Biomedical Communication

Corona Virus Disease 2019: Origin, Transmission, Diagnosis, Vaccine and Treatment: A Review Article

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ABSTRACT

Corona virus is considered as the major pathogen that primarily threats the human respiratory system. Corona virus has been known to cause a systemic infection, which means affecting the entire body in its specific host. Moreover, natural recombination makes some of them capable to adapt greatly and jump the species barrier, causing pandemics or epidemics. Previous corona virus outbreaks that have been characterized as pathogens, caused a serious problem to public health including the Middle East respiratory syndrome (MERS)-CoV, and the severe acute respiratory syndrome (SARS)-CoV. In December 2019, the first case was reported. The emergence of Novel Corona virus named as Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2), which is considered the causative agent of Corona Virus Disease 2019 (COVID-19). The genome of SARS-CoV-2 is 29.9 kb. In SARS-CoV-2 the conventional methods were used to detect any viral infectious which mainly depends on the computed tomography, serology and molecular tests. The commonly molecular technique used to detect the presence of SARS-CoV-2 is reverse-transcription polymerase chain reaction (RT-PCR). However, there are several drugs available that have high antiviral activity against viruses especial SARS-CoV-2 as camostat mesylate and umifenovir. The mainly route of transmission is person-to-person contact with either symptomatic or asymptomatic patients. ORF8 is an accessory protein that considers one of the more rapidly evolving proteins in beta corona virus. There are many different functions of SARS-CoV-2 ORF8.

KEY WORDS: CORONA VIRUS, COVID-19, ORF8, RT-PCR, SARS-COV-2, WUHAN CITY.

INTRODUCTION

Corona virus is considered as the major pathogen that primarily threats the human respiratory system and has been known to cause a systemic infection that means affecting the entire body in its specific host (Su et al., 2016; Rothan & Byrareddy, 2020). Moreover, natural recombination makes some of them capable to adapt greatly and jump the species barrier, causing pandemics or epidemics (Bchetnia et al., 2020). This infection may lead to serious symptoms and mortality (Bchetnia et al., 2020). Previous corona virus outbreaks have been characterized as pathogens that caused a serious problem to public health including the Middle East respiratory syndrome (MERS)-CoV and the severe acute respiratory syndrome (SARS)-CoV (Rothan & Byrareddy, 2020). There are other four families of Corona virus known to cause mild respiratory infection in human to include: 229E, OC43, NL63 and HKU1 (Xia et al., 2016). However, those viruses have an envelope characterized by spikes on their surface under the electron microscope like a crown. The presence of these projections gives it the name of Corona virus. These viruses are considered as positive-sense RNA viruses ranging from 60 nm to 140 nm in diameter (Chan-Yeung and Xu, 2003, Walls et al., 2020).

Here we present the appearance of corona virus over time (https://www.who.int). First of all, the emergence of the severe respiratory syndrome was in 2002 in the Guangdong province of southern China, then prevailed to the five continents (https://www.who.int). The new Corona virus origin in bats and then spread to human by the intermediate host of raccoon dogs and palm civet cat (Chan-Yeung & Xu, 2003; Kan et al., 2005; Wang et al., 2006). In 2003, the virus was identified and given the name Severe Acute Respiratory Syndrome Corona virus (SARS-CoV) (https://www.who.int.; Memish et al., 2013). However, SARS-CoV affected 8422 people, and the majority of cases were in Hong Kong and China (Memish et al., 2013). The mortality rate of SARS-Cov reached up to 11% (https://www.who.int.) (Memish et al., 2013). In 2012, the novel Corona viruses of bat origin, emerged in the Kingdom of Saudi Arabia

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(Memish et al., 2020) and then spread to 27 countries (Walls et al., 2020).

It was identified as the Middle East respiratory syndrome corona virus (MERS-CoV), affected 2494 individuals with 858 deaths (the mortality rate of 34 %) (Walls et al., 2020). The inter mediator host of MERS-CoV was found to be the dromedary camels (Memish et al., 2013; Raj et al., 2014; Walls et al., 2020). In late 2019, a group of patients visited a hospital in China, they were suffering from pneumonia of an unknown etiology (Bogoch et al., 2020; Wang et al., 2020; Yang et al., 2020). Epidemiologically these patients associated with wet animals and seafood wholesale market whereas many wildlife species are being sold such as frogs, bats, birds, rabbits and snakes in the Wuhan City of Hubei Province of China (Bogoch et al., 2020; Wang et al., 2020; Yang et al., 2020). However, the potential outbreak of corona virus was early predicted by given the estimate of a reproduction number for the Novel Corona virus which was considered significantly larger than 1 (range from 2.24 to 3.58) (Bogoch et al., 2020; Wang et al., 2020; Yang et al., 2020).

In December 2019, the first case was reported (Yang et al., 2020). Then, from the 18th to the 29thof December 2019, five patients were suffering from an acute respiratory syndrome and one among these patients died (Yang et al., 2020). On January 2ed, 2020, 41 patients have been laboratory-confirmed COVID-19 infection, less than half of these patients were suffering from chronic disease as, cardiovascular disease, diabetes and hypertension (Yang et al., 2020). COVID-19 is rapidly prevalence from the Wuhan City of China to the whole world (Wang et al., 2020) and is capable to infect children with minor effect (Chawla et al., 2020).

