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PROVEN TREATMENTS FOR VIRAL DISEASES: BASIS TO FINDING CURE FOR COVID-19 PANDEMIC

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ABSTRACT

The unprecedented rise of cases of Coronavirus Disease (CoVid-19) with around 5 Million confirmed cases across the globe and 348,000 deaths (as of May 16 data from the World Health Organization) since its first occurrence in December 2019 at Wuhan, China, is quite alarming because comparing it to other beta-coronaviruses like Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) and other human infecting viruses, this novel corona virus spreads rapidly. The reason for its rapid outbreak as stated by the different journals we reviewed could be genetic recombination event at spike protein (S) in the Receptor-Binding Domain (RBD) region that may have enhanced its transmission ability. This review presents current knowledge on the genetic characteristics of CoViD-19 in comparison to previous coronaviruses as it is of paramount importance to understand its genetic components and structure to study its pathogenicity for the production of drugs and vaccines because until now there has been no reported cure to treat this disease. We also presented updated clinical trials and on-going treatments conducted by numerous scientists all over the world who are exploring proven treatments and available therapeutic drugs which might have the potential cure to end this pandemic.

KeyWords: COVID-19, Clinical Trials, Genetic Comparison, Therapeutic drugs, Treatments, SARS-CoV2

Introduction

The name coronavirus was derived from the latin word *'corona'* which represents the crown-like spikes on the outer surface of the virus that belong to Coronaviridae family in the Nidovirales order. [1] They contain a single-stranded RNA as a nucleic material and are minute in size (65-125nm in diameter and from 26-32kbs in length). [4] Four subgroups of coronaviruses family include: alpha (α), beta (β), gamma (γ) and delta (δ) coronavirus. [1] Alphacoronavirus and Betacoronavirus infect mammals while Gammacoronavirus and Deltacoronavirus mainly infect birds, fishes, and sometimes mammals [1]. Coronaviruses can infect multiple hosts because of its loosely attached receptor-binding domain (RBD). [1, 11]Specific genes in ORF1 downstream regions are also found in all coronaviruses in the 5'-3' order as S, E, M and N which encode proteins for viral replication, nucleocapsid and spikes formation and constitute the major structural proteins of coronaviruses.[2, 3,4] (Figure 1)

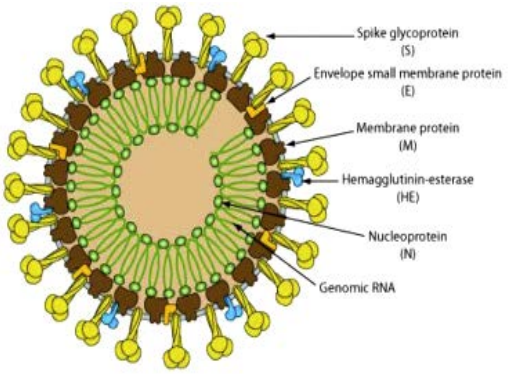

Figure 1: Schematic of a coronavirus- genetic structure of novel coronavirus. From Biowiki (http://ruleof6ix. fieldofscience.com/2012/09/a-new-coronavirus-should-youcare.html). **[2]**

Recently, Group of Chinese Researchers discover a new sequence of coronavirus that fell within the subgenus Sarbecovirus of the genus Betacoronavirus which began infecting humans at Wuhan, China last December 2019 and now considered the fastest coronavirus that became pandemic. Because of its unfamiliar etiology, they named this virus, Wuhan coronavirus or 2019 novel coronavirus (2019-nCov). Months later, it was named SARS-CoV2 for the virus and the disease as CoViD-19 by the International Committee on Taxonomy of Viruses (ICTV). It was named SARS-CoV2 upon seeing a close similarity of this virus to that of Severe Acute Respiratory-Related coronaviruses (SARr-CoV) which occurred in 2003. [2, 1, 4]

