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Life cycle, Transmission, Precautions, and Anti-viral drugs associated with SARS-COV-2: A systematic review

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Abstract

An unusual outbreak of the unknown pneumonia-like disease in Wuhan city, Hubei province of China was initially noticed in December 2019 this was later found out to be a new virus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which broke out as a superior pandemic in 2019. This particular virus has caused paramount health and economic crisis across the world. Besides SARS-CoV-2, there are 6 major known species under the Coronavirus which causes frequent human respiratory infection. These species include SARS (Severe Acute Respiratory Syndrome), MERS-CoV-2 (the Middle East Respiratory Syndrome Coronavirus), along with the less virulent species i.e. NL63, 229E, OC43, and HKU1. The current review article tends to help the scientific community by giving out a description of the life cycle, transmission precautions, and anti-viral drugs that revolve around the novel Coronavirus disease.

Keywords: SARS-COV-2, transmission, anti-viral drugs, life cycle, Receptor Binding Domain, ACE2

Introduction

The examples that are profound in the history of the world about various epidemics and pandemics like H1N1(during 1976, 2006, 2009), the Ebola virus outbreak (in the United States in 2014) has garnished the attention of the world quite often[1]. Recently, during December 2019, a newly identified β- coronavirus causing was reported to show a cluster of pneumonia-like cases in the Hubei territory of the People's Republic of China[2]. SARS-CoV-2 is a single-stranded and non-segmented RNA belonging to a diverse group of viruses that originate from animals. To date, there are a total of 7 coronaviruses that can infect humans[3]. According to the study of[4], A closely, related Pangolin-CoV (SARS- CoV-2) was first reported and discovered from dead Malayan Pangolins. Human coronaviruses were first described in the 1960s from the patients who reported common cold. Since then, Severe Acute Respiratory Syndrome(SARS) and the Middle East Respiratory Syndrome(MERS) were discovered as the two pathogens that can cause fatal respiratory diseases in humans[5]. COVID-19 is the seventh branch of the coronavirus family which affects humans. Further, it has been classified under the ortho-coronavirinae subfamily and within the subgenus sarbecovirus[6]. World Health Organization (WHO) has categorized Coronavirus under β CoV of group 2B [7]. This SARS-CoV-2 contains the typical coronavirus structure like spike protein and other expressed nucleoproteins, poly-proteins, and sheath proteins, such as RNA polymerase, 3-chymotrypsin-like-protease, papain-like protease, helicase, glycoprotein, and confederate proteins[8]. Spike protein present in SARS-CoV-2 contains a 3D structure in the Receptor Binding Domain region to maintain the Van der Waals forces[9]. Study of reports about the first instance that occurred in 2002-2003 when a new virus of the beta origin that of bats was crossed over with humans via the intermediate host of palm civet cats in the Guangdong territory of the People's Republic of China[10]. Primary symptoms of SARS-CoV-2 incorporate illness, hem, muscular soreness, and dyspnea. It is also seen that some of the patients show atypical symptoms like diarrhea and vomiting[11]. Cases in the initial and next phases of the disease are designated for old ones, more likely to be male, and also likely to have displayed to the seafood market[12]. The elder people and people with underlying disorders like hypertension, chronic obstructive pulmonary condition, diabetes, cardiovascular disorder are more likely to develop SARS-CoV-2, even leading to fatalities[2].

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2. Origin and Life cycle of COVID-19:

Despite being characterized in the early 1960s, coronavirus still requires elaborative study to understand them better as they have caused many global pandemics such as the SARS-CoV and MERS that had led to socioeconomic and psychological losses in the past[13]. And the world is going through a critical period caused by the COVID-19. To concede COVID-19, it becomes a key point to study its origin and life cycle.