The novel Corona virus named as Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2), which is considered the causative agent of COVID-19 (Al-Tawfiq & Memish, 2020). SARS-CoV2 had generated a new century of pandemic in late 2019 in Wuhan City of Hubei Province, China (Al-Tawfiq & Memish, 2020). On 22 March, 292.142 confirmed cases among them 12,748 death reported by the World Health Organization (Al-Tawfiq & Memish, 2020). Although China was the epicenter of COVID-19, the number of new cases seemed to rapidly decline (Al-Tawfiq & Memish, 2020). Subsequently, the new epicenter was the Eastern Mediterranean region (EMR) and Europe (Al-Tawfiq & Memish, 2020). As in mid-March of 2020, the total number of cases reached 18,060 with 1010 death and 19 out of 22 countries affected reported by the WHO EMR, the majority of cases was in the Islamic Republic of Iran (Al-Tawfiq & Memish, 2020).

On the 12th of July 2020, the number of cases reached 12,698,995 with 564,924 death (2.3 %)(Li & Ren 2020). Until now, SARS-CoV-2 affected 214 countries and territories and the most affected countries were Europe and America with 4,051,387 and 7,748,030 respectively (Li et al., 2020). As on January 30, 2020, SARS-CoV-2 has reported epidemics as a public health emergency of international concern by the World Health Organization (Li et al., 2020). However, on March 11, 2020, WHO declared that SARS-CoV-2 changed from epidemic to pandemic (Li et al., 2020). It was found that SARS-CoV, MERS-CoV and SARS-CoV-2 originated from the bat (Zhou et al., 2020). In SARS-CoV-2 suggest the potential intermediate hosts are snakes and pangolins but this requires more confirmation (Lam et al., 2020; Wan et al., 2020).

The key success of viruses is their evolution (Sanjuán and Domingo-Calap, 2016). Moreover, the type of nucleic acid is one of the main factors that affect the mutation type and subsequently the evolution (Sanjuán & Domingo-Calap, 2016). In addition, RNA viruses and single strain-viruses mutate rapidly than DNA viruses and double-strain viruses (Sanjuán & Domingo-Calap, 2016). These mutations have an impact on the pandemic particularly if they increase the severity of illness as in the severe acute respiratory syndrome corona virus (SARS-CoV-2) (Sanjuán & Domingo-Calap, 2016). The Discovery of novel variant is through sequencing (Leung et al., 2021). The Covid-19 genomics UK consortium performs sequencing for more than 200,000 viruses until date (Tang et al., 2020). January 18th 2021, which revealed the identification of highly infectious variants B1.1.7 and found another similar variant in South African B1.351 (Tang et al., 2020).

Now, the new variant in the UK spread to Australia and Europe (Elfiky & Ibrahim). However , the new variant in the UK reveals nine different mutations for the spike protein (D1118H, D614G, 69–70, S982A, 145, T716I, N501Y, P681H and A570D) (Elfiky & Ibrahim). N501Y mutation present in both variants of SARS-CoV-2 (Elfiky & Ibrahim). N501Y mutation is located in the receptor-binding domain (RBD) of the spikes which is known to interact with the receptor of host cell ACE2 (Elfiky & Ibrahim). The ACE2 is responsible for the recognition and entry into the host cell (Elfiky & Ibrahim). The genome of SARS-CoV-2 is 29.9 kb (Wu et al., 2020). It has 14 open reading frame that encodes 27 proteins (Malik et al., 2020; Wu et al., 2020).

In 5'-terminal region of the genome, 15 non-structural proteins essential for viral multiplication encoded by ORF1 and ORF2 (Malik et al., 2020; Wu et al., 2020). Meanwhile, the 3-terminal region of the genome encodes functional structural proteins as, an envelope protein (E), spike (S), membrane protein (M), nucleocapsid (N) and 8 accessory proteins (Malik et al., 2020; Wu et al., 2020). The computational genomic analysis and phylogenetic revealed that to invade the host's cell, SARS-CoV-2 differs from MERS-CoV which utilizes (DPP4) and shares with SARS-CoV the same human cell receptor (ACE2) (Wan et al., 2020). However, ACE2 is an ectoenzyme receptor attached to the plasma membrane of the host cell, present in many tissues including the kidney, lower respiratory tract, gastrointestinal tract and heart (Imai et al., 2010). The structure pattern analysis suggests SARS-CoV-2 binds with ACE2 by greater affinity about more than 10 folds than SARS-CoV, thus provides more than the threshold desired for viral infection (Wrapp et al., 2020).