SARS-CoV 2 is a member of beta (β) group of coronaviruses with genomic structure and life cycle that is a spherical or pleomorphic enveloped particles containing single-stranded (positive-sense) RNA comprised of capsid which contains nucleoprotein in its matrix [2,1,4]**.** This virus possess a typical coronavirus structure with spike protein and envelop which bears club-shaped glycoprotein projections. It also expressed 3-chymotrypsin-like protease, RNA polymerase, papain-like protease, helicase, glycoprotein, and accessory proteins which are other polyproteins, nucleoproteins, and membrane proteins found in coronavirus. [1, 2, 5, 6] (See Figure 1)

This 2020, our world is facing a major global upheaval because of the novel coronavirus: SARS-CoV-2 that causes COVID-19 that affected millions of people, killed thousands of lives and brought us the new normal. Until now, there has been no reported cure to end the transmission of this disease, although several scientists and researchers all over the world are in relentless discovery to decipher its cure through relying to some proven therapies used before to treat *Severe Acute Respiratory Syndrome* (*SARS) and Middle East Respiratory Syndrome (MERS)* that are genetically similar to SARS-CoV2. Hence, with this prevailing case, the focus of our narrative review is to identify the different proven therapeutic options for previous Coronaviruses (like SARS and MERS-CoV) and other viral Diseases as basis of treatment for CoVid-19 pandemic.

We ought to specifically understand the genetic characteristics and comparison of CoViD-19 with previous coronaviruses and other viral diseases that could have the potential basis to finding cure for its transmission, and present current experiments/clinical trials/ innovations and therapeutic drugs to treat this pandemic.

1 Genetic Characteristics of CoViD-19

Notably, the 2019-nCoV strains were less genetically similar to SARS-CoV (about 79%) and MERS-CoV (about 50%) upon comparing the difference of their spike proteins (S) at 3' end**.** [4, 2]The arrangement of nucleocapsid protein (N), envelope protein (E), and membrane protein (M) among them also varies differently (See figure 2) [2]

Phylogenetic analysis in the study of Lu et.al (2020) revealed that the five subgenera closely related reference genomes as well as representative beta-coronaviruses of CoVid-19 have formed five well supported branches [4] (See Figure 3)

The two bat-derived SARS-like strains from Zhoushan in eastern China (bat-SL-CoVZC45 and bat-SL-CoVZXC21) and the ten 2019-nCoV which they extracted from Wuhan formed clade 2. (Figure 3) This concretizes the Blastn search of the complete genomes of 2019-nCoV which revealed that its most closely related viruses on GenBank were bat-SL-CoVZC45 (sequence identity 87·99%) and bat-SL-CoVZXC21 (sequence identity 87·23%) [4]

The other subgenus Sarbecovirus classified were the two SARS-CoV-related strains from *Rhinolophus sp.* from Bulgaria and Kenya which formed clade 1; and SARS-CoV strains from humans and many genetically similar SARS-like coronaviruses from bats collected from southwestern China that formed clade 3. [4] However, genetic evidence also indicates that although the closely related viruses of CoVid-19 were bat-SL-CoVZC45 and bat-SL-CoVZXC21**,** it did not cluster with them in the 3b tree (Figure 3) but instead formed a distinct clade with other Beta coronaviruses, indicative of potential recombination events in 3b. [4,1] This further highlights the idea that the 2019-nCoV is a novel beta coronavirus. In addition, the 2019-nCoV was distinct from SARS-CoV in a phylogeny of the complete RNA-dependent RNA polymerase (RdRp) gene**.** [4]

