larger particle would provide a deposition in the upper respiratory tract and thereby reduce the systemic absorption. In addition, the higher dose would provide a prolonged effect clinically. The results showed that the formulation is well tolerated for up to seven days at a 20 mg daily dose. Prolonged administration of the drug for more than seven days caused severe respiratory effects and reduced forced expiratory volume by 1 s (FEV_1). Antibodies, IgG and or IgA were found in 15–18 subjects, 30 days after dosing. Only one subject from a single dose cohort developed IgE. It was believed the drug could safely be used against influenza virus infection only for a period limited to 5–7 days. Repeated administration of the drug was not advisable [99].

4.8. Rupintrivir

Rupintrivir also known as AG7088 is a selective and irreversible human rhinoviral 3C protease inhibitor. It is a synthetic compound with poor aqueous solubility and low oral bioavailability. Rhinovirus is the most common viral infection causing the common cold. The 3CP protease enzyme is responsible for the replication of rhinovirus. Rupintrivir binds and inhibits this enzyme and thus prevents the replication of rhinovirus in the respiratory tract cells [52,105–108]. Rupintrivir (AG7088) is developed by Agouron Pharmaceuticals Inc., San Diego, Calif, a subsidiary of Pfizer for the treatment of common cold [109].

In an initial phase II, clinical trial, 2% rupintrivir intranasal suspension was administered multiple times daily to 202 human volunteers, who were experimentally exposed to human rhinovirus just before 24 h of treatment. Rupintrivir was well tolerated with a 33% reduction in viral titre and a significant reduction in cold symptoms [29]. However, blood-tinged mucus and some nasal passage irritation were reported in test subjects [110]. Based on these results, rupintrivir progressed to large scale phase II/III trials to treat naturally occurring rhinovirus infections. In the US a large-scale multicentre trial was initiated at more than 50 sites. A double-blind, placebo controlled clinical trial was performed by giving intranasal rupintrivir to humans suffering from cold, within 36 h of first cold symptoms. Unfortunately, rupintrivir failed to show efficacy against naturally occurring human rhinovirus (HRV) infections and therefore, the development of intranasal rupintrivir is halted [111].

4.9. Remdesivir

Despite several deaths of humans worldwide due to covid-19 infection, there is no inhalable formulation of antiviral available for this pandemic. Scientists are working hard to get an effective and safe inhalable antiviral formulation for covid-19 infection. Remdesivir is such drug repurposed and under investigation for inhalation delivery. It is an antiviral drug that was developed for the treatment of Ebola virus infection. It is a prodrug of parent adenosine analogue, GS-441524. Several ongoing clinical trials have investigated the effectiveness of remdesivir against Covid-19 infection [112,113]. Currently, remdesivir is available in the form of a lyophilized powder for reconstitution, and concentrate solution. A group of researchers formulated remdesivir dry powder inhalation by thin film freezing [114]. The formulation was optimized using different carriers such as captisol, mannitol, lactose, and leucine and their different ratios. DPIs using leucine and captisol showed better aerosolization behaviour and good physical and chemical stability after one month of storage at normal room conditions. Captisol DPI also exhibited faster absorption of the drug into the blood in rats [114]. Another animal study showed conversion of remdesivir to GS-441524 both in the lungs and plasma of hamsters at the level sufficient to produce antiviral activity [115]. The effect of inhaled remdesivir against early stage Covid-19 was characterized in a recent clinical trial. However, the study was halted due to unsatisfactory lung deposition [116]. Another ongoing phase 1 clinical trial studies the safety, tolerability, and pharmacokinetics of inhaled nanoparticle formulation of remdesivir on healthy subjects [117].