The main antigen presented on the envelope of the virus is a spike protein which consists of ~ 150 kDa (Letko et

al., 2020).Consequently, spikes form a transmembrane homotrimer prominent from the surface of the virus to bind to the host's receptor (ACE2) (Qinfen et al., 2004; Weiss & Navas-Martin, 2005). Spike protein consists of two main functional subunits, the first one called subunit S1, plays a role in binding to the host's cell receptor ACE2, and the second is called subunit S2,it is important for viral fusion process to the host-cell surface (Qinfen et al., 2004; Weiss & Navas-Martin, 2005). Since, SARS-CoV-2 are enveloped viruses , the virus is able to enter the host cell by endocytosis (Qinfen et al., 2004; Weiss & Navas-Martin, 2005, Letko et al., 2020).

Phylogenetic analysis revealed that SARS-CoV, SARS-like corona virus and SARS-CoV-2 which was isolated from bats belong to another clade that differs from MERS-CoV (Lu et al., 2020; Zhou et al., 2020). The whole-genome identify between SARS-CoV-2 and SARS-corona virus in bat (SARSr-CoV-RaTG13) is 96% and between SARS-CoV and SARS-CoV-2 is 79.5% (Lu et al., 2020; Zhou et al., 2020). SARS-CoV-2 is distinct from SARS-CoV and MERS-CoV in the rapid spread and that it is more contagious, now SARS-CoV-2 affecting around 214 countries(https://www.who.int.).

Clinical features: The symptoms associated with Covid-19 in the earliest 41 patients varied from major to atypical symptoms (Huang et al., 2020). The major initial symptoms include fever, cough, malaise, in 98%, 76%, and 44% of the 41 patients, respectively while the less common symptoms included headache and diarrhea in 8%, 3% of the patients (Huang et al., 2020). As for a typical symptoms, and according to the epidemiological data from the National Health Commission of China (NHCC), 42 out of 1099 patients have experienced diarrhea and diarrhea may associated with longer duration of more than 10 days (Eastin & Eastin, 2020). Different phases of COVID-19 epidemic have affected an overall clinical features that associated with SARS-CoV-2 (Guan et al., 2020a; Wang et al., 2020). The majority during the first and second phases were old males who had an exposure to the seafood market with a mortality rate ranges from 4.3-15%, which is higher by 1.36% than late phases (Guan et al., 2020a; Wang et al., 2020).

The higher mortality rate in first and second phases is either because of medical conditions and chronic disease, such as diabetes and high blood pressure (Cheng et al., 2020; Guan et al., 2020a). Or because of the high pathogenicity of the virus during its earliest phases (Cheng et al., 2020; Guan et al., 2020b). However, asymptomatic infections were also reported earlier in almost 900 cases (Novel, 2020; Wei et al., 2020).

Routes of transmission: While the main route of SARS-CoV and MERS-CoV transmission is via nosocomial transmission (Elfiky, 2020). The mainly route of transmission is person-to-person contacting with either symptomatic or asymptomatic patients (Elfiky, 2020). It is been estimated that over 31% of the patients have travelled to Wuhan, China and 72.3% have contact with them (Elfiky, 2020). SARS-CoV-2 has been approved to spread mainly through droplets of respiratory system and person-to-person close contact (Qu et al, 2020). Yet, there are growing assumptions that the virus can be spread also through aerosols (Van Doremalen et al., 2020). Furthermore, virus in aerosols perhaps remain infectious on different surfaces for days while in aerosols for minutes or hours (Van Doremalen et al., 2020).

Diagnosis and molecular techniques: Different biomarkers related to specific microorganism known to cause disease, these can be used in the diagnosis of the disease as in the COVID-19 (Taleghani & Taghipour, 2020). However, the biomarker can often be the genetic material of microorganisms, which leads to the development of several molecular tests (Taleghani & Taghipour, 2020). The molecular assay first required to collect the samples from any infected region then extract the genetic material to detect the target gene (Taleghani & Taghipour, 2020). Moreover, there is another biomarker that can be used for diagnosis purpose which is a molecule involved in the body immune response against the antigen (Taleghani & Taghipour, 2020). This biomarker include the immunoglobulin present in the blood that fights against the antigen which in turn leads to the development of serology techniques that detect this interaction (Taleghani & Taghipour, 2020).

Another diagnosis method as well, is to take look at an infected organ which its functions influenced by specific microorganisms then detect the difference between the concentrations of biomarkers (Taleghani & Taghipour, 2020). The abnormalities in the inflammatory markers, chest, kidney markers, liver functions as cystatin C and creatinine are used in the diagnosis of COVID-19 cases (Taleghani & Taghipour, 2020).

Molecular tests (nucleic acid amplification): The commonly molecular technique used to detect the presence of SARS-CoV-2 is reverse-transcription polymerase chain reaction (RT-PCR) (Kelsoe et al., 2012). According to WHO and the Food and Drug Administration (FDA), it's considered as a routine diagnosis to confirm infected cases with SARS-CoV-2 (Kelsoe et al., 2012). Mainly, it's a biochemical reaction (Kelsoe et al., 2012), it is known in the polymerase chain reaction (PCR) technique Deoxyribonucleic acid (DNA) is used as the first template ,while in the case of (RT-PCR) Ribonucleic acid (RNA) is used (Kelsoe et al., 2012). The process of reverse transcription depends on the enzyme reverse transcriptase, which uses a single stranded-RNA to produce single stranded-DNA then this single strand converts to double-stranded DNA before its used in the PCR reaction as a template (Carter & Shieh, 2015; Yan et al., 2020). Even though efforts made to raise the number of conducted PCR test per day (Xue & Jin, 2020). But, there are some limitations consider as an obstacle to this technique among this non-availability of kits and PCR reagents, false-negative detected in a patient has SARS-CoV-2 and it takes a relatively longer time (Xue & Jin, 2020).

