Review Article

UPDATE ON COVID-19 INFECTION AND IVEMECTIN TREATMENT

Abstract

Coronaviruses are a group of related RNA viruses that cause disease in mammals and birds. Covid-19 infection is caused by a single stranded RNA virus called SARS-CoV-2 that is similar to the severe acute respiratory syndrome coronavirus (SARS-CoV). The aim of this review is to identify how covid-19 infects man, the preventive approach and treatment possibility with ivemectin drug. The possible main source of transmission is thought to be a close contact with infected person or animal and respiratory droplets while the mucous membrane; conjunctiva, mouth, nasal cavity, and throat are the main routes of transmission. The virus enters the human through the ACE2 receptor which are found in the mucous membrane. This is an important step for coronavirus infection establishment. To stay safe from coronavirus, physical distancing, wearing of face mask, keeping rooms well ventilated, avoiding crowds, cleaning/washing your hands, the use of hand sanitizers and coughing into a bent elbow are precautionary measures to avoid contracting the infection. Ivemectin blocks the initiation of the binding of the viral protein to the cytoplasmic receptor (imp α/β). The inhibitory role of ivemectin prevents further increase in the viral load. Ivemectin drug could be a remarkable medical breakthrough for the lasting treatment of the infection, however, more clinical trials are suggested in this area.

Keywords: ivemectin, covid-19, infection, SARS-CoV-2

1.0 Introduction

Coronaviruses are a group of related RNA viruses that cause disease in mammals and birds. In humans and birds, they cause respiratory tract infections that can range from mild to lethal. Mild illnesses in humans include some cases of the common cold (which is also caused by other viruses, predominantly rhinoviruses), while more lethal varieties can cause SARS (Severe Acute Respiratory syndrome), MERS (Middle East Respiratory Syndrome), and COVID-19. In cows and pigs they cause diarrhea, while in mice they cause hepatitis and encephalomyelitis. Coronaviruses constitute the subfamily orthocoronavirinae, in the family coronaviridae, order Nidovirales, and realm Riboviria. (Fan, *et al.*, 2019). They are enveloped viruses with a positive-sense single-stranded RNA genome and a nucleocapsid of helical symmetry. (Cherry, *et al.*, 2017). The genome size of coronaviruses ranges from approximately 26 to 32 kilobases, one of the largest among RNA viruses. (Woo, *et al.*, 2010). They have characteristic club-shaped spikes that project from their surface, which in electron micrographs create an image reminiscent of the solar corona, from which their name derives. A novel coronavirus (nCoV) is a new strain that has not been identified in humans previously. Once scientists determine what coronavirus it is, they give it a name, (as in the case of COVID-19, the virus causing it is SARS-CoV-2). Most coronaviruses are not dangerous. (WebMD, 2020).

Table 1.0: Below is a table, showing the comparative analysis of biological features of SARS-CoV and SARS-CoV-2.

Features	SARS-CoV	SARS-CoV-2	References
Emergence date	November 2002	December 2019	(Hui, *et al.* 2020 and huang, *et al.* 2004).
Area of emergence	Guangdong, China	Wuhan, China	
Date of fully controlled	July 2003	Not controlled yet.	
Key hosts	Bats, palm civets and Raccon dogs.	Bat	(Lu, *et al.* 2020, Perlman, 2020, and Bolles, *et al* 2020)
Number of countries infected	26	109	(Vera, 2020)
Entry receptors in humans	ACE2 receptor	ACE2 receptor	(Vera, 2020), Derebail, *et al.*, 2020, and Shi, *et al*. 2003)
Signs and symptoms	Fever, malaise, myagia, headache, diarrhea, shivering, cough, and shortness of breath	Cough, fever, and shortness of breath	(Riou, *et al.* 2020, Chan, et al. 2003)
Disease caused	SARS, ARS	SARS, COVID-19	(Shi, *et al.*, 2003)
Total infected patients	8098	3.27m	(Austin, 2020)

Total recovered patients	7322	1m	
Total died patients	776 (9.6% mortality rate)	235000 (3.6% mortality rate)	(Austin, 2020)