5. Inhalation therapeutics of miscellaneous agents against respiratory viral infection

Several pharmaceutical industries are developing various inhalable formulations for the treatment of respiratory viral infections. Some of the formulations are under the clinical development phase. Triazavirin is an antiviral drug developed by Russia for per-oral delivery. It is in the clinical development phase against SARS-CoV-2 coronavirus. An animal study of triazavirin aerosol inhalation in mice showed 85% bioavailability that is nearly four times higher than that for the traditional per-oral delivery [118]. The use of intranasal liposomal poly ICLC has been explored for prophylaxis, and treatment as well as a vaccine adjuvant against the highly pathogenic avian influenza A/H5N1 virus [119,120]. Nasal administration of liposomal poly ICLC in mice before or shortly after influenza infection has shown inhibition of viral replication, providing a significant reduction in pulmonary viral titres and a higher survival rate of infected mice [121]. Intranasal administration of antiviral agents like CL-387626 [122], RF-641 [122–124], JNJ-2408068 [125–129] and AS-1411 [130] have shown good antiviral activity in various animal models for RSV infection. Poly ICLC [131,132], ALX0171 [133], ALN-RSV01 [134], and MDT-637 [135–137] were also studied in human subjects for their effectiveness against respiratory viral infections as shown in Table 2. Inhalation therapeutics of miscellaneous agents against respiratory viral infections in various animal models are given in Table 1.

Table 1
Inhalation therapeutics of miscellaneous agents against respiratory viral infection in various animal models.

Antiviral agents	Mechanism of action	Formulation and route of administration	Animal model	Clinical effectiveness	References
Triazavirin	Inhibits synthesis of viral RNA	Aerosol delivery of triazavirin solution using an ultrasonic nebulizer	Mice	SARS-CoV-2	[118]
Poly ICLC	Antiviral immune response via activation of Toll-like receptor-3 (TLR3) that produces INF-α, β, and γ to stimulate innate and adaptive immunity including natural killer cells' activation	Two intranasal doses (1 mg/kg body weight) of liposomal poly ICLC	Mice	Seasonal and avian influenza viruses	[120,138, 139]
CL-387626	Blockage of RSV fusion by targeting F protein	intranasal administration of a single 30 mg/kg dose	Cotton rats	RSV	[122]
RFI-641 (optimization of the lead compound CL-387626)	Blockage of viral F protein mediated fusion and cell syncytium formation	Intranasal administration of RFI-641 solution into the nostrils by using a micropipette	Mice, cotton rats and African green monkeys	RSV	[122–124]
JNJ-2408068 (formerly known as R170591)	Interacts with the F protein and inhibits RSV fusion	Small droplet aerosol inhaled by Aero-Mist nebulizer	Cotton rats	RSV	[125–129]
AS1411	Inhibits virus entry into the host cells	Intranasal administration (50 mg/kg)	Mice	An anticancer compound has been repurposed for RSV treatment	[130]

6. Inhalable formulation of non-antiviral drugs repurposed for Covid-19 infection

Several non-antiviral drugs are repurposed for the treatment of covid-19 infections [140]. However, the clinical trial data report from multiple drugs showed the ineffectiveness of hydroxychloroquine, ivermectin, lopinavir-ritonavir and interferon in covid-19 infection. The use of azithromycin is also not beneficial for a hospitalized covid patient based on negative recovery data from clinical trials [141]. As this article is focusing only on the inhalable formulation of respiratory viral infections, some inhalable formulations of non-antiviral drugs that are repurposed mainly for covid-19 infection are discussed below. However, these studies and hypotheses need to be validated using clinical trials.

6.1. Tamibarotene

Tamibarotene (Amnolake® Nippon Shinyaku and Tokyo, Japan) is a new synthetic retinoid drug currently available as a tablet for an oral suspension containing 2 mg of tamibarotene. It is used for the treatment of relapsed or refractory acute promyelocytic leukaemia in Japan. Tamibarotene is repurposed to give broad spectrum antiviral activity. However, the oral administration of this drug for the treatment of respiratory viral infections may give inadequate lung distribution. The high oral dose of tamibarotene to achieve effective concentration in the lung may cause toxic effects due to extensive systemic exposure. Recently a team of researchers from the University of Hongkong developed an inhalable dry powder formulation of repurposed tamibarotene by spray freeze-drying technique using 2-hydroxypropyl-β-cyclodextrin to increase the solubility of poorly soluble tamibarotene. The inhalable powder showed desirable physicochemical and aerodynamic properties for inhalation. The formulation gave rapid absorption and higher bioavailability compared with an intraperitoneal injection of the pure drug in animals. The formulation showed broad spectrum antiviral efficacy against SARS-CoV-2, Middle East respiratory syndrome coronavirus, and influenza A H1N1 virus in mouse and hamster models. The efficacy was comparable or superior to the commercially available remdesivir and zanamivir against a specific virus. There is no inhaled powder formulation available for Covid-19 treatment. Therefore, tamibarotene dry powder could be effective against covid-19 treatment, especially for prophylaxis and treatment for outpatients [142].