2.1. Origin

Many human coronaviruses have been known to originate from Bats[14]. But many researchers had that the snakes could be the possible host[15], but this was rejected as the genomic studies of COVID-19 related it with SARS-like bat viruses and supported that bats could be the possible host[3] and it is also to be noted that the rational coronavirus NL63 had a common relative with a bat coronavirus (ARCoV.2) that occurred between the year 1190to 1449 CE[16] and also received a mutual parent with different bat coronavirus (GhanaGrp 1 Bt CoV) that occurred between the years 1686 to 1800CE and more recently, the SARS-CoV that occurred in the year 1986 has also been confirmed to have been originated from bats[17]. To extirpate the virus, more investigations have to be implemented to identify the zoonotic origin that generated the overdrive to humans[18].

2.2. Life cycle

The life cycle of SARS-CoV-2 can be classified into four stages namely (a) entry and attachment, (b) replicase protein expression (c)replication and transcription, (d)assemble, and release. Studying the life cycle in detail, it remains the same with all the coronavirus family members.

2.2.1. Attachment and entry

The structural appendage of the virion to the host cell is triggered by interplays between the S protein and its receptors. The sites of receptors binding domains within the S1 domain of a coronavirus Spike protein varies according to the virus[19]. Some have receptor binding proteins at the N-terminus of the S1 domain and others are known to have receptor binding sites at the C-terminus[20]. The spike protein receptor synergy is the chief purpose for a coronavirus to encroach into a host sorts. Coronaviruses use their peptidases being their cellular receptor. It is unclear how peptidases are appropriated here, and as the virus enters they manage to employ Amino Peptidase N as their receptors and some others use angiotensin-converting enzyme2 and dipeptidyl-peptidase as their receptor to gain entry into the human cells. The foregoing manner is followed by insertion of the microorganism to the host cytosol which is achieved by acid-dependent proteolytic fracture of spike protein by a cathepsin or different protease which is supported by the combining of viral and cellular sheaths. The spike protein cleavage happens at two sites within the S2 portion of the protein, while the first protein is vital for separating receptor binding domains of the spike protein[21]. The above fusion generally occurs at the cleavage in S2 that is followed by the insertion into the protein forming an anti-parallel six-helix bundle that releases the viral genome into the host cell[22].

2.2.2. Replicase protein expression

The following step in the life series of the coronavirus is the translation of the replicase gene that occurs from the virion Ribo Nucleic Acid. The replicase gene encodes pair of big ORFs namely the rep1a and rep1b whose mode of action is to express the following terminal poly-proteins pp1a and pp1b. to express pp1a and pp1ab the virus appropriates a slaggy or polished sequence (5'-UUUAAAC-3') and a pseudoknot of RNA which starts ribosomal frameshifting from rep1a which is an end codon thus happening in the translation of pp1a and pp1ab[23][24]. Poly-proteins pp1a and pp1ab are known to use the nsps1-11 and 1-16 respectively.in pp1ab, nsp11 from pp1a becomes pp1b. the coronaviruses are known to encode two to three proteases that cleave replicase poly-proteins[25]. After the described process many nsps combine to form a replicase transcriptase system to produce certain conditions that are favorable for the RNA synthesis and paves way for RNA replication and transcription of sub-genomic RNAs. There are several other enzyme domains that the nsps owns including that play an essential function in RNA replication[26].

2.3.3. Replication and transcription

Protein expression is directly followed by translation and the assembly of viral replicase complexes. Viral RNA synthesis occasions both genomic and sub-genomic RNAs. Sub-genomic RNAs act as mRNAs for the structural and accessory genes which go downstream about the replicase poly-proteins and the entire subgenomic RNAs are 3' co-terminal with the full-length viral genome plus they appear in the disposition of nested RNAs, a unique quality of the virus nidovirales. Both genomic and subgenomic are produced through negative-strand and only 1% of the positive counterparts contain poly-uridylate and anti-leader sequences[27]. It is also to be noted that cis-acting progressions are necessary during the replication of RNAs in the virus. Inside the 5'UTR there is an appearance of a projected loop, a pseudoknot, and a hypervariable region[28]. But, the stem-loop and the pseudoknot at the 3' terminal flap, and hence cannot befall at the identical time[29] making the various structures to arrange alternate degrees of RNA-synthesis, although precisely which stands are organized and specific values of their method of operation are concealed. Close to this, most of the replication in these viruses depends

on how the leader and body TRS segments fuse during the making of sub-genomic RNAs. This was initially thought to happen during the discontinuous extension of negative strands negative stand RNA[30]. Finally, these particular viruses are known to recombine with the aid of both similar and non-similar recombination plus their ability to recombine is similar to the strand switching capacity of that RdRp.