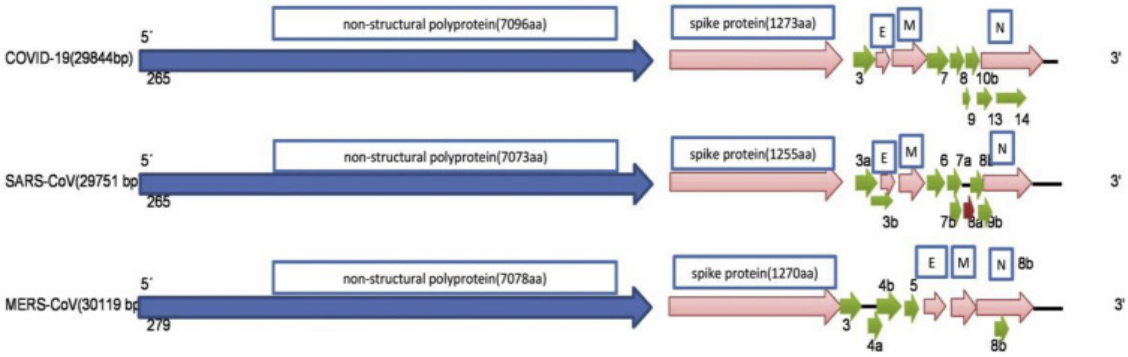

Figure 2: The 5' UTR and 3' UTR and coding region of COVID-19, SARS-CoV, and MERS-CoV. The differences in the arrangement of the envelope (E), membrane (M), and nucleoprotein (N) among COVID-19, SARS-CoV, and MERS-CoV are shown at 3' end**.** [2,4]

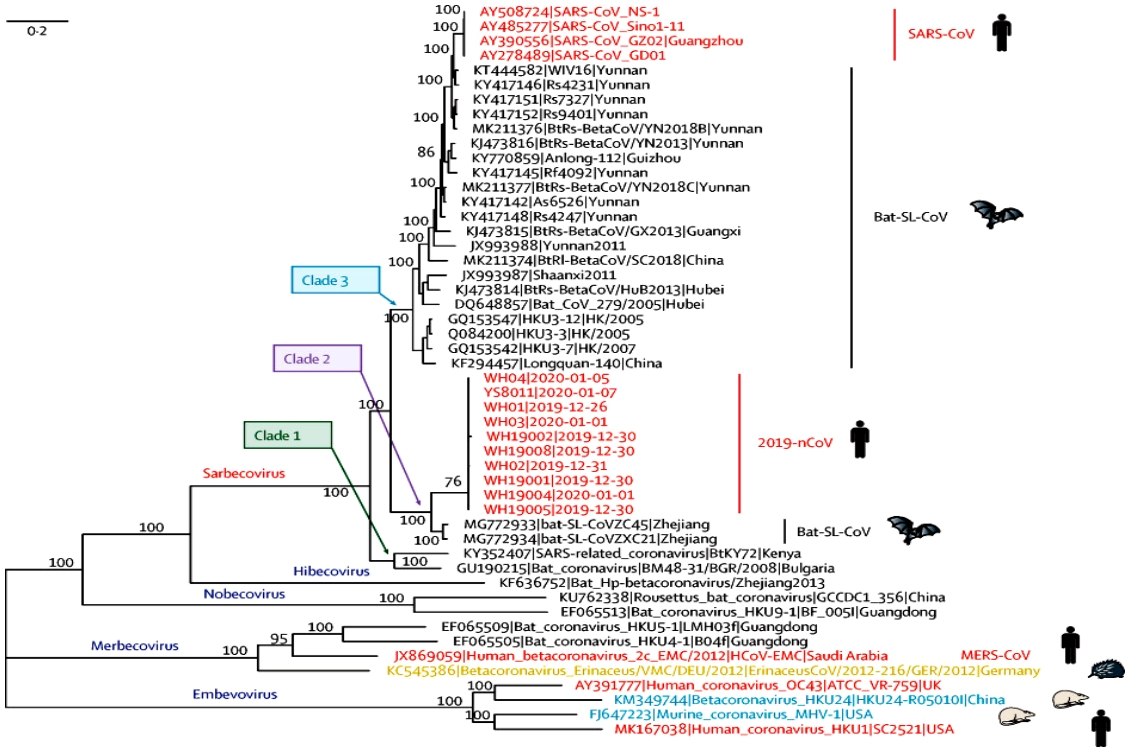

Figure 3: Phylogenetic analysis of full-length genomes of 2019-nCoV and representative viruses of the genus Betacoronavirus:2019-nCoV=2019 novel coronavirus. MERS-CoV=Middle East respiratory syndrome coronavirus. SARS-CoV=severe acute respiratory syndrome coronavirus**.** [4]

