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Review

SARS-CoV-2; from vaccine development to drug discovery and prevention guidelines

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Abstract: All species of coronavirus may cause infections in birds which is known to us since the 60s, but recently, from Nov 2019, the disease emerged in humans from the seafood market in Wuhan city. The previous viral outbreaks like SARS-CoV and MERS-CoV have also shown a greater mortality rate when transmitted to humans than other animals. An emerging concern in the 2019 novel coronavirus (SARS-CoV-2) is in terms of developing vaccine or discovery of new drugs to overcome the current viral pandemic. In this rapid-review, we aim to update the available data on coronavirus with the latest findings and achievements. So far, great steps have been taken such as hrsACE2 by a Swedish team from Karolinska Institute. Monash University announced the efficacy of Ivermectin to overcome COVID-19. The CRISPR/Cas13d as a new innovative therapeutics based might overcome the challenge of COVID-19. those strains of virus which lacking E protein-encoding regions are the perfect choice for vaccine development.

Keywords: COVID-19; vaccine; drug discovery; hrsACE2; ivermectin; famotidine

1. Introduction

According to the WHO (World Health Organization), diseases, especially with the viral cause, will be a serious issue and endanger global health. Since the beginning of the 21st century, a couple of viral outbreaks shocked the world such as SARS-CoV, H1N1 influenza, and MERS-CoV in 2003, 2009, and 2012, respectively. The last of this kind named the coronavirus disease 2019 (COVID-19) observed for the very first time on 17th Nov 2019 in Wuhan, China [1]. Further research suggested that this virus began from Wuhan's seafood wholesale market and the latest finding showing that Pangolin-Cov has 91.02% homology to COVID-19 [2]. As of now, coronavirus infection has been reported in 213 countries where the highest number reported from the USA and following with Brazil, India, Russia, Peru, Chile, Spain, the UK, Mexico, and Iran [3]. Countries from the Middle East and South America due to lack of transparency standing in a lower place in the ranking of COVID-19 prevalence and mortality, but evidence showing that the situation is worse than their claims. The contingency of the virus more than expected that forced WHO on 30th Jan. 2020 declared the state of emergency and changed the status to the pandemic by 11th March 2020. As of 8th July 2020 near 12 million cases have been reported worldwide with more than 547,000 mortality [4]. In the healthcare section only in the united states of America more than 5400 doctors, nurses, and other health care providers infected, and unfortunately, more than dozens of them passed away due to the infection only till the end of April [5]. Fifteen top the list countries are mostly from developed and western countries; however, the main reason is that developed countries such as USA, France, the UK, Italy ranking in the higher place is the true application of "freedom of information" and "Human rights" in such countries which is indeed lacking in 90% of middle eastern and also African countries and; So, the real rate of positive cases and mortality officially manipulated due to lacking transparency throughout the system.

2. Etiology, history, and origin

Based on the genomics analysis, coronaviruses have been categorized into 4 subdivisions: α, β, δ, and γ CoVs. The α-CoVs group includes species such as Porcine epidemic diarrhea coronavirus (PEDV), Feline coronavirus (FeCoV) and Human coronavirus 229E (HCoV-229E); the β-CoVs group includes species like Human coronavirus HKU1 (HCoV-HKU1), Middle Eastern respiratory syndrome coronavirus (MERS-CoV), Severe acute respiratory syndrome coronavirus (SARS-CoV) and Bat coronavirus (BCoV); and finally γ-CoVs includes species such as Turkey coronavirus (TCoV) and Avian infectious bronchitis virus (IBV) [6]. The SARS-CoV-2 belongs to the *Betacoronavirus* group. Phylogenic analysis disclosed that SARS-CoV-2 has 90% homology to bat—SL coVZC45 and Bat-SL-CoVZXC21, and had about 80% homology to SARS-Cov and 50% homology to MERS-Cov [7]. By enlarge, all species of this family can cause enteric, respiratory, neurological, and hepatic diseases in animals such as cattle, camels, bat, and 7 species HCoVs have the power to infect humans. Identification of human coronavirus back to 60s, but the rest discovered in the 21st century [8].

3. In other animals

Tiger: Bronx zoo, New York city, announced that a tiger's test reported positive for novel coronavirus.