2.3.4. Assembly and Release

After all the above processes and replication of subgenomic RNA, the viral structure proteins S, E, and M [31]are subjected to translation and inserted into the endoplasmic reticulum in which the proteins are transported from the secretory pathway within the endoplasmic reticulum-Golgi intermediate compartment (ERGIC)[32]. N protein encapsidated by the viral genomes shoots into these ERGIC containing viral structural proteins, therefore making sophisticated virions[33]. Protein synergies required to assemble the virus particles are provided by the M proteins, but these M proteins are not sufficient for virion production, as (VLPs) virus-like particles cannot be performed by the M protein singly, therefore, the M protein is expressed along with the E protein which functions together to produce envelops and leads to the formation of Virus-like particles[34]. Virus-like Protein production is further enhanced by the N proteins indicating that the union of encapsidated genomes into ERGIC advances viral expansion. The foundation of S protein occurs later but is no needed for the assembly[35]. When compared to all the other structural proteins, M protein is plentiful while E is simply present in the virions[36]. Consequently, making it more possible that M protein paves way for envelope maturation[37]. The M protein also binds to the nucleocapsid promoting the achievement of virion assembly which gets planned to the C-terminus of the endo-domain of M including CTD of N-protein. However, it has been strange how the ERGIC interacts with the M-protein in the appearance of nucleocapsid complexed with virions RNA and gets into the viral envelope[38]. After the assembly, virions are moved to the cell surfaces within vesicles and released by exocytosis[26].

3. Transmission of the virus

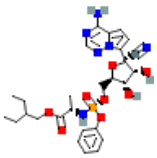
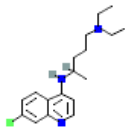
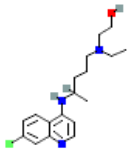
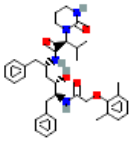
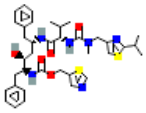
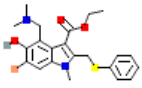
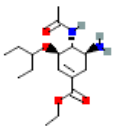
The frequency of the contagious disease relies on three main conditions: 1. Source of infection. 2. Routes of transmission and 3.Suspectible host. World Health Organization (WHO) has reported that the Covid-19 virus is transmitted by respiratory droplets and communication courses[39]. Droplet transmission leads to the appearance of microorganisms in the droplets cruces, which are mostly considered to be the particles less than 5μm in diameter. These droplets emerge from the disappearance of more comprehensive droplets or that which exist within the dust particles. These particles may be already present in the atmosphere for a long period and can also transmit to others over greater than 1m of distances. WHO has also suggested that COVID -19 can also transmit through airborne in specific circumstances and settings in the procedures that generate aerosols are performed. (i.e. endotracheal intubation, bronchoscopy, open suctioning, treatment of nebulized therapy, standard ventilation ere intubation, utilizing the subject to the recumbent posture, disconnecting the patient from the ventilator, non-invasive, positive-pressure ventilation, tracheostomy, and cardiopulmonary resuscitation)[40]. A key factor of the transmission of COVID-19 is the high level of virus residing in the upper respiratory tracteven among the pre-symptomatic patients, which distinguishes it from SARS-CoV-1 where replication occurs in the lower respiratory tract [20]. Viral load in SARS-CoV-2 constructs symptom-based apprehension of the virus more powerful. According to various studies conducted reports show that Unlike SARS AND MERS, patients diagnosed with COVID-19 have shown high viral loads even when there are no symptoms(asymptomatic)[41]. A study also shows that a person with high viral loads was detected in the higher respiratory individuals of SARS-CoV-2 infected patients, and viral shedding pattern patients resembles that of influenza patients [42]. This suggests that SARS-CoV-2 might stay for a while like influenza viruses [43]. The human to human transmission of the virus according toSheeren*et al*was reported to occur when exposed to coughing, sneezing, respiratory droplets, or aerosols of an infected person. Inhalation of these aerosols through the nose or mouth can penetrate the human body (lungs)[44]. Physical and social distancing measures importance to reduce the transmission of the COVID-19 infection. This measure secure physical distance between people of at least one meter, which in turn reduces contact with the infected person and contaminated surface while encouraging and maintaining virtual connection within the families and communities[45].