1.1 Comparison of CoViD 19 to other well-known coronaviruses

Coronaviruses contain a spike protein (S) that is functionally divided into the S1 domain, responsible for receptor binding and the S2 domain, responsible for cell membrane fusion. [4, 18] Both the N-terminal domain and the C-terminal domain of the S1 domain can bind to host receptor. The envelope spike (S) protein mediates receptor binding and membrane fusion is crucial for determining host

tropism and transmission capacity. [4, 1]

2019- nCoV possess a notable difference with a longer spike protein (S) compared with the bat SARS-like coronaviruses, SARS-CoV, and MERS-CoV[4]**.** This difference in this spike protein (S) also supports recent studies which also indicated notable variations between SARS-CoV and SARS-CoV2 that includes absence of 8a protein and fluctuation in the number of amino acids in 8b and 3c protein in SARS-CoV2[1, 7]. The spike glycoprotein of SARS-CoV-2 is the mixture of bat SARS-CoV and a not known Beta-CoV suggesting that Wuhan coronavirus is modified via homologous recombination. [4, 8].

The phylogenetic analysis of beta coronaviruses further revealed that the receptor-binding domain of 2019-nCoV was closer to that of SARS-CoV even though they fell within different clades (See figure 4A)[4]**.** The analysis revealed that like other betacorona-viruses (MERS-CoV and SARS-CoV), the receptor-binding domain of n-CoV 19 was composed of a core and an external subdomain (figure 4B-C**).** [4] Notably, the external subdomain of the 2019-nCoV receptor-binding domain was more similar to that of SARS-CoV (figure 4A-lineage B).