The specimen from the lower respiratory tract (broncho alveolar lavage fluid) was used to diagnose cases in the early stage of the outbreak (Huang et al., 2020). The process of sample collection is painful to the patient and requires skilled operator and suction device (Yang et al., 2020). Broncho alveolar lavage fluid is not considered as feasible

for routine diagnosis and SARS-CoV-2 monitoring (Yang et al., 2020). For the time being, the alternative sample collection includes sputum, oropharyngeal swabs and nasopharyngeal swabs which are more safe to patients, simple and rapid (Yang et al., 2020).

A recent study conducted in 2020 has revealed the differences between samples, sputum swap reflected a high-level of positive rate with various degrees of illness severity then nasopharyngeal swabs followed by oropharyngeal swab display low-level of the positive result (Guan et al., 2020b; Huang et al., 2020). In some severe cases, viral RNA is not detectable in the upper respiratory tract sample. As current studies displayed only a small cluster of COVID-19 patients (28%-33.7%) produced sputum (Guan et al., 2020b; Huang et al., 2020). So, the nasopharyngeal swabs are one of the most applicable samples and used worldwide in the COVID-19 diagnosis (Guan et al., 2020b; Huang et al., 2020).

RT-PCR: RT-PCR is a reverse transcription process in which viral RNA converts into complementary DNA (cDNA) then a designed fluorophore-quencher probe and primers are added to amplify the gene of interest –cDNA and detect the existence of SARS-CoV-2(Freeman et al.. 1999; Kojima et al., 2002). To begin with, is RNA extraction from the specimen from the lower or upper respiratory tract (CDC). Moreover, it is recommended to collect specimens from the upper respiratory tract such as, nasal aspirates, oropharyngeal swabs, nasopharyngeal swabs and nasopharyngeal washes (CDC). Meanwhile, specimen collected from the lower respiratory from patients suffering from cough such as , tracheal aspirates, sputum and broncoal veolar lavage (BAL)(CDC). Subsequently, extracted RNA is then added to a mixture consist of probes, primers, precursors, buffers and enzyme, reverse transcriptase, forward and reverse primers, nuclease-free water, nucleotides and a fluorophore-quencher probe (CDC). rRT-PCR cycling conditions are determined by U.S CDC, but two remaining major variables are probe and primer design and choosing target sequence for amplification (Taleghani & Taghipour, 2020).

Particularly, SARS-CoV-2 genome has three main conserved regions: N gene, E gene and RdRP gene which locates in the open reading frame ORF1ab (Wood et al., 2019). In the meantime, most SARS-CoV-2 detection diagnostic kits rely on targeting E gene and RdRP (Wood et al., 2019). These genes have fewer detection limits and high-level of sensitivity in comparison with N gene (Wood et al., 2019). However, any negative result could be an indication to a low viral load and not to virus absence and it may be associated with sampling errors (Wood et al., 2019). The following is a summary of available commercial RT-PCR kits in the market of pharmaceutical companies. On March 13, 2020 , Viractor Erofins released their kit under the name SARS-CoV-2 rRT-PCR test (Eurofins). This test have used upper respiratory samples including: nasopharyngeal swabs, nasal wash, nasal swab, oropharyngeal swabs and nasopharyngeal wash ,also the lower respiratory sample was used as BAL swab (Eurofins).

Later on April 24 , 2020 , BGI Genomics Co. Ltd. (Shenzhen, China) launched their Real- Time Fluorescent RT-PCR detection Kit (BGI, 2020). This kit contains automated specimen preparation system and RNA kit for extraction in addition to the polymerase chain reaction (PCR) which gives the results of 192 samples within 4 hours (BGI, 2020). Both types of lower and upper respiratory specimens can be applied to automated specimen preparation system as BAL fluid, nasopharyngeal swabs, nasal aspirates, oropharyngeal swabs and nasal washes (BGI, 2020). Regarding SARS-CoV-2 kit cross-reactivity challenges was investigated for 50 pathogens without cross-reactivity (BGI, 2020). The fully automated fast test developed by bosch to detect the presence of SARS-CoV-2 with an accuracy of about 95% according to the quality standards of WHO (Global, 2020). This test depends on the micro-array and multiple PCR for SARS-CoV-2 detection (Global, 2020).