6.2. Hydroxychloroquine

Chloroquine and hydroxychloroquine are anti-parasitic drugs that have been repurposed for Covid-19 treatment. Inhaled hydroxychloroquine was studied in the treatment of Covid-19 infection [143]. It was recommended that inhaled aerosols of hydroxychloroquine at a lower dose level of 20 mg per day should be given in early prophylaxis and treatment [143]. Low dose of 2–4 mg per inhalation of hydroxychloroquine, is proposed to reach a sufficient therapeutic level in the lungs to give an antiviral effect [144]. However clinical trials didn't suggest any benefits of using these drugs in Covid-19 infection [145].

6.3. Colloidal silver

Based on previously experimented data on the antiviral effect of colloidal silver, inhalation of silver nanoparticles droplet aerosol was evaluated against Covid-19. The real effective minimum inhibitory concentration (MIC) of silver nanoparticles, in various respiratory locations was investigated. The effective MIC can be achieved using aerosolising dosages of 2 cc of a 100 μg/mL colloidal silver source for the upper airways and bronchial tree and 6 cc of a 200 μg/mL colloidal silver source for lung alveoli delivery. If a breath actuated ultrasonic nebulizer is used, this would be reduced by a factor of 3. It is concluded that early stage treatment of respiratory viral infection using colloidal silver nanoparticles can be effective [146].

6.4. Heparin

Repurposing of heparin, an anticoagulant in the treatment of SARS-CoV-2 is suggested in a focused review [147]. Unfractionated heparin has anti-inflammatory, mucolytic and antiviral activity [148]. Administration of unfractionated heparin via nebulizer is expected to inactivate the SARS-CoV-2 virus and prevent its entry into the host cell [147]. Inhaled freeze-dried plasminogen showed effectiveness in treating lung lesions and hypoxemia in patients suffering from Covid-19 infection [149].

6.5. Angiotensin-converting enzyme 2

Inhalation of angiotensin converting enzyme (ACE 2) to treat SARS-CoV-2 infection is hypothesized. It was proposed to produce modified recombinant soluble human ACE2 molecules, which resemble the molecules on the surface of respiratory mucosa. The molecules will be delivered via Respimat® inhaler to the newly diagnosed Covid-19 patients. It was assumed that the virus will bind to these modified molecules and don't infect the host cell [150].

Table 2
Example of inhaled antiviral drugs and their clinical development status.

