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Could Molnupiravir Have an Ameliorative Effect in Pets with COVID-19?

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Abstract: Since the last months of 2019, SARS-CoV-2, commonly referred to as COVID-19, has impacted the global economy and health care industries. Previous studies on SARS-CoV-2 have shown that it can also affect household pets. Coronaviruses have long been associated with pets, and prophylaxis is provided through vaccination programs. Today, although the levels of those requiring intensive care and death rates are decreasing through the extensive vaccination program initiated for humans, there is still no effective treatment for humans or pets. SARS-CoV-2 can spread and infect animals through similar mechanisms to that of humans. Like other types of coronavirus, Feline Infectious Peritonitis (FIP)-like multi-organ failure can develop in pets with COVID-19. Until now, supportive treatment has been performed to prevent severe cases and improve the quality of life. Molnupiravir, approved for emergency use by the FDA, is a prodrug of ribonucleoside analog with a low incidence of adverse side effects. Studies have shown that Molnupiravir has a preservative effect by preventing SARS-CoV-2 viral replication. Therefore we propose that Molnupiravir may also be used as a protective agent for pets and thus prevent multiple organ failures.

Keywords: COVID-19; pets; Molnupiravir; SARS-CoV-2; viral infection.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as the cause of prominent pneumonia cases in Hubei Province of China in late 2019 [1] [1]. Its rapid spread caused it to become a global pandemic. Daily increasing rates of mortality and morbidity caused alarm across the World, and this uneasiness caused people to ask various questions regarding COVID-19. One frequently asked question was whether COVID-19 could be transmitted from cats and dogs. At this time, there is no evidence to provide a definitive answer. Contrarily, many reports about domestic animals show that SARS-CoV-2 infected them and reported in the World Organisation of Animal Health (OIE) [2]. Infections mainly occurred in animals living in households with their owners or caretakers who had contracted COVID-19, showing the possibility of human-to-animal transmission [3]. While cats and ferrets showed high susceptibility to SARS-CoV-2, it was stated that dogs have a relatively low susceptibility

to the virus [4]. Studies have shown that other tissues, such as the lungs, are affected in these animals and humans [5]. However, no specific treatment has been found for COVID-19 in pets. Therefore, this study proposes that Molnupiravir may be a potential candidate for COVID-19 treatment in animals.

The SARS-CoV-2 infection leads to domestic pets' inconspicuous or mild digestive and respiratory problems, including diarrhea, vomiting, runny nose, breathing difficulties, and cough. Severe symptoms in pets appear extremely rare compared to humans but are not impossible. Since it causes health problems in animals and humans, its treatment in animals has also become an important issue. The broad-spectrum antiviral drug, Molnupiravir, is currently used for the emergency treatment of human coronaviruses, and it has also been reported to have a positive effect on Influenza. Due to the known positive effects of Molnupiravir, we suggest it may also be an effective treatment for cats and dogs infected with COVID-19.

2. Animal CoV Infections

Although the effects of coronaviruses are currently well known in humans, they also cause life-threatening diseases in livestock and domestic animals such as pigs, chickens, cows, dogs, and cats [6]. Bovine coronaviruses (BcoV) are a global concern affecting both the respiratory and enteric systems and causing severe diarrhea in calves. This has become a major fear of the cattle industry due to the severe losses it causes and the rapid spread among other ruminants [7]. A similar situation is found with the Transmissible gastroenteritis virus (TGEV) and porcine epidemic diarrhea virus (PEDV), which results in high mortality and morbidity in piglets [8]. Canine enteric coronavirus (CcoV) is a widespread infection in dogs and is highly associated with diarrhea [9]. Symptoms are mostly seen as mild diarrhea in young dogs, and if other pathogens are involved in the infection, more severe symptoms may occur [10]. Feline infectious peritonitis virus (FIPV) is a fatal infection of domestic cats caused by a specific strain of coronaviruses. The disease is mainly seen in cats younger than two years of age and presents in two forms, wet and dry [11]. The wet form refers to fluid accumulation in body cavities, whereas in dry FIPV, fluid accumulation is almost nonexistent. It also causes inflammation in one or more organs, such as the eyes, brain, intestine, or other body organs [12].

In general, FcoVs do not cause a severe illness, only mild diarrhea, as seen in CcoV. The virus that infects cats will replicate and mutate, causing a severe infection known as Feline infectious peritonitis (FIP). FIPV is macrophage trophic [13] and may cause an elevation in the rate of cytokine expression, known as a cytokine storm, resulting in more severe and lethal disease [14].