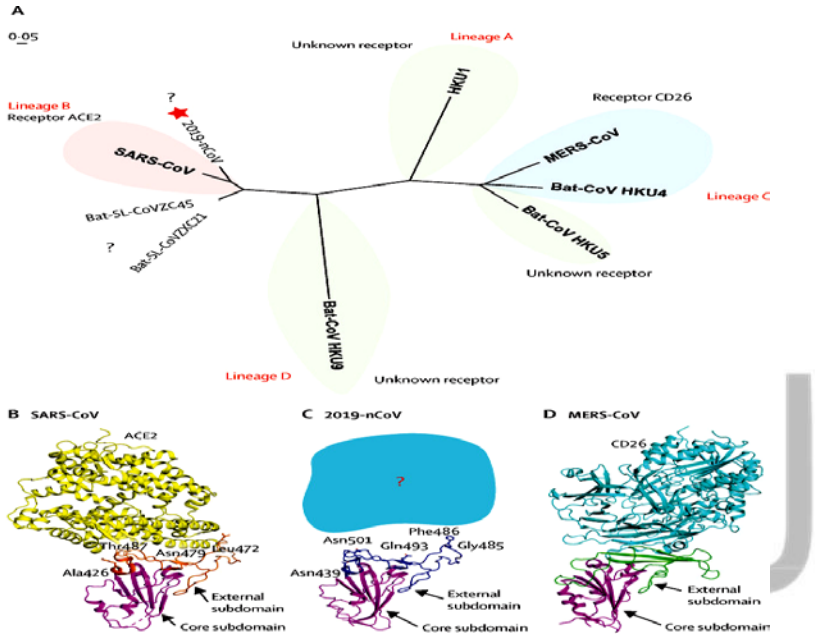

Figure 4: Phylogenetic analysis and homology modelling of the receptor-binding domain of the 2019-nCoV, SARS-CoV, and MERS-CoV (A) Phylogenetic analysis of the receptor-binding domain from various betacoronaviruses. The star highlights 2019-nCoV and the question marks means that the receptor used by the viruses remains unknown. Structural comparison of the receptor-binding domain of SARS-CoV (B), 2019-nCoV (C), and MERS-CoV (D) binding to their own receptors. Core subdomains are magenta, and the external subdomains of SARS-CoV, 2019-nCoV, and MERS CoV are orange, dark blue, and green, respectively. Variable residues between SARS-CoV and 2019-nCoV in the receptor-binding site are highlighted as sticks. CoV=coronavirus. 2019-nCoV=2019 novel coronavirus. SARS-CoV=severe acute respiratory syndrome coronavirus. MERS=Middle East respiratory syndrome coronavirus**.**[4]

Notably, the external subdomain of the 2019-n-CoV is similar to that of SARS-CoV (figure 4A-lineage B).[4] In a fluorescent study, it was confirmed that the SARS-CoV-2 also uses the same ACE2 (Angiotensin-Converting Enzyme 2) cell receptor and mechanism for the entry to host cell which is previously used by the SARS-CoV. [1, 9, 10] Because of this idea, there are a lot of researchers who published their studies in the Journal of International Science eager to find out whether or not the proven treatments for SARS-CoV could also be employed to CoViD-19 positive patients.

However, despite these similarities, several key residues responsible for the binding of the SARS-CoV receptor-binding domain to the ACE2 receptor were also found that is variable in the 2019-nCoV receptor-binding domain (including Asn439, Asn501, Gln493, Gly485 and Phe486; 2019-nCoV numbering), indicating a possible genetic recombination that could possibly enhance the transmission of this virus thus making CoViD-19 as the fastest transmitted disease that became pandemic (Science Daily, 2020) [4]

2 On-going Clinical Trials/ Previously Used Therapies as basis for CoViD-19 treatment

Due to the urgent demand on an antiviral drug because of the rapid transmission of CoViD-19 which was considered global pandemic by the World Health Organization in February 2020, there are se-veral studies conducted to try different therapies with the use of several drugs that had been effective for the previous diseases caused by coronavirus (SARS and MERS-CoV) and other human-infecting viruses. Studies were conducted to test whether those treatments could also be effective as cure for CoViD-19 today.

2.1 Glucocorticoid therapy

Recently Chinese Researchers administered glucocorticoids therapy to CoViD-19 positive cases. This treatment was proven effective to patients who have severe SARS-CoV symptoms during the SARS epidemic in the year 2003 and MERS-CoV in 2012. Although, notably it wasn't accepted to treat MERS-CoV because of some adverse effects.[19]

Researchers have investigated if glucocorticoid therapy may also be applicable to CoViD-19 patients since these 3 diseases are connected to the same virus but with different strains. They used an open labeled, randomize controlled trial with 48 severe CoViD-19 positive patients who have experienced respiratory distress, oxygen saturation, and arterial partial pressure of oxygen, septic shock, and critical organ failure from Chongqing Public Health Medical Center. In one of the studies conducted, they compared 2 groups wherein one group are treated with glucocorticoid therapy and the other one is not (control). The subjects were then invited for 28 day follow-up with a 4 scheduled visit points and samples were collected for laboratory testing such as blood and urine for different tests. Adverse events in the duration of the study were also documented which include mild side effects of taking glucocorticoid such as hypokalemia, glucose intolerance, hypertension, and pancreatitis, cutaneous hematologic, immunologic and neuropsychological effects.[19]

Results of the study revealed that out of 48 patients who were included, twenty of them showed positive effects of Glucocorticoid treatment. There is a significant decrease in their D-dimer (cytokine levels, monocyte chemo attractant protein-1 and TH1 chemokine IFN inducible proteins which increases as indicator of CoViD-19 infection) after 5-8 days of the therapy. However, results also showed that there is no difference in the mortality rate as some patient experienced mild symptoms only but there are also patients who developed severe respiratory illnesses. Furthermore, the use glucocorticoid therapy is still debatable until now because of its previous result with MERS-CoV positive patients.