2.0 Sources of Infection

The source of origination and transmission are important to be determined in order to develop preventive strategies to contain the spread of the infection. In the case of SARS-CoV, the researchers initially focused on raccoon dogs and palm civets as a key reservoir of infection. However, only the samples isolated from the civets at the food market showed positive results for viral RNA detection, suggesting that the civet palm might be secondary host. (Ken, *et al.*, 2005). In 2001, the samples were isolated from healthy persons of Hongkong and the molecular assessment showed 2.5% frequently rate of antibodies against SARS-coronavirus. These indications suggested that SARS coronavirus may be circulating in humans before causing the outbreak in 2003. (Zheng, *et al.*, 2004). Later on, Rhinolophus bats were also found to have anti-SARS-CoV antibodies suggesting the bats as a source of viral replication (Paden, *et al.*, 2018). The Middle East Respiratory Syndrome (MERS) coronavirus first emerged in 2012 in Saudi Arabia (Memish, *et al.,* 2013). MERS-coronavirus also pertains to beta-coronavirus and having camels as a zoonotic source or primary host. (Paden, *et al.*, 2018).

In a recent study, MERS-coronavirus was also detected in Pipistrellus and transmitting medium of the virus (Huynh, *et al.*, 2012 and Lau, 2013). Initially, a group of researchers suggested snakes be the possible host, however, after genomic similarity findings of novel coronavirus with SARS-like bat viruses supported the statement that not only bats could be the key reservoirs. Further analysis of homologous recombination revealed that receptor binding spike glycoprotein of novel coronavirus is developed from a SARS-CoV (CoVZXC21 or CoVZC45) and yet unknown Beta-o Paden, *et al.* 2018. (Chan, *et al.,* 2020). Nonetheless, to eradicate the virus, more work is required to be done in the aspects of the identification of the intermediate zoonotic source that caused the transmission of the virus to humans.

3.0 Route of Transmission

The high transmission rate of coronavirus has raised many questions about the possible means of infection transmission. Due to uncertainty of the main transmission routes, the infection control policies were faced with more challenges. The possible main source of transmission is thought to be the close contact and respiratory droplets. (Falahi *et al.*, 2020). The mucous membrane (conjunctiva, mouth, nasal cavity, or throat) is the main transmission route. Coronavirus gains entry into the host cell by recognizing and binding to the host receptor ACE2 distributed from the conjunctiva (Wan *et al.*, 2020). A larger amount of the virus were assembled and release into the human lungs through the respiratory tract, resulting in various types of fever, cough, or ground-glass opacity of lung on CT examination results or even respiratory failure (Huanjie *et al.*, 2020). SARS-CoV-2 mainly spread from person to another via small respiratory droplets from the nose or mouth when a person confirmed with Covid-19 coughs or exhales. These droplets lands on objects and surfaces around a person. Others may become infected by breathing in the droplets or touching these surfaces or objects, then touching their eyes, nose, or mouth. The risk of contracting SARS-CoV-2 from someone without symptoms is very low. However, many people with SARS-CoV-2 experience only mild symptoms, particularly true in the early stages of the disease. Some cases reported that the conjunctivitis was the first symptom and they had a history of close contact with infected persons. (Chen, *et al.*, 2020; Lu, *et al.*, 2020). There is a speculation that there may be a risk of tears and conjunctival transmission. Growing evidence shows that the virus attacks multiple organs in the body.

3.1 Eye Infection and Ocular Route

During the SARS-CoV-2 outbreak, some patients developed symptoms of conjunctivitis. Some even suffered the ocular diseases in clinical diagnosis before fever and cough (Chen, *et. al.*, 2020). There have been case reports in which many ophthalmologists were found to be infected through routine diagnosis and treatment with only their eyes unprotected (Chen, *et al.*, 2020; Xia, *et al.*, 2020). Therefore, if conjunctivitis as the initial symptom of confirmed COVID-19 patients was neglected and contracted without comprehensive measures, the infectious tears and body fluids containing the virus could infect other persons (Belser, *et al.*, 2013; Lu, *et al.*, 2020). Those results suggested that the eyes route of transmission existed (Chen, *et al*., 2020; Huang, *et al.*, 2020). According to Deng, *et al*. (2020), macaques can be infected with SARS-CoV-2 via conjunctival route. Huanji, *et al*., (2020) suggests that the SARS-CoV-2 transmitted and infected via eyes including two routes. One is direct contact and the other is indirect contact transmission. The direct route is that droplets with virus enter through the eyes. Another route is through indirect contact infection, that is, accidentally touching the virus droplets with your hands and rubbing those hands on your nose or eyes which may cause conjunctival infection. Once SARS-CoV-2 has infected and replicated in the eyes, it will be transmitted through two ways; outward transmission, eye secretion, or tears with virus contaminating the hands, and then there is a risk of viral through the hands. Another route is an inward transmission. If the virus infects a person via the eyes, conjunctival secretions, and tears can flow into the mouth through the nasopharyngeal tube which will ultimately reach the lungs or gastrointestinal tract and more infections may occur. Moreover, increasing reports each day suggests that SARS-CoV-2 cases began with eyes redness and tingling as the leading symptoms, and the literature also suggests that viruses can infect the human body through the conjunctiva. (Lu, *et al.,* 2020; and Wang, *et al.,* 2020). These outcomes showed that few new cases of COVID-19 began with conjunctivitis as the first symptom, and SARS-CoV-2 contained on the eye surface may enter into the nasal cavity and throat through drain tears. SARS-CoV-2 can be transmitted through the nose-eye, possibly via the way of increased oral pressure caused by coughing or sneezing, and reverse transmission of the virus through the nasolacrimal duct to the dacryocyst and then infect the conjunctival cornea. (Sun, *et al.,* 2020; Zhou, *et al.,* 2020). Thus, this route is a two way transmission route. The lacrimal route via the drainage of tear fluid including virus from punctum in the upper and lower eyelid through canaliculi to the lacrimal sac, and further through the nasolacrimal duct to the nasal cavity, would be another pathway available for SARS-CoV-2 infection. During replication in the ocular tract, there will be a continuous influx of virions to the nasal cavity, and respiratory infection maybe established. The possibility of subclinical and/or prolonged virus replication in the eye, followed by continuous transfer to the respiratory tract cannot be excluded.