However, this device is made up of two main parts: Vivalytic analyser and cartridge including basic reagents (Global, 2020). It's considered the first completely automated test for COVID-19 diagnosis which detects and record the result in less than two hours and a half electronically (Global, 2020). This device can test nine pathogens as influenza B and A simultaneously (Global, 2020). On 21 March 2020, one of the most rapid molecular test has emerged for SARS-CoV-2 , which was developed by Cepheid (Capheid, 2020). In this kit, manual specimen preparation will take less than one minute and the results could be released in about 30 minutes (Taleghani & Taghipour, 2020). Although, previous developed PCR test shared the same step of RNA extraction that is essential prior PCR cycles, but they have few differences in between (Taleghani & Taghipour, 2020). Covid-19 serological test: Serology tests are based on processing blood sample which used to identify infection and distinguish between a recent or previous infection based on immune responses (Bastos et al., 2020). Different serological tests for COVID-19 detection will be discussed below.

The rapid diagnostic test (RDT): It is a rapid and simple test based on the lateral flow immunoassay (LFIA) technology, and it is used in many countries, including the U.S., China, and Singapore (Bastos et al., 2020). The RDT test works by detecting the antigens and antibodies in blood sample (Bastos et al., 2020). In antigen detection, the RDT test directly detects the virus's presence, which indicates that the virus is replicating (there is an active infection) (Espejo et al., 2020). Furthermore, in antibody detection, RDT test detects the immunoglobulin A, immunoglobulin M, and immunoglobulin G (Espejo et al., 2020). The test detects the immune system's response to the virus in the form of antibodies produced in the course of active infection (Espejo et al., 2020). Moreover, the test detects the antibodies that persist following the previous existence of the virus (Ghaffari et al., 2020). The sample that was taken for the antigen test includes oropharyngeal, nasal, or nasopharyngeal swab (Ghaffari et al., 2020).

The antibody test sample is venous blood or finger stick blood (Ghaffari et al., 2020). The antigen and antibody RDT tests may be a priority for different purposes (Ghaffari et al.,

2020). The RDT test results can either be a true positive, a true negative, a false positive, or a false negative (Espejo et al., 2020).

Enzyme-linked immunosorbent assay (ELISA): ELISA test is a lab-based quantitative or qualitative test that uses a patient's serum, plasma, or blood to test for COVID-19 (Alharbi et al., 2020). ELISA test is depending on a plate coated with the viral protein of interest (Alharbi et al., 2020). An example of such a protein, could be the viral spike protein (Alharbi et al., 2020). Later ,The protein is then incubated along with the patient's sample. If the patient's sample contains antibody to the viral protein, the two parts will bind together, forming a complex(Antigen-Antibody complex) (Alharbi et al., 2020). Following the complex formation, detection can be accomplished (Alharbi et al., 2020). The detection can take place by using another wash step of antibodies that a fluorescent or color-based readout (Alharbi et al., 2020).

In COVID-19's context, the test detects for certain antibodies (IgM and IgG) in the patients serum (Alharbi et al., 2020). The test is slower than the RDT test, it requires two to three hours compared to the RDT test, which takes between 15 to 35 minutes (Alharbi et al., 2020). The test is applicable to determine the absence or the presence (quantitative) of the antibodies formed against the virus (Sakamoto et al., 2018). Though the test is applicable in shading light into the presence of the virus and antibodies produced by the immune system against the virus, the test cannot determine whether the antibodies can inhibit the viral replication (Sakamoto et al., 2018). Moreover, the test allows for simultaneous analysis without the pre-treatment of samples (Sakamoto et al., 2018). Furthermore, also the challenge of antibody instability and the high possibility of a false negative, or positive reads (Sakamoto et al., 2018, Alharbi et al., 2020).

Antivirals drugs for SARS-CoV-2 infection:

Fusion inhibitors: Enveloped viruses penetrate the host cell by fusion (Gasmi et al., 2020; Kumar et al., 2020; Matsuyama et al., 2020; Zhang & Liu, 2020). Which could be inhibited by fusion inhibitors which consist of antivirals (Gasmi et al., 2020; Kumar et al., 2020; Matsuyama et al., 2020; Zhang & Liu, 2020). However, there are several drugs available with high antiviral activity against viruses especially SARS-CoV-2 as camostat mesylate and umifenovir (Gasmi et al., 2020; Kumar et al., 2020; Matsuyama et al., 2020; Zhang & Liu, 2020).

Baricitinib: Basically,SARS-CoV-2 like other viruses by the receptor-mediated endocytosis enters inside the host cell (Lu et al., 2020). Moreover, the AP2-associated protein kinase 1[AAK1] used to regulated the endocytosis process (Lu et al., 2020). The process of viral assembly and viral entry can be blocked through the disruption of AAK1 (Lu et al., 2020). Janus kinase inhibitors (JAK) as in baricitinib have a high potential activity to bind and then disrupt AAK1 (Richardson et al., 2020). Subsequently, the baricitinib could be used to disrupt both inflammatory-mediated immune response associated with SARS-CoV-2 and viral entry (Richardson et al., 2020). Therapeutic utilization of baricitinib is related to the occurrence of viral reactivation, neutropenia and lymphocytopenia (Praveen et al., 2020). However, baricitinib may lead to increase the occurrence of co-infection since the patients infected with SARS-CoV-2 suffer from a reduction in the count of lymphocyte (Praveen et al., 2020).