Antiviral Drugs	Trade name (sponsor)	Dosage form	Delivery method	US FDA approval	Clinical development	Therapeutic indication	References
Ribavirin	Virazole®, Bausch Health US	Lyophilized powder to be reconstituted for inhalation solution (20 mg/ml)	Small particle aerosol generator (SPAG®-2) nebulizer	12/31/1985	Marketed	Respiratory syncytial virus (RSV) infection	[20]
Zanamivir	Relenza® GlaxoSmithKline, Middlesex, UK	Prophylaxis and treatment dose 5 mg	Inhalation	07/26/1999	Marketed	Influenza A and B infection	[161,162]
Laninamivir	Inavir®, Daiichi Sankyo Company Ltd, Tokyo, Japan and Biota pharmaceuticals, Alpharetta, USA	Prophylaxis dose: 20 mg Treatment dose: for adults 40 mg and for children <10 years old 20 mg	Inhalation	Not approved	Marketed (Japan only) since 2010	Influenza A and B infection	[55]
Interferon-β-1a (SNG001)	Synairgen Research Ltd.	Two syringes each containing 0.65 mL of nebulizer solution once a day to the hospitalized patients of Covid-19 for 14 days	Inhalation of nebuliser solution using ultra nebulizer	Trial failed	Phase III was completed on 10 February 2022	SARS-CoV-2 causing COVID-19	[86,87]
Cidofovir ((NanoFOVIR™)	Nanotherapeutics. Inc.	5 mg/kg dose of inhaled NanoFOVIR™ rabbit pox virus infecting rabbits	Inhaled dry powder	Trial failed	Preclinical trial	Variola major infection causing smallpox	[93]
Rupintrivir (AG7088)	Agouron Pharmaceuticals (Pfizer subsidiary)	Intranasal Rupintrivir (8 mg) sprays, two or five times a day as prophylaxis for 5 days or as a treatment for five times a day for 4 days	Nasal spray (2% suspension)	Trial halted	Phase II	Natural human rhinovirus (HRV) infection	[111,163]
Remdesivir (GS-5734™)	Gilead Sciences	31, 62 and 39 mg once a day for Part A, B, and C patients respectively for 5 days	Aerosolized solution	Trial halted	Phase I b/2a	Covid-19	[116]
Remdesivir (GS-5734)	NeuroActiva, Inc.	Inhaled formulation at a dose of 1 mg/kg once a day for 3 days or 2 mg/kg once a day for 5 days	Inhaled Nanoparticles	Ongoing trial	Phase I	SARS pneumonia	[117]
DAS181	Ansun Biopharma, Inc.	Nebulization of 4.5 mg qd for 7 or 10 days; and 2.5 mg qd for 7 or 10 days	Nebulization	Under investigation	Phase III	Human parainfluenza infection in immunocompromised persons	[102]
ALX-0171	Ablynx, Sanofi	3 mg/kg, 6 mg/kg, and 9 mg/kg	Inhalation	Under investigation	Phase IIb	RSV infection in infants and toddlers	[133]
MDT-637	Teva Branded Pharmaceutical Products, R&D Inc.	Twice a day administration of dry powder aerosol inhaler of MDT-637 at a dose of approximately 132 mcg	Dry powder aerosol inhaler	Trial discontinued	phase IIa trial	RSV-A	[136]
ALN-RSV01	Alnylam Pharmaceuticals	0.6 mg/kg via PARI eFlow® 30 electronic nebulizer	Nebulization	Under investigation	Phase IIb	Lung transplant patients infected with RSV	[164]
CS-8958	Daiichi Sankyo Co., Ltd.	Powder to be inhaled at a high dose of 40 mg and a low dose of 20 mg	Inhalation	Under investigation	Phase III	Human Influenza infection	[165]
FluMist® Quadrivalent	MedImmune, LLC	Vaccine administered in the form of intranasal spray at a dose of 0.1 mL per nostril, 1 or 2 doses	Intranasal	Initial U.S. Approval: 2003	Marketed	Influenza A or B infection	[37]
Poly-ICLC (Hiltonol®)	Oncovir, Inc.	Safety cohort (Cohort A): 2 cycles of study drug Expansion cohort (Cohort B): 3 cycles of study drug	Intranasal	Under investigation	Phase I-b	COVID-19	[131]
Hydroxychloroquine sulfate	Pulmoquine therapeutic, Inc.	Aerosolized hydroxychloroquine sulfate solution was administered via Aerogen nebulizer to the healthy volunteers at an initial dose of 20 mg (cohort A1, 1 ml of 20 mg/ml), with subsequent doses of 50 mg (Cohort A2, 1 ml of 50 mg/ml)	Oral aerosolized inhalation	Further studies were suggested	Phase I	SARS-Cov-2	[166]
Hydroxychloroquine	Mansoura university, Egypt	Covid patients receive supportive and symptomatic treatment directly through nebulization or using DPIs	Ready to use inhalable forms	–	Not applicable	Covid −19	[167]
Hydroxychloroquine		Healthy volunteers received hydroxychloroquine	Dry powder		Phase I	Covid-19	[168,169]

(*continued on next page*)

Table 2 (*continued*)

Antiviral Drugs	Trade name (sponsor)	Dosage form	Delivery method	US FDA approval	Clinical development	Therapeutic indication	References
	University medical center Groningen, Netherland	inhalations in a single ascending dose of 5, 10 and 20 mg, using Cyclops dry powder inhaler		Further studies were suggested			

6.6. Salinomycin

Repurposing of salinomycin, a broad-spectrum antibiotic in the form of inhalable nanostructured lipid carriers for SARS-CoV-2 is also hypothesized [151]. Salinomycin has shown a broad spectrum of antibacterial, antifungal, antiparasitic, antiviral and also antitumor activity [151]. The poor oral bioavailability and undesired systemic side effects restrict its use in covid-19. Encapsulation of salinomycin in nanostructured lipid carrier for pulmonary delivery can improve its absorption at the covid infection site [151].