As previously mentioned, currently, there is no definitive treatment for COVID-19 in cats and dogs. On the other hand, although FIP has been considered an incurable disease for many years, only supportive treatment is applied, as in COVID-19. There are three main approaches to treating FIP [15]. The first approach is to modify the immune system of the patient affected by FIP. Cytokines are used to modify the immune system, but their efficacy is limited [12]. Since FIP is an immune-mediated disease, immunosuppressive drugs like dexamethasone are used to suppress the inflammatory response, which constitutes the second approach [15]. Thirdly, the use of antiviral drugs to inhibit FcoV replication directly [16]. In

addition, supportive treatment is applied to improve the patient's quality of life, including the drainage of fluid accumulated in the body and blood transfusions.

3. Pet Models for SARS-CoV-2

Various animal models, including domestic and laboratory animals, have been used to assimilate SARS-CoV-2 in fundamental clinical studies clinically. Before conducting experimental trials, it is necessary to consider whether the animals are suitable for a given human disease [7]. Animal models are not expected to mimic human disease exactly, only to meet specific criteria. To choose an animal model, evaluation is made under five main headings: species, complexity, disease simulation, predictivity, and face validity [17]. Species structurally and functionally closer to humans are considered the most suitable candidates [7]. The animal model should respond to any questions regarding the complexity of the disease down to the smallest detail and take advantage of this complexity of disease simulation. Other criteria required for the animal model to be considered appropriate are how the drug affects the outcome of the disease and how the animal reflects the symptoms [7]. As mentioned before, not every animal has the same susceptibility to the virus. Some are highly susceptible, others less susceptible, and some resistant. Since cats show high susceptibility to SARS-Cov-2, it has been the main topic of studies for this disease. Like cats, ferrets have also been frequently the subject of studies due to their susceptibility to SARS-CoV-2 [18]. Although dogs are susceptible to the virus, it is not as high as cats and ferrets. However, they still take part in the trials. Besides, mice, Syrian hamsters, Cynomolgus macaques, and Rhesus Macaques [19] are used as animal models for COVID-19. While viral RNA was present in rectal swab samples taken from dogs, it was not found in the organs of euthanized dogs. Only some infected dogs were seroconversion positive, which proved that dogs are mildly susceptible to SARS-CoV-2 [20].

Furthermore, the seroconversions and oral, nasal, and rectal swabs were mild in two dogs naturally infected by their owners. Their symptoms, which lasted around 14 days, were mild and disappeared within this time frame [20]. Unlike dogs, viral RNA was present in the soft palate, tonsils, trachea, and small intestine of euthanized cats, but it was absent from the lungs of those infected. Although, histological examination revealed massive lesions in the nasal and tracheal epithelium and lungs. A study on the susceptibility of cats to SARS-CoV-2 revealed that young cats show higher susceptibility to the virus than older individuals. Moreover, close contact of uninfected cats with infected ones increased susceptibility to the virus [18].

4. Covid-19 and Pets

SARS-CoV-2 spreads via respiratory droplets and aerosols [21]. Since the COVID-19 pandemic, it was only thought that there is the human-to-human transmission. However, many studies have reported the possibility of another route of transmission. The COVID-19 case in pets was firstly reported in Hong Kong, China, as the Pomeranian dog tested positive in February 2020. Shortly after, a German Shepherd dog in the same country was found to be positive for SARS-CoV-2 [22]. Also, a similar case was reported in a cat from Liège, Belgium, in late March 2020 [22]. Unlike dogs in China, illness-related symptoms were observed in cats, including diarrhea, vomiting, and difficulty in breathing [23]. While high positivity was found in the swab samples taken from the cat, it was weakly positive in dogs. These three cases

emerged because their owners also tested positive, indicating the potential for human-to-animal transmission. Studies have shown that animals living in a household get the illness from close contact with their positive tested owner or caregiver [24]. For instance, a tiger kept at the Bronx Zoo reported a COVID-19 positive by National Veterinary Services Laboratories (NVSLs) of the United States Department of Agriculture (USDA). This transmission is thought to have been caused by the asymptomatic SARS-CoV-2 positive zookeeper [22]. Another study was conducted in Northern Cyprus in March 2020; when the first case of COVID-19 was reported in Northern Cyprus, no infection was detected in domestic animals. As a result of ongoing studies, SARS-CoV-2 B.1.1.7 variant with N501Y mutation in the domestic cat was reported [4]. According to the World Organisation for Animal Health (OIE) [25], several similar cases regarding domestic animals have been reported in several countries (Russia, Germany, and the United States). Almost 50 cases of cat and dog COVID-19 have been reported in OIE, and it is thought that the spread of this infection among pets may pose a serious problem in the emergence of new mutations in the future [26, 27]. ACE2 receptor models in various species, including bats, ferrets, dogs, cats, and humans, have structural similarities [28], thus having similar affinity levels for SARS-CoV-2. Thereby, it is thought that the mechanism of action of COVID-19 in pets and humans may be almost the same.