Umifenovir: It also known as arbidol (Kadam & Wilson, 2017). In the fusion mechanisms of influenza viruses, the hemagglutinin envelope glycoproteins can be targeted by the uses of Umifenovir which is considered a nucleoside antivirals (Kadam & Wilson, 2017). A recent study conducted in china demonstrate that Patients treated with umifenovir monotherapy reveal negative viral transformation and SARS-CoV-2 was not detected within 14 days (Zhu et al., 2020).

Camostat mesylate: Also, the fusion step can be inhibited by a serine protease inhibitor as in the Camostat mesylate (Uno, 2020). However, SARS-CoV-2 can enter the host cell through the use of either TMPRSS2 receptors or/and ACE-2 receptor but camostat mesylate inhibits TMPRSS2 receptors (Matsuyama et al., 2020; Uno, 2020). The expression of SARS-CoV-2 spike protein (S) is down regulated which prevent the surface fusion and then block the viral entry into the host cell (Gasmi et al., 2020; Matsuyama et al., 2020). The previous study suggests the entry of SARS-CoV into the human bronchial epithelial cell can be prevented by using camostat mesylate (Kawase et al., 2012). Moreover, an In vitro study found that cysteine protease inhibitor as E-64d and camostat mesylate can efficiently inhibit the binding between SARS-CoV-2 and TMPRSS2 (Wang et al., 2020). Now, in Germany (Bose & Basu, 2020) and Denmark (Sharma et al., 2021) ongoing study taking place to evaluate the effectiveness of combination medication of camostat mesylate and hydroxychloroquine vis-a-vis only single hydroxychloroquine through the clinical trials (Sharma et al., 2021).

Protease inhibitors: Accordingly , COVID-19 protease inhibitors can be used as, atazanavir, lopinavir and darunavirfor treatment (Ferreira et al., 2020; Kadam & Wilson, 2017). Through the use of Computer-aided drug design techniques, a number of drugs such as elbasvir, eravacycline, carfilzomib, lopinavir and carfilzomib are able to disrupt the main viral protease in SARS-CoV-2 (Wang, 2020).

Lopinavir: Lopinavir have showed a possibility to inhibit SARS-CoV-2 at half-maximal effective concentration which is the drug concentration titre that triggers a response midway between the maximum and the baseline after a specified exposure period of 26.36 μM (Choy et al., 2020). The use of lopinavir to treat COVID-19 patients in China leads to an increase in the count of eosinophil (Liu et al., 2020). A recent study found that the combination between ritonavir and lopinavir acts as inhibitors to the main viral protease of SARS-CoV-2 (Liu & Wang, 2020). Moreover, in the clinical trial and in vitro showed that in a combination mixture of lopinavir-ritonavir which is known as Kaletra®, a high antiviral activity against SARS-CoV (Chu et al., 2004). In some countries lopinavir-ritonavir

combination was used as an emergency therapy to treat COVID-19 patients (Cao et al., 2020; Lim et al., 2020). According to WHO options clinical trials for "solidarity" COVID-19, can use the combination of Lopinavir-ritonavir and interferon (INF)-β (Yavuz & Ünal, 2020). Ritonavir-lopinavir combination have resulted in low viral load and improved the symptoms of patients (Zhu et al., 2020).The lung damage could be inhibited by the use of a combination of umifenovir and ritonavir-lopinavir (Deng et al., 2020). A recent study showed the use of lopinavir-ritonavir leads to a better clinical outcomes (Guan et al., 2020b).

Darunavir: Additionally, Darunavir was used as an anti-HIV drug to treat HIV infection but it was recommended to be used for use in Italy to treat COVID-19 infection (Nicastri et al., 2020). In vitro studies showed that the combination use of darunavir with cytochrome P-450 inhibitors as cobicistat or ritonavir, could inhibit SARS-CoV-2 replication activity (Harrison, 2020). Clinical trials are ongoing to assess the efficacy of the combination of darunavir with hydroxychloroquine and other antiviral drugs to treat COVID-19 infection (Kongsaengdao & Sawanpanyalert, 2020). In addition, clinical trials are underway to evaluate the combination of darunavir along with cobicistat (Sarkar et al., 2020). PREZCOBIX® is used as a treatment for COVID-19 which is a fixed dose of the combination of cobicistat and darunavir (Sargent et al., 2021).

Reverse transcription inhibitors: It is another strategy to control SARS-CoV-2 infection by targeting the step of the reverse transcription, through RdRp blocking prevent viral replication (Frediansyah et al., 2020). There are number of inhibitors like nucleoside reverse transcriptase translocation inhibitors (NRTTIs), nucleoside reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs) and nucleotide reverse transcriptase inhibitors (NtRTIs) (Frediansyah et al., 2020).