3.2 Fecal-Oral Transmission Route

Generally, many respiratory pathogens, such as influenza, SARS-CoV and MERS-CoV, cause enteric symptoms, so is SARS-CoV-2 (Holshue, *at al.,* 2020). Diarrhea was observed in a considerable number of patients. In early reports from Wuhan, 2-10% of patients with COVID-

19 had gastrointestinal symptoms such as diarrhea or vomiting. Abdominal pain was reported more frequently in patients admitted to the intensive care unit than in individuals who did not require intensive care, and120% of patients presented with diarrhea and nausea 1-2 days before the development of fever and respiratory symptoms (Yeo, *et al.*, 2020). The study found that the detection of SARS-CoV-2 nucleic acid positive in a few feces of patients with confirmed COVID-19 cases indicated the presence of a live virus. Nashan Zhong and Lanjuan Li teams have isolated SARS-CoV-2 from the fecal swab specimens of the pneumonia patient with COVID-19 separately. These findings showed the presence of live viruses in the feces of patients. Fecal transmission mode accounts for a small proportion of respiratory virus transmission. Most of the virus transmitted through the feces are enteroviruses, and respiratory viruses are mainly transmitted through droplets and contact. However, more than 15% of cases showed that the anal test of several patients had become positive at the later stage, while the chest radiographic evidence and viral clearance in respiratory samples from the upper respiratory tract showed significant improvement, so fecal formation route cannot be ignored. Pan, *et al*. (2020) reported that the viral load of the stool samples were less than those of the respiratory samples, so whether the excretion of feces in vitro during the recovery period is infectious remains to be further studied. Considering the evidence of fecal excretion of SARS-CoV-2, the virus can also be transmitted via the fecal-oral transmission route or retransmitted via the formation of aerosols in virus containing feces. The transmission route of the tract may not be a single transmission. It may be a medium for other routes.

4.0 Pathogenesis

4.1 Key Features and Entry Mechanism of Human Coronavirus

All coronaviruses contain specific genes in ORF1` downstream regions that encode proteins for viral replication, neuclocapsid and spikes formation (Van, *et al.,* 2012). The glycoprotein spikes on the outer surface of coronaviruses are responsible for the attachment and entry of the virus into host cells. The receptor-binding domain (RBD) is loosely attached among virus, therefore, the virus may infect multiple hosts. (Raj, *at al.* 2013; Perlman, *at al*. 2009). Other coronavirus recognize aminopeeptidases or carbohydrates as a key receptor for entry to human cells while

SARS-CoV and MERS-CoV recognize exopeptidases (Wang, *et al.,* 2013). The entry mechanism of a coronavirus depends on the cellular proteases which includes, human airway trypsin-like protease (HAT), cathepsins and transmembrane protease serine 2 (TMPRSS2) that split the spike protein and establish further penetration changes (Glowacka, *et al.*, 2011; Bertram, *et al.*, 2011). MERS-CoV employs dipetidyl peptidase 4 (DPP4), while HCoV-NL63 and SARS-CoV require antigiotensin-converting enzyme 2 (ACE2) as a key receptor (Wang, *et al.*, 2013; Raj, 2013). SARS-CoV-2 possesses the typical coronavirus structure with spikes protein and also expressed other polyproteins, nucleoproteins, and membrane proteins, such as RNA polymerase, 3-chymotrypsin-like protease, papain-like protease, helicase, glycoprotein, and accessory proteins (Wu, *et al.,* 2020; Zhou, *et al.*, 2020).