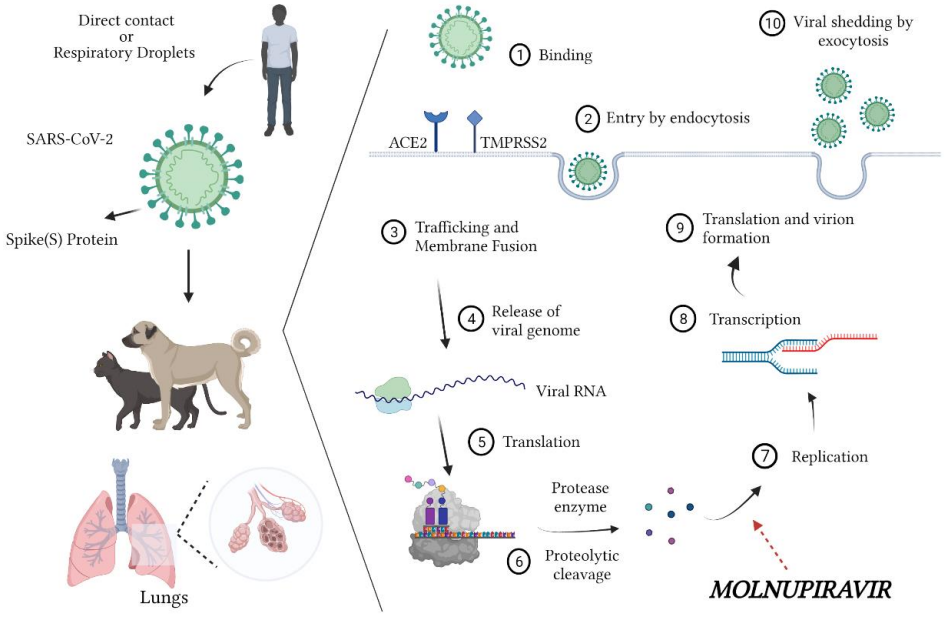

Figure 1. Possible mechanism of SARS-CoV-2 in pets. SARS-CoV is mainly transmitted from humans by direct contact or respiratory droplets and settles in the lung alveoli of pets and other animals. The virus binds to ACE2 and TMPRSS2 receptors in the host via its S proteins thereby, viral entry has begun(1) Entry of the virus to the host cell occurs by endocytosis(2) followed by internalization of the virus and fusion with a cell membrane(3) Then virus releases its viral genome into the cytoplasm of the host cell(4) and its translated to form polyproteins(5), that cleaved by protease enzymes(6) Its followed by the replication of the viral genome(7) and transcription of viral structural proteins(8) They translated and virion formation takes place(9) The virus then exits by exocytosis and spreads to other animals(10) This figure was created with BioRender.com.

5. Covid-19 and Molnupiravir

Coronaviruses belong to the family *Coronaviridae* and subfamily Orthocoronavirinae, consisting of four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus and Deltacoronavirus* [29]. The first two groups usually infect mammals. For instance, FCoVs