6.7. Niclosamide

Niclosamide, a poorly water-soluble anthelmintic medicine has shown broad spectrum antiviral activity against SARS-CoV-2 infection. Inhalation of dry powders of niclosamide prepared by thin film freezing method has shown remarkable effect in SARS-CoV-2 infected rats and Syrian golden hamsters. After a single inhaled dose of the formulation, the drug remained in the lung for at least 24 h at a concentration more than the reported IC50 and IC90 for SARS-CoV-2 [152].

Inhalation and intranasal administration of niclosamide at doses up to 50.4 mg (6 mL of 1% niclosamide solution) and 2.5 mg respectively indicated an acceptable safety profile and tolerance in healthy volunteers [153].

6.8. Steroids

Inhalation of ciclesonide, a steroid has shown antiviral activity in three cases of Covid-19 infection [154]. It was reported that inhaled ciclesonide can remain in the lungs for a long time and thus inhibits viral proliferation and provide local anti-inflammatory effects.

6.9. Furosemide

Wang et al. [155], proposed repurposing of furosemide a loop diuretic in the treatment of covid-19. Inhaled furosemide can reduces lipopolysaccharides induced pro-inflammatory cytokines level [155].

6.10. HMG-CoA reductase inhibitors

HMG-CoA reductase inhibitors (statins) have been proposed in various studies to be used as an adjunctive therapy for Covid-19 [156–158]. It is proposed that statins may improve endothelial and vascular functions in covid-19 infected patients [159]. Statins have successfully tested in animals against influenza viruses. It is also shown from studies that the patients taking regular statins had a faster recovery from flu and lower mortality rates. Among various statins available, simvastatin, and rosuvastatin have shown activity against viral influenza [160]. Recently a hypothesis was made to use statins as aerosols to combat Covid-19. Statins would be given in two forms i.e., as a nasal spray and as an inhaler. The aim is to deliver statins as nasal aerosols directly into the lungs and destroy the lipid membrane of virus, causing virus death and reducing viral load in the lungs [160]. The already established cardioprotective and anti-inflammatory effects of statins would be added benefit in covid-19 therapy.

7. Conclusion

This review article tried to give details of the antiviral agents that can be administered in the form of aerosols. Table 2 contains examples of inhalable antiviral agents and their clinical development status. Unfortunately, there are very few approved inhaled antiviral agents for the treatment of respiratory viral infections. Several types of research, have been conducted for the formulation of inhalable dosage forms. However, very few studies are conducted on the preclinical and clinical levels. The lack of safety and efficacy data on inhalable antivirals is a matter of concern. It is hereby suggested that more clinical studies are essential to the further development of such advanced formulations. Viruses have developed various tremendous strategies to get unaffected by the existing antivirals. There is an urgent need for new virus-fighting drugs. As we know virus uses host cell machinery to grow and multiply in numbers, scientists are facing challenges to develop the antivirals that stop the virus without damaging the host cells too. However, the progress in knowledge of viral life cycles gives new opportunities to target these notorious pathogens. The changes in human behaviour, commercial globalisation, mass movement of large number of people, and environmental factors, create new opportunities for the spread and establishment of common or novel viral infections. It is difficult to predict the emergence of new viral infections. The recent global pandemic, COVID-19 caused considerable loss of human lives. However, the virus is still mutating itself and giving scientists new challenges to develop novel antivirals with unique and robust mechanisms of action that have broad spectrum antiviral activity. The high cost of developing new drugs, the specificity of an antiviral drug for one single infection, and the need for an accurate diagnosis of infection significantly limit antiviral drug development.

7.1. Future prospective

The scourge of COVID-19 has rushed scientists to find treatments. Unfortunately, viral infections require more cleverness from antiviral designers. The identification and testing of potential medications for unknown future infections and the early safety testing on humans would be beneficial for acting against any future viral outbreaks. Collaborative efforts of scientists, academic centres, pharmaceutical companies, and nongovernmental organizations are going on to develop novel antiviral treatments. During this time, industries and government agencies are investing more funds and resources in the development of antiviral drugs and vaccines. Scientist are focusing on developing an inhaled version of the existing antivirals for the treatment of respiratory infection. Various inhalable formulations of antiviral drugs are under clinical trial. It is expected that more antivirals would be available in the form of inhalation in a few years.

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