2.2 IVIG (Immunoglobulin): an Adjuvant Therapy

Two Egyptian Researchers conducted a study on the use of an antibody called IVIG (immunoglobulin) as a therapy for CoViD-19 patients. This therapy had been proven effective treatment for diseases that attacks the immune system like Kawasaki disease and Guillan-Bar syndrome. Researchers investigated if Immunoglobulin treatment can also be used in treating CoViD-19 patients since the virus also targets the immune system of the patients. Immunoglobulin treatment is the mixing of antibodies to treat a number of health conditions. [20]

It has been reported that immunoglobulin treatment can deny fast - mediated cell death. Immunosuppressive effects of immunoglobulin therapy had been the most common theory. IVIG can increase the expression of the inhibitory Fc receptor and shorten the half life of self - interacting antibodies. Immunoglobulin therapy's ability to depend on preventing pathogenic immune responses through this me-chanism is based on the presence of a sialylated glycan. With the use of IVIG (immunoglobulin) it can join to a number of receptors on T cells and B cells (lymphocyte) that are relevant to auto reacti-vity and induction of tolerance to self, being immunosuppressant, anti-inflammatory and it also removes abnormal antibodies through complement system. [20]

Allah S (2020) published this study in the Journal of of International Science with the use of immunoglobulin as an adjuvant therapy for the decrease of PO2 in arterial blood gas analysis, increase liver enzyme levels, increase ferritin value and decrease number of lymphocytes which are adverse effects of CoViD – 19 infection. The study revealed that CoViD – 19 positive cases who were included in the study experienced lymphopenia because the virus directly infects and kills their lymphocytes once it carry its ACE2 receptors. After taking this treatment, patients have successfully removed abnormal antibodies through a complement system and because of this result the researchers concluded that this is an effective adjuvant therapy for CoViD-19. [20]

2.3 Chloroquine Treatment

Cortegiani et.al (2020) conducted a systematic review on the efficacy and safety of chloroquine and chloroquine related formulations in patients with SARS-CoV-2 pneumonia and other related in-vitro studies. In-vitro studies suggested the use of chloroquine, an immunomodulant drug traditionally used to treat malaria in 1960. This is effective in reducing viral replication in other infections,

including the coronavirus related diseases such as SARS-CoV and MERS CoV**.** [21]

The use of chloroquine has been approved by World Health Organization and is in the model list of essential medicines since 1940. The participants in this study were 234 patients from Asia. Results showed that there is sufficient pre-clinical rationale and evidence regarding the effectiveness of chloroquine for treatment of CoViD-19 as well as evidence of safety from long-term use in clinical practice for other indications to justify clinical research. [21]

2.4 Hydroxychloroquine and azithromycin Treatment

French Researchers investigated on the use of hydroxychloroquine and azithromycin as treatment for CoViD-19 since hydroxychlorine is an analogue of chloroquine and has been proven to have an anti- SARS CoV activity in-vitro. It has been used as treatment for SARS-CoV in 2003. Hydroxychloroquine is way better than chloroquine since it can be used for long term purposes, it can also be used with high dosage and there are only minimal concerns when it comes to drug-drug interaction. The study was conducted in the Mediterranee Infection University Hospital Institute in Marseille. The subjects of this study where 42 CoViD-19 positive patients aged 12 years old and above, without allergy to Hydroxychloroquine and are not pregnant. Twenty six (26) patients received hydroxychloroquine and sixteen (16) were control patients. The RNA was then assessed through real-time reverse transcription-PCR. After the treatment, significant differences were observed in the patients from di-fferent treatment styles. This revealed that patients who were treated with hydroxychloroquine together with azithromycin cleared the nasopharyngeal ca-rriage of the coronavirus that causes CoViD-19. Signi-ficant reduction of the viral carriage had been also significantly observed from the subjects of the study compared to the controlled group. As a conclusion, azithromycin added to hydroxychloroquine was notably more efficient for virus elimination.[22]