Remdesivir: Remdesivir is a nucleotide analogue that has a broad spectrum of antiviral drug properties against most of the single stranded RNA (ssRNA) viruses such as corona viruses (involved both SARS-CoV-2 and MERS-CoV) , Hendra virus , Ebola virus, Nipah virus, Marburg virus , Lassa fever virus, respiratory syncytial virus and Junin virus (Al-Tawfiq, Al-Homoud, & Memish, 2020; Ko et al., 2020). It is designated as GS-5734 , when entering into the host cell the GS-5734 metabolized to GS-441524 which is able to decrease RNA replication of MERS-CoV, SARS-CoV, endemic and zoonotic human delta corona virus at an in vitro conditions (Gordon et al., 2020). Remdesivir is a nucleotide reverse-transcriptase inhibitors (NtRTIs) (Tikkinen ett al., 2020). It is considered an inhibitor for RNA-dependent RNA polymerase (RdRp) (Al-Tawfiq et al., 2020). It acts on changing of viral the exonuclease function that leads to the disruption of proofreading, reducing viral RNA replication and production decline (Al-Tawfiq et al., 2020). It is recommended to treat severe cases of COVID-19 because it can prevent viral replication (Harrison, 2020).

Ribavirin: It is a guanine derivative analogue and has an antiviral activity against hepatitis C virus (HCV) (Graci & Cameron, 2006). In Vitro study revealed that it has antiviral effect in SARS-CoV-2 infection It functions by disrupting the polymerase activity, prevents the step of RNA capping which is important to RNA stabilization then the viral replication will be obstructed (Graci & Cameron, 2006). Moreover, ribavirin disrupts the function of the inosine monophosphate dehydrogenase enzyme, which results in blocking guanosine production then enhances the degradation of viral RNA (Graci & Cameron, 2006). Ribavirin is recommended in combination with either lopinavir-ritonavir or IFN alpha (Drożdżal et al., 2020). In addition, it can be used either by oral or intravenous route (Elfiky, 2020).

Current status and technology used in the development of SARS-Cov2 vaccine worldwide: Corona viruses are single stranded enveloped RNA virus, it consist of few proteins which have a significant role in the virus structure (S protein, E protein, M protein , and N protein) most of vaccine manufacturers target the S protein as a vaccine antigen rather than using an inactivated vaccine (van Doremalen, Lambe, et al., 2020). There are about 48 candidate vaccines in clinical evolution are either in Phase 1, 2, or 3 and about 164 candidate vaccines in preclinical evaluation (Van Doremalen et al., 2020). A number of them have reached advanced stages of development and showed encouraging results (Van Doremalen, Lambe, et al., 2020). In this review, few vaccines that have reached the latest stage of development will be discussed.

ChAdOx1 nCoV-19 Vaccine: It is known as oxford vaccine referring to chAdOx1 nCoV-19 vaccine, additionally, known as AZD1222 referring to the co-development of the vaccine by university of oxford, VACCITECH, and AstraZeneca (Van Doremalen et al., 2020). It is a promising vaccine for SARS-CoV2 from anon-replicating viral vector category. It is a chimpanzee adenovirus vector vaccine; using adenovirus as a gene delivering system by inserting spike protein gene to E1 locus of ChAdOx1 then using human embryonic kidney 293 cell line to increase the number of the viral particle which later was purified to be ready as a vaccine later purified it to be ready vaccine. It is considered a suitable vaccine for covid-19 based on the strength of immune response that it can elicit from one dose and it cannot replicate (Van Doremalen et al., 2020). Therefore, it would not cause an infection which ensures the safety of the vaccine for in elderly and children (Van Doremalen et al., 2020).

It was first tested on mice and Rhesus macaques and showed adequate immunogenicity. Phase I /II clinical trial was randomized controlled, tested on 5 different locations in the UK on 1090 healthy volunteers aged 18-55 y either received ChAdOx1 nCoV-19 (n=543) or MenACWY meningococcal conjugate vaccine (n=534) to compare, both vaccines are single dose delivered intramuscularly. The vaccine showed an increase in antibody titer however, the booster dose had a much efficient response. It reflected enough safety and immunogenicity in this trial (van Doremalen, Lambe, et al., 2020). Phase III was multicenter study in different countries with 30000 participants to ensure the safety and immunogenicity (Van Doremalen et al., 2020).

On November 18, 2020, the preliminary results of phase III were published, and they found that the efficacy of preventing infection reaches an average of 70%, but in the same study, two regimens of vaccination were given (Folegatti et al., 2020). A prime dose followed by a boost dose after a month has an efficacy of 62% (Folegatti et al., 2020).The other regimen includes a half dose followed by a full dose after a month generated an efficacy of about 90% (Ramasamy et al., 2020).