4. Precautions to be followed against COVID19

To curb or control any particular disease, precautions are the primary and most vital necessity to safeguard mankind from deadly pathogens. Generally, precautions vary from one pathogen to another, in this case as SARS-CoV-2 is the pathogens that spread through modes of aerosols or droplets when an infected person coughs or sneezes[46]. To date, as there are no antiviral agents or vaccines reported against the disease, it becomes vital for us to take the necessary precautions which are as follows[47].Common methods include washing hands with soap frequently and staying indoors most of the time, by avoiding crowded areas and public gatherings[48]. Naïve age groups like infants, aged and pregnant women have to be importantly safeguarded from the virus. When pregnant women are taken into consideration, those who have a travel history should isolate themselves for 14 days in-order check or withdraw the overdrive of the virus to other family

members and Mothers who gave newborns must refrain themselves from breastfeeding their child according to the National Health Commission of China though there are no shreds of evidence of transfer of the virus from one person to another[48]. It is also advised that pregnant women are supposed to monitor their temperature frequently[49]. When it comes to children, it remains unclear why they remain less susceptible to the virus when compared to other age groups[50]. Isolation of suspected cases is necessary to curb the disease, it is also advised to use alcohol-based sanitizers and to have immunity-boosting foods[10].

Table.1: List of clinical drugs suggestively used for COVID-19 treatment

Anti-viral drug	*Structure*	*Molecular weight*	*PubChem ID*
Remdesivir		602.6g/mol	121304016
Chloroquine		319.9g/mol	2719
Hydroxychloroquine		335.9g/mol	178396
Lopinavir		628.8g/mol	92727
Ritonavir		720.9g/mol	392622
Arbidol		477.4g/mol	131411
Oseltamivir		312.4g/mol	65028
Favipiravir		157.1g/mol	492405

5. Anti-viral drugs in the management of COVID19

The Covid-19 disease has proven to be a challenge to almost all the countries in the world. There are no proven drugs or therapeutic agents or vaccines against the COVID19 currently. Clinical management of the virus includes \prevention of infection and supportive care including oxygen support and mechanical ventilator support. The treatment also includes certain anti-viral drugs that have been used to treat various diseases to control COVID-19 which are to be discussed systematically in Table.1 [51].

5.1 Remdesivir

Remdesivir is a phosphoramidite pro-drug of adenosine C-nucleoside and also a known broad-spectrum antiviral agent synthesized and developed by Gilead Sciences in 2017 as a treatment for Ebola virus infection[52] and also Nipha virus infection[53] which is currently used in many countries for the prescription of COVID19. In animal studies, it's proven that remdesivir can reduce the viral content in the lungs of mice infected with MERS-CoV, and prevent pathological damage to the lungs[54]. Holshue et al reported that administering a subject infected with COVID-19 and pneumonia with remdesivir showed promising results in the USA[55]. It is also to be noted that Wang et al. found out that remdesivir potently blocks SARS-Cov2 infection at a low range of concentrations of remdesivir [56]. As an RNA-dependent RNA polymerase (RdRp) inhibitor, remdesivir inhibits coronaviruses in respiratory epithelial cells[57]. John et al (2020) subjected 1063 SARS-CoV-2 positive patients to randomization and found that group patients recovered in a shorter period who were administered with remdesivir group and also concluded that the Kaplan-Meier estimates by the mortality of 14 days and saw that the remdesivir group showed 7.1% and 11.9% with placebo indicating remdesivir outstood other drugs[58].