2.5 Hydroxychlorine Treatment

Magagnoli et.al (2020) conducted a study on the possible outcomes of using hydroxychlorine treatment for treating coronavirus. Hydroxychlorine is an antimalarial and immunomodulatory drug used for treating malaria in 2016. This drug had given highlighted because of previous studies conducted that it was an effective drug to kill CoViD-19. This study was conducted to analyze the association of hydroxychloroquine and azithromycin to be used in treating CoViD-19. The participants in this study were 385 CoViD-19 positive patients in United States Veterans Health Administration Medical Centers whether they are in patient or outpatient. The subjects identified were then classified into three groups with different treatments. Subjects who will be treated with hydroxychlorine (HC) are patients who had a dispensed drug during hospitalization. Subjects who received hydroxychlorine and azithromycin will belong to the (HC and AZ) treatment group. And the last group was patient who did not have any exposure to hydroxychlorine and azithromycin (control). They have used Fine and Gray competing proportional hazards model to assess the association between treatment status and study outcomes. After the treatment, the researchers have found out that in the hyroxychlorine group there are 27 deaths, 25 deaths in the hydroxychlorine and azithromycin group and only 18 deaths in the no treatment group. The results of the study showed that the use of hydroxychlorine with or without azithromycin has not proven effective for treating CoViD-19. It is because there is an increase of mortality rate to subjects in the hydroxychlorine treatment compared to the other treated groups. [23]

3 Current treatments and therapeutic drugs for CoViD-19 pandemic

In hope to lessen the number of mortality rates, repurposing treatments from previous viruses and diseases was taken into consideration to manage the disease. Currently, there are at least 1,303 ongoing and completed CoViD-19 studies listed on the World Health Organization's International Clinical Trials Registry Platform (Clinicaltrials, 2020).

Wu, R. et al (2020) conducted studies about the most current pharmacotherapeutics prescribed in the treatment of severe cases of CoViD-19 patients (See Table 1). Therapeutic Drugs such as antivirals remdesivir, hydroxychloroquine, chloroquine, lopinavir, umifenovir, favipiravir, and oseltamivir were used to suppress the ability of the virus to replicate and inhibit its capacity to multiply and reproduce whereas, supporting agents such as Azithromycin, Vitamin C (Ascorbic Acid), Corti-costeroids, Nitric Oxide and Epoprostenol, Sirolimus, Tocilizumab, Sarilumab and Anikinra were used not to directly kill the virus but to block cytokine production that could lead to cytokine storm, associated to the worse outcome of CoViD-19. There were other miscellaneous drugs mentioned, however the results of each studies suggests a thorough exploration of its effect against the virus. [13]

Cell and plasma-based therapy such as mesenchymal stem cell (MSC) therapy and convalescent plasma therapy has also emerged in hope to treat the disease [14]. Both therapy claims to have beneficial effect to CoViD-19 patients. For instance, the study on conva-

lescent plasma transfusion done by Shen C, Wang Z, Zhao F, et al. (2020) to five critically ill CoViD-19 patients have contributed to the clearance of the virus and also the improvement of symptoms. [15]

Mesenchymal stem cell therapy on the other hand, was highly recommended in the study of Golchin, A. et al (2020) because it is easily accessible and can be isolated from various tissues such as bone marrow and adipose tissues, including in umbilical cord, dental pulp, menstrual-blood, buccal fat pad, fetal liver, etc. Multipotent stem cells therapy can easily expand to clinical volume in a suitable period of time. It can also be stored for repetitive therapeutic usage. Clinical trials of MSCs so far haven't shown adverse reactions to allogeneic MSC and the Safety and effectiveness of MSCs have been obviously documented in several clinical trials. [16]

Meanwhile, traditional Chinese medicine has a systematic approach on treating the disease. It does not specifically proves its role in killing the virus but rather in decreasing inflammation and preventing infection. The study of Luo et al (2020) concluded that traditional Chinese medicine is more effective if given during the early onset of the disease. [17]

The specific treatment against CoViD-19 is still unknown. Currently, management of the disease is controlling or minimizing the symptoms brought about the virus. Although there were promising results of the studies, the treatment still needs to undergo several phases of clinical trials to solidify its evidence of effectiveness.