Moderna Vaccine mRNA-1273: Mainly, It is a mRNA-based vaccine (Corbett et al., 2020) .Whereases mRNA is capsulated by lipid nanoparticle (LNP) that codes for S protein to elect immune response in the human body (Corbett et al., 2020). This vaccine is co-developed by Moderna, NIAID, Lonza, Catalent Inc and BIOQUAL (Corbett et al., 2020). The preclinical phase which was applied on rhesus monkey had induced a high level of antibody, and helper T-cells type 1,besides that it showed that there was not viral replicating(Corbett et al., 2020). These results lead to phase I clinical trial, it was accomplished in the USA on 155 healthy participants males and non-pregnant females aged 18-99years (Corbett et al., 2020). The vaccine was sufficient in inducing antibody response (Jackson et al., 2020). Phase II was done on 600 participants aged 18 and above with two doses either 50 μg or 100 μg and it showed a favorable response with higher doses (Jackson et al., 2020). Phase III is currently ongoing with 30000 participants (Jackson et al., 2020). The company announced on 16 November 2020 that the vaccine has 94.5% efficacy in preventing covid-19 based on 95 participants' results (investors.modernatx.com, 2020). On December 18, 2020, the FDA authorized the emergency use of the Moderna COVID-19 Vaccine (Jackson et al., 2020).

Sinovac Biotech Vaccine: This vaccine was developed by Sinovac Biotech in China (Gao et al., 2020). It is a potential vaccine that belongs to inactivated viral vaccines category, by using inactivated SARS-CoV-19, it was isolated from different patient then one strain was chosen CN2 vaccine development (Gao et al., 2020). In the preclinical phase, the vaccine was used in Rhesus Macque to evaluate immunogenicity and protective effect and it showed partial or complete protection (Gao et al., 2020). Phase I/II was generated done on human subjects aged 18-59 years , that resulted by using two doses of 6 μg/0.5 mL or 3 μg/0.5 mL of the vaccine ,which produced specific neutralizing antibodies (Bangash et al., 2020).

Phase III clinical trial introduces in different countries (Bangash et al., 2020). Until now it is in use in china only (Bangash et al., 2020). Many other vaccines have reached an advanced stages of development mainly, located in the USA, China, Russia, Japan, and Europe (Zhou et al., 2020). Cansino biologics is developing a non-replicating viral vector vaccine using adenovirus type-5 (Ad5)-vector (Zhou et al., 2020). The results of Phase I/II showed safety of vaccine and its ability to elicit an immune response after one immunization dose (Zhou et al., 2020). The vaccine is now in Phase III trials in many countries, Saudi Arabia is one of these countries with at least 5000 volunteers (McMurry et al., 2021). BioNTech and Pfizer announced that their mRNA vaccine has an efficacy over 94% and it was approved by the FDA for Emergency Use Authorization (EUA) on December 11, 2020 (McMurry et al., 2021).

The Role of ORF8: ORF8 is an accessory protein that is considered as one of the most rapidly evolving proteins in beta corona virus (Ceraolo & Giorgi, 2020; Cui et al., 2019; De-Sousa et al., 2020; Laha et al., 2020; Lau et al., 2015; Lu et al., 2020; Mohammad et al., 2020). However, the replicating of SARS-CoV-2 and SARS-CoV does not require the expression of ORF8 (Muth et al., 2018). Through the early transmission of SARS-CoV-2 from person to person, 29 nucleotides have been deleted [Δ29], the milder disease is correlated with the splitting of ORF8 into ORF8b and ORF8a (Muth et al., 2018). The decreased occurrence of hypoxia and milder illness in SARS-CoV-2 was associated with the deletion of 382 nucleotides [Δ382] (Gong et al., 2020; Su et al., 2020; Young et al., 2020).

SARS-CoV-2 ORF8 is a protein which consists of 121 amino acids, containing an N-terminal signal sequence ,followed by a predicted Ig-like fold (Tan et al., 2020). The endoplasmic reticulum (ER) can be imported via a signal sequence from the ORF8 protein of both SARS-CoV-2 and SARS-CoV (Gordon et al., 2020). SARS-CoV-2 ORF8 can interact with various proteins of the host inside the ER lumen that involves the interaction with numerous factors including the degradation associated with ER (Gordon et al., 2020). ORF8 supposed to be secreted rather than stored in ER, in SARS-CoV-2 infections the ORF8 antibodies are of the major markers (Hachim et al., 2020). There are different functions about SARS-CoV-2 ORF8. ORF8 over expression in the cells can lead to disrupting the IFN-I signaling (Li et al., 2020). SARS-CoV-2 ORF8 can down regulate MHC class I (MHC-I) inside the cells (Zhang & Holmes, 2020; Zhang et al., 2020).

CONCLUSION

The recent novel coronavirus-19 SARS-CoV-2 spread throughout China and has become a serious public health issue globally. This outbreak poses a heavy burden on both the economic and health status of human beings. However, bats are considered as the key reservoir. Until now, there are no promising prevention strategies or anti-viral drugs have been developed against SARS-CoV-2. However, researchers are working on developing drugs to treat COVID-19 patients. Furthermore, there are many companies working on developing the SARS-CoV-2 vaccine. But it also needs rapid animal-based and human trials because this vaccine needs 3 to 10 months for commercialization.

Case Report (Human Studies) Ethical Clearance Statement: The Current Case Report/ Studies were Conducted as Per the Guidelines of SCARE.

Riaz A Agha et al., (2020). The SCARE 2020 Guideline: Updating Consensus Surgical Case Report (SCARE) Guidelines. doi: 10.1016/j.ijsu.2020.10.034. Epub 2020 Nov 9.

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