belong to the *Alphacoronavirus* [30], while SARS-CoV-2 is in the genus *Betacoronavirus* [31]. CoVs are in enveloped structure, and they are positive sense and single-stranded ribonucleic acid viruses with a size of about 26-32 kb [32]. Its virion is spherical and has four structural proteins on its surface: Nucleocapsid (N), Spike (S), Transmembrane (M), and Envelope (E). The S proteins can form a crown-like (corona in Latin) shape when viewed under an electron microscope, giving coronavirus its name [33] and playing a significant role in SARS-CoV-2s' invasion into the host, making it a therapeutic target. Angiotensin-Converting Enzyme 2 (ACE2) acts as a kind of stabilizer by counteracting ACE activity, which is a component of Renin Angiotensin Aldosterone System (RAAS) [34]. The virus enters and invades the host cell through these ACE2 and TMPRSS2 receptors and starts to replicate [35] (Figure 1). ACE2 is found in various tissues, including the heart, kidney, lungs, and even oral flora; they all become targets of the virus [36, 37], and it is stated that over-expression of the enzyme increases both replication and severity of the disease [38]. After virus replication, ACE2 activity decreases, which is followed by the activation of ACE1 enzyme and excessive release of interleukin (IL)-1, IL-6, and Tumor necrosis factor-a (TNF-a), known as proinflammatory cytokines [39]. Under normal conditions, these cytokines are essential to the body's immune response to infection [40]. However, their release in high amounts in a short time can lead to the development of a problem called acute respiratory distress syndrome (ARDS), resulting in multiple organ failure (MOF) [41]. Rapid over-expression of cytokines is defined as cytokine storm or hypercytokinemia and has been associated with severe symptoms and death due to COVID-19 [39]. Thus, a cytokine storm can turn a mild situation into a severe one. Dyspnea, one of the most well-known symptoms of COVID-19, turns into ARDS with the formation of the cytokine storm. Since both viral infection and cytokine expression play a role in the disease pathogenesis, treatment should be directed accordingly. While antiviral therapy forms the basis of the treatment, the use of immunomodulators is essential to control the exaggerated immune response of the host [42].

There is no specific treatment for COVID-19 today, but various drug groups and antiviral drugs are being tried for SARS-CoV-2 patients. Molnupiravir (EIDD-2801) is a potent candidate and has been the subject of many studies due to its effectiveness on human coronavirus [43, 44]. It is effective against many infections caused by RNA viruses, including Middle East respiratory syndrome coronavirus (MERS-CoV), influenza viruses, Venezuelan equine encephalitis viruses, and coronaviruses [45]. It is a prodrug of nucleoside derivative β-D-N^4-hydroxycytidine (NHC) triphosphate in third-phase clinical trials. It exerts its antiviral effect through copying errors during viral replication [45]. In other words, it blocks an enzyme required for viral replication and thus reduces viral RNA in SARS-CoV-2 patients (Figure 1).

Molnupiravir was recently approved in the UK for its use in COVID-19 treatment [46]. Unlike other approved antiviral drugs used for the treatment of COVID-19, molnupiravir is administered orally. A previously published study reported that twice-daily administration of EIDD-2801 to infected ferrets reduces the viral burden in the upper respiratory tract and prevents transmission to uninfected animals [47]. Additionally, there are studies involving Molnupiravir on Influenza in ferret models, which have been proven to have a dose-dependent effect [48]. Influenza, which is very common worldwide and causes severe symptoms, particularly in older adults and the immunocompromised, is an infectious disease we often encounter in animals [49]. There is a vaccine-like COVID-19, but various antiviral drugs have been tried with limited effectiveness. The results of these studies [47, 50] and the fact that Influenza has similar symptoms, such as coughing, fever, and muscle and body pain, just as

COVID-19, have provided us with a possible window of opportunity. It does not show any toxicity and adverse side effects, making it suitable for clinical use for COVID-19 [51]. It impacts cytokines during and after the virus enters the host cell, as it has a pleiotropic effect. For the body to fight the virus, high interferon levels are observed; first, which then decrease, preventing the severe effect of a cytokine storm [47]. Currently, another nucleoside analog, Remdesivir, is used as an antiviral drug in the COVID-19 treatment. Concurrently, it has been proven that Molnupiravir is 2-10 times more potent than Remdesivir in preventing viral replication [52]. In addition, Remdesivir synthesis is expensive and complicated, and its intravenous administration makes it unsuitable for pandemic conditions [51]. Thus, attention has turned to develop another SARS-CoV-2 replication inhibitor, Molnupiravir.

6. Conclusions

In light of these findings, it has been shown that COVID-19 can pass from humans to pets by similar mechanisms and cause cytokine expression. SARS-CoV-2 can cause symptoms similar to those in humans, especially cats, and even cause multiple organ failure, as in FIP caused by other coronaviruses such as FCoV. Currently, agents used in FIP treatment have been tried in pets infected with COVID-19, but a complete treatment has not yet been provided. When we evaluated the mechanism of action of Molnupiravir on COVID-19, it was stated that it inhibited cell proliferation by preventing replication and thus showed a protective effect. However, Molnupiravir has not been tested in clinical practice in veterinary medicine until today. Therefore, we think that this drug, which has a low potential for side effects, may have a therapeutic effect on possible COVID-19 disease in pets and thus prevent multiple organ damage.

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Conflicts of Interest

The authors declare no conflict of interest.

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