5.2. Chloroquine and Hydroxychloroquine

Both drugs have been used for treating various diseases like Lupus erythematosus, rheumatoid arthritis, and malaria while both the drugs are similar in structure[59]. In comparison with hydroxychloroquine, hydroxychloroquine is known to be less toxic due to the carriage of a –OH but still exhibits similar activity by targeting lysosome which is potent in graft-versus-host diseases in humans[60]. SARS-CoV-2 is susceptible to Chloroquine by preventing virus-cell heating by interfering with ACE2 expression[56]. Gautret et al in his study shows that hydroxychloroquine is effective in treating COVID-19 and is efficient in receiving the viral nasopharyngeal presence of SARS-CoV-2[61]. As per Colson et al (2020), 20 clinical studies in China where SARS-CoV-2 tested patients when administered with the combination showed better results in the treatment of the virus.

5.3. Lopinavir-Ritonavir

Lopinavir a, protease inhibitor which is highly preferred for HIV-1 protease is administered with ritonavir. The combination was first marketed by Abbott and named as

Kaletra in 2000[62]. When Lopinavir was individually randomized under an open-label clinical trial with COVID-19 infected patients, it showed that Lopinavir-ritonavir on the concentration of 400mg/mg, orally twice a day showed very poor results[63]. But a study from Korea claims that the administration of this combination proves to be effective[64]. Cao et al (2020) in their study have tested 99 subjects who had tested positive for the SARS-CoV-2 virus under randomization were administered with Lopinavir and ritonavir to check their potency in the patients. It was observed that the combination had just made slight clinical improvement while the percentage in which the patients were tested for viral RNA presence remained the same[63]. Contradicting to the above result Lim et al (2020) found out that a Korean man who tested positive for SARS-CoV-2 was administered with Lopinavir and ritonavir combinations and was observed that the viral load steadily decreased when tested through RT-PCR[64].

5.4.Arbidol

Also called umifenovir is a derivate of indole carboxylic acids that were first developed in Russia in 1988 and are used to treat prophylaxis and infections associated with influenza virus A or B and other arboviruses [77]. The major mechanism of this virus is to block the virus-cell membrane fusion as well as to inhibit virus-endosome fusion and interference with phospholipids[66]. A cohort study by Deng et al shows that a combination of LPV-RTV with Arbidol improves the glum conversion rate of SARS-CoV-2 and enhanced chest CT scan[67]. Zhu et al (2020) in his comparative study have found out that Arbidol when compared to ritonavir and Lopinavir, showed that patients administered with Arbidol had less to no viral loads while the viral load was found much in the Lopinavir and ritonavir administered patients hence proving Arbidol to be a stronger drug against SARS-CoV-2[68].

5.5. Oseltamivir

Oseltamivir, branded as Tamiflu is a drug that has been used to treat influenza A and B. the particular drug's mode of work is to target the neuraminidase that is distributed on the surface of the influenza virus and prevents its spread to the human body[69]. Though Tamiflu doesn't provide any activity against the SARS-CoV-2 it is administered with Chloroquine and favipiravir[70].

5.6 Favipiravir

This particular is branded by the Fujifilm Toyoma Chemical, Japan in the year 2014 to treat avian influenza which is resistant to neuraminidase inhibitors[71]. The method of action of favipiravir is such that the drug initially enters the infected cells by endocytosis and then it gets transformed through phosphoribosylation into an active favipiravir ribofuranosyl phosphate[71]. Recent studies have shown that favipiravir acts as an experimental agent against single-stranded positive-sense RNA virus, the SARS-CoV-2[56].

Conclusion

The outbreak of Covid-19 (Coronavirus) has become a clinical and economic threat to countries worldwide. However, knowledge about this virus remains limited. World Health Organization has taken numerous measures to control this pandemic. The emerging COVID-19 which is caused by SARS-Cov-2exhibits strong infectivity but is less virulent when associated with SARS and MERS in the duration of mortality and morbidity. The pace and volume of clinical trials began to investigate potential therapies for COVID-19 highlighting both the need and capability to produce high-quality evidence even in the middle of a pandemic. To date, no therapies are effective. The current article adds more strength to researchers and the public on the mentality of the virus.

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Conflict of Interest

No known conflict of interest.

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