Antiviral Agents
Remdesivir
Hydroxychloroquine and Chloroquine
Lopinavir-Ritovinavir
Umifenovir (Arbidol)
Favipiravir (Avigan)
Oseltamivir (Tamiflu)
Supporting Agents
Azithromycin
Vitamin C (Ascorbic Acid)
Corticosteroids
Nitric Oxide and Epoprostenol
Sirolimus
Tocilizumab
Sarilumab
Anikinra
Miscelleneous Agents and Therapies
Angiotensin-Converting Enzyme 2 Receptor
Ibuprofen
Thiazolidinediones
Indomethacin
Colchicine
Niclosamide and Ivermectin
Nitazoxanide and Tizoxanide
Anticoagulation
Traditional Herbal Medicines.

Table 1. List of Therapeutic Drugs for Treating COVID-19 as of May 11, 2020 [17]

Conclusion

SARS-CoV 2 is a member of beta (β) group of coronaviruses with genomic structure and life cycle that is a spherical or pleomorphic enveloped particles containing single-stranded (positive-sense) RNA associated with a nucleoprotein within a capsid comprised of matrix protein. In comparison to other coronaviruses, 2019-nCoV has longer spike protein (S) compared with the bat SARS-like coronaviruses, SARS-CoV, and MERS-CoV. However, phylogenetic analysis of beta coronaviruses suggests that the external receptor-binding domain (RBD) of 2019-nCoV was closer to SARS-CoV. The only difference between the two was SARS-CoV has absence of 8a protein and fluctuation in the number of amino acids in 8b while 3c protein in SARS-CoV-2. The rapid spread of SARS-CoV 2 worldwide cause an urgent demand on antiviral drug. Its similarity to other coronaviruses stirred scientists to try therapies using several drugs that had been effective from previous diseases caused by coronavirus (ex. SARS-CoV, MERS-CoV). Glucocorticoid, hydroxychloroquine with azithromycin, chloroquine and imuunoglobulin are some of the therapies used to treat previous viral diseases and now

being tested for effectiveness in treating CoViD-19.

Among the four mentioned treatment, there were two treatments that showed promising result to manage CoViD-19 patients, these are IVIG (immunoglobulin) and hydroxychloronique. Other antiviral drugs are still under clinical trials for its effectivity such as remdesivir, lopinavir, umifenovir, favipiravir, and oseltamivir. These were also supported with other drugs such as vitamin C (ascorbic acid), corticosteroids, nitric oxide and epoprostenol, sirolimus, tocilizumab, sarilumab and anikinra. Moreover, the exploration of using mesenchymal stem cell (MSC) therapy, convalescent plasma therapy and traditional Chinese medicine shows favorable results in treating CoViD-19.

The treatment for CoViD-19 was closely anchored with the previous treatment for MERS-CoV and SARS-CoV. The previous treatments for coronaviruses were used to serve as a guide and baseline in predicting the result of the present treatment for CoViD-19. However, regardless of how similar SARS-CoV-2 to both coronaviruses, especially to SARS-CoV, most treatments have not enough evidence in treating CoViD-19. Moreover, the effectiveness of treatments could also be connected with the study design, sample size and drug combination. It is important to identify the structure, basis of replication and pathogenicity of CoVid19 in order to find way for special treatment and prevention. Researchers must also look into the difference in the length of the spikes in CoViD-19 which would most likely play an important role in the pathogenesis and treatment of this virus.

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