5.0 Preventive Measures

According to the World Health Organization (WHO), the following guidelines if followed will help to curb the spread of coronavirus. To stay safe from coronavirus, precautions such as physical distancing, wearing of face mask, keeping rooms well ventilated, avoiding crowds, cleaning/washing your hands, the use of hand sanitizers and coughing into a bent elbow or tissue. The following measures can also be taken to prevent infection from the virus: maintaining at least 1-meter distance between yourself and others to lower the risk of infection when they sneeze, cough, or speak. Maintain an even greater distance between yourself and others when indoors. The further away, the better; make wearing mask a normal part of being around other people. The appropriate use, storage, and cleaning or disposal are essential to make masks as effective as possible (WHO 2021). WHO further advises that we thoroughly maintain good hygiene by regularly and thoroughly cleaning our hands with alcohol-based hand rub or wash them with soap and water. We must also avoid touching our eyes, nose, and mouths; clean and disinfect surfaces frequently especially those which are regularly touched, such as door handles, faucets and phone screens (WHO 2021). For those who feel unwell, the following guidelines are to be followed as directed by the WHO. Know the full range of the symptoms of coronavirus of which the most common are, fever, dry cough, and tiredness. Other symptoms that are less common and may affect some patients includes loss of taste or smell or both, aches and pains, headache, sore throat, nasal congestion, red eyes, diarrhea, or skin rash. WHO advised that anyone with the slightest of the symptoms such as fever, cough, or headache should stay at home and self-isolate, while those who have fever, cough, and difficulty in breathing should seek medical attention immediately by first calling by telephone, or following the direction of their local health authority, (WHO, 2020).

6.0 Ivemectin Treatment

Ivemectin is a broad spectrum anti-parasitic agent that has been recently discovered to have a broad spectrum of anti-viral activity. (Gotz, *et al.,* 2016). Covid-19 infection is caused by a single stranded RNA virus called SARS-CoV-2 that is similar to the severe acute respiratory syndrome coronavirus (SARS-CoV). Studies on the virus (SARS-CoV) provided suggestions that ivemectin could be effective against SARS-CoV-2.

6.1 Mechanism of Covid-19 Infection

Coronavirus is a single stranded virus enveloped with proteins. The viral protein binds with importin α/β (a nucleo-cytoplasmic transit receptor) that is responsible for mediated transport of viral proteins in and out of the nucleus of the host cell. The binding results in the translocation of the virus into the nucleus of the host cell, therefore, directing the activities of the host cell to replicate, produce more virions, enhance infection and reduce antiviral response. (Caly, *et al.,* 2020).

6.2 Mode of Action of Ivemectin

Ivemectin blocks the initiation of the binding of the viral protein to the cytoplasmic receptor (imp α/β) which is necessary for the transport of the virus to the nucleus where it alters host cell activities. The inhibitory role of ivemectin prevents further increase in the viral load since the replication process was interrupted.

In an in-vitro study conducted by Caly, *et al.,* (2020), cells infected with SARS-CoV-2 were treated with a single dose of 5uM of ivemectin. After 24hours, RT-PCR results showed 93% reduction in viral RNA present in the supernatant, meaning unreleased of virions in sample treated with ivemectin while 99.8% reduction was reported in cell-associated viral RNA meaning unreleased of unpackaged virions with ivermetin treatment. Further incubation to 48hours showed a reduction in the viral load by 500 folds in 48hours after treatment. No toxicity was reported in the study. Since ivemectin is FDA-approved parasitic drug that has been in use for a long time without any cause of withdrawing the drug from the market could mean that the drug is relatively safe for use, hence the safety of the drug may not be a clinical concern however, more clinical trials are required to validate biological trials before considering the drug effective for treatment of covid-19 infection.

Conclusion

Covid-19 is a global pandemic with identifiable routes of transmission and prevention plans. The study of ivemectin drug could be a remarkable medical breakthrough for the lasting treatment of the infection. While WHO and other drug regulatory agencies are yet to endorse ivemectin for the treatment of covid-19 infection, more studies are needed on the therapeutic and toxic effect of ivemectin with established dosage for human.

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