Pets: Dr. Farina Mustaffa from faculty of Veterinary Sciences, UPM Malaysia, announced that a cat from Belgium and a dog from Hong Kong reported positive for SARS-CoV-2 both of the owners also found to be COVID-19 positive [9].

4. Transmission

By the end of 2019 a couple of SARS-CoV-2 disease cases connected to the Wuhan city Fish wholesale market, and transmission route of animal-human predicted. However, the following cases did not come in touch with suspected animals. Consequently, the results found to be that this virus can transmit from human to human too. The possibility of transmission before symptoms develop seems to be infrequent, although it cannot be excluded. Moreover, there are suggestions that individuals who remain asymptomatic could transmit the virus. The above finding showing that the best way to Covid-19 pandemic is isolation. Like other pathogens of the respiratory system such as rhinovirus and flu, the disease communication is thought to be by droplets via sneezing or coughing. Transmission via droplets and aerosols is one of the challenges. Aerosol transmission is also possible in case of protracted exposure following aerosol generation such as suction of tracheal secretions, bronchoalveolar lavage, intubation of the COVID-19 patient in a closed space. The data analysis showing that in most cases the spread is between patient and health care workers and family members [10].

5. Genome structure and pathogenesis

SARS-CoV-2 is a +ssRNA virus with a diameter of 60 to 140 nanometer with spike-like structures that can be observed under an electron microscope. Consequently, for coronavirus can infect man including NL63, HKU1, OC43, and 229E, so far reported in humans and general causes respiratory diseases, but in a mild form. CoVs are enveloped with nucleocapsid [11]. To describe SARS-Cov-2 pathogenic nature its genome should be studied. This type of coronavirus possesses a positive single-strand RNA in its almost 30 kb length; which makes SARS-Cov-2 the heaviest and also the largest RNA virus. The RNA virus has a 5’ cap and a 3’ poly-A tail. RTC (replication-transcription complex) is responsible for the virus transcription, which is wrapped in a double-membrane capsule and through sequences of sgRNAs synthesis (sub-genomic RNA) [12]. Besides, transcription termination happens at the CCAAT box, which can be found between open reading frames (ORF) which has a templet function to produce sub-genomic mRNA. In a unique coronavirus genome, a minimum of 6 ORFs shall be found [13]. Each coronavirus expresses exclusive proteins that are encoded by assigned sgRNA. Coronavirus virulence mechanism and its pathophysiology and specially SARS-Cov-2 associated structural and NSPs (nonstructural proteins). For example, scientists reported that NSPs can suppress the immune system of the host. Amid structural proteins properties, the capsule (envelope) possesses a critical key role in pathogenicity during construction and release of genetic material. However, many of these features (e.g., those of nsp 2, and 11) have not yet been described [13,14].

6. Clinical features

The covid-19s clinical features are widely different and depend on the patient’s condition, from asymptomatic, mild, or severe to critical respiratory failure which necessarily needs a mechanical

ventilator in an ICU (intensive care unit) and there are chances of MODS (multiple organ dysfunction syndromes) or septic shock. Signs and symptoms of COVID-19 may appear 2 to 14 days after exposure and include fever, dry cough, shortness of breath or dyspnea, fatigue, myalgia, sore throat, headache, diarrhea, vomiting, and loss of smell or taste [15,16]. In one of the first reports on the disease, Huang *et al*. illustrated that patients (n. 41 patients) suffered from fever, malaise, pertussis, and dyspnea. Chest computerized tomography (CT) scans showed pneumonia with abnormal findings in all cases. About a third of those (13 patients, 32%) required ICU care, and there were 6 (15%) fatal cases in the above study [15].

The authors of the Chinese CDC report divided the clinical manifestations of the disease by their severity:

- Mild disease: non-pneumonia and mild pneumonia; occurred in 81% of cases.
- Severe disease: dyspnea, more than 30 respirations per min, blood oxygen saturation (SpO2) ≤ 93%, occurred in 14% of cases.
- Critical disease: respiratory failure, septic shock, and/or multiple organ dysfunction (MOD) or failure (MOF); occurred in 5% of cases.

Wenzhong and Hualan from China reported that attacks the 1-Beta Chain of Hemoglobin and captures the porphyrin to inhibit human heme metabolism, the analysis proven that surface glycoprotein and ORF8 shall bind to porphyrin. Simultaneously ORF10, ORF3a, and ORF1ab proteins may manage to strike the heme unit of 1 beta chain of hemoglobin to detach the Fe from the porphyrin. This strike will lead to lesser hemoglobin capacity to carry O_2 or CO_2. The pulmonary cells have severe sensitivity to inflammation and poisoning because of the capability to O_2 to CO_2 continuously, which subsequently end up in a glass-like structure in a lung CT scan [17].

Mild cases of Pneumonia may present signs like mild pyrexia, pertussis, pharyngitis, rhinitis, cephalgia, malaise, and myalgia. In contrast to other human coronaviruses, symptoms like diarrhea are rarely presents. In moderate cases, symptoms such as dyspnea may present. In severe cases of pneumonia high fever also seen along with respiratory distress and dyspnea which count as more than 30 breaths per minute associated with hypoxia. The diagnosis of ARDS (Acute Respiratory Distress Syndrome) needs clinical criteria. ARDS is redolent of severe onset of critical symptoms of respiratory failure. People with underlying conditions such as chronic lung disease, cardiovascular disease, hypertension, diabetes, and malignancy, as well as the elderly, are more likely to develop a severe disease [18]. Brown *et al* from Stanford reported that in a study of 517 people who tested positive for COVID-19, they also evaluate the cases for the chance of any co-infection like a respiratory syncytial virus, Influenza A & B, adenovirus, rhinovirus, and bacterial pneumonia. Surprisingly, 127 out of 517 COVID-19 cases were positive for one of the above infections too [19].

7. Diagnostic and laboratory findings

The WHO recommends collecting samples from upper and lower respiratory tracts such as naso-oropharyngeal and bronchoalveolar lavage or endotracheal aspirate, respectively [18]. The Bronchoalveolar lavage (BAL) sampling has to perform on mechanically ventilated patients only. Because the samples collected from the lower part of the respiratory system may remain +ve for a longer period. The obtained samples need to be kept at 4ºC. In the research center or lab, the viral genome amplification done by RT-PCR (reverse polymerase chain reaction) that includes ds-DNA synthesis

from on ss-RNA. After completion of this stage, we look for conserved domains throughout the viral genome. The probes hat usually utilized depended on the preliminary genome sequence deposited to databanks by Shanghai Public Health Clinical Center & School of Public Health, Fudan University, Shanghai, China on Virological.org. if the outcome of the test is +ve, the next suggestion is to repeat the test for the confirmation. By considering the lab tests in the preliminary phase of the COVID-19, a decreased or normal total WBC and lowered lymphocytes can be observed. Decreased lymphocyte shall be a negative prognosis factor. Elevated liver enzymes values, muscle enzymes, LDH, and also C reactive protein may be found. Yet the procalcitonin level would be in range. In critical and terminal patients, the D-dimer test showing increased value and decrease in blood lymphocytes have been observed besides coagulation disorder and high amylase, etc. [18]. The latest study by Cheng *et al*, conducted in admitted patients in a hospital in China suggesting that patients with higher creatinine and blood urea nitrogen (BUN) and acute kidney injury (AKI) showed a greater risk for in-hospital mortality rate in COVID-19 cases [20].

8. Treatment of COVID-19

As of now, there is no vaccine or drug to combat the SARS-CoV-2 virus, but currently, much research going on in the field of vaccine development or even drug discovery. The conventional therapy in ICU wards usually includes symptomatic management such as oxygen therapies in case severe COVID-19. In late March 2020, Aaron Miller and his team from the New York Institute of Technology reported that with BCG vaccination policies showed a better recovery rate of confirmed cases than countries without compulsory BCG vaccination like Italy, USA, and the Netherlands. Based on these epidemiological studies 2 clinical trials are underway to prove this claim [21].

So far, there is no absolute treatment or cure for COVID-19. Currently many reports on trial either on vaccines or new drugs going on worldwide [27]. Here going to discuss available antiviral medicines and compare their class of action:

- Nucleotide analogs drugs such as Remdesivir.
- Protease inhibitor such as Lopinavir/Ritonavir.
- Neuraminidase inhibitors such as Oseltamivir.
- Small molecules such as umifenovir (available only in China and Russia and could not get FDA approval.
- DNA synthesis inhibitors such as lamivudine, disoproxil, and tenofovir.
- Antimalarial drugs such as chloroquine and hydroxychloroquine (Plaquenil).
- 3CLpro inhibitor such as vinylsulfonic acid.

Plaquenil is also prescribed and meanwhile in control clinical trials regarding human immunodeficiency virus treatment and also in a recent clinical trial with patients on COVID-19 treatment. Hydroxychloroquine in combination with azithromycin was effective in patients with COVID-19 [22,23].

The latest and much spoken antiviral drug is Fujifilm developed Favipiravir which is announced on 9th April that they began II phase of its clinical trials under FDA guidelines [24]. Dr. Kylie Wagstaff from Monash University-Australia announced that in there *in vitro* study on Ivermectin -a conventional antiparasitic drug- after 48 hrs demonstrated a significant action to kill SARS-CoV-2 and now getting ready for in vivo study in a couple of weeks. Ivermectin is a cheap (around $0.12 for a complete course

of treatment) and widely available drugs which previously also proven to be a good choice against Dengue, Influenza, Zika, or even HIV viruses [25]. In another announcement, Prof Arturo Casadevall from Johns Hopkins proposed that the standards method of plasma isolation can be especially for health-care workers. In this convalescent plasma therapy, plasma of cured person from COVID-19 taken, were isolated and transferred to a designated person [26]. This method obtained FDA approval. On 4th April Vanessa Monteil announced that she and her team successfully test a new drug named hrsACE2 in vitro with no toxicity and significant potency to recovery from COVID-19 infection [27]. Jokinen et al reported that patients with a history of exposure to IgG positive (*mycoplasma pneumonia*) have greater recovery or even resistance to SARS-CoV-2 in comparison to other patients. The reason is re-programmed immune cells [28]. In late April New York city hospital reported a significant recovery rate by patients who took heartburn medicine of famotidine.

9. Cutting-edge advancement in treatment

The latest effort in the field of immunomodulatory therapy done by Pluristem Therapeutics Inc, based in Haifa-Israel, a pioneer in stem cell therapy in the clinical trial stage. Previously successfully passed the tests in CLI (critical limb ischemia), muscle regeneration after hip fracture operation the last but not least in treatment of ARS (acute radiation syndrome) all above are in late phase III stages. On 7th April, Yaki Yanay, CEO of Pluristem Therapeutics announced that all 7 patients found positive for the COVID-19 showing 100% satisfactory results after treated by a single 300-million-cell-dose of PLX-PAD, an allogeneic mesenchymal-like cell therapy [29]. Other treatments under investigation and clinical trials such as intravenous immunoglobulin (IVIG) and recombinant interferon beta (IFN beta-1a and IFN beta-1b), and corticosteroid therapy (methylprednisolone, dexamethasone, and hydrocortisone) can be considered for the treatment of severe COVID-19 patients [30,31]. The use of immunosuppressive drugs has been considered, given that the proposed tissue damage in COVID-19 appears to be caused by cytokine storms. Recent clinical trials have been conducted using tocilizumab as an interleukin 6 inhibitor, with promising results in the treatment of patients with COVID-19 [32,33].

10. Coronavirus vaccine challeneges

The challenges underway of vaccine development are including (1) safety of the developed vaccine; (2) Providing longer protection time; (3) 50+ people; as vaccines usually don't respond so well on older people like on younger generations. By March 2020 many research centers, pharmaceutical, and biotech companies announced first-hand trials on developing vaccines. The preliminary trials announced as follow:

- The University of Queensland reported an investigation on the potential molecular-clamp-like-structure vaccine. The concept of this vaccine is to regulate and manage viral protein orderly to trigger an immune response [34].
- VIDO-InterVac (International Vaccine center) in collaboration with the University of Saskatchewan, joint project granted by the federal government of Canada to develop a vaccine that will go under *in vivo* trial in March/April 2020 and will go for human testing in later 2021 [35].
- MIGAL Galilee research institute- Israel, in scientific cooperation of IIBR took the first step towards *in vivo* trial on a rodent which reported on 2nd April 2020 [36].

- Chinese Center for Disease Control and Prevention has been announced the preliminary try on developing a vaccine with the help of the University of Hong Kong [37].
- On 29th Jan'20 Henneke Schuitemaker, CEO of Janssen Pharmaceutical companies announced that Jenssen co-developing an oral vaccine with their American-based biotechnology sister company [38].
- Washington University-St. Louis reported their project on developing a vaccine on 5th March'20 [39].
- Emergent Biosolutions announced that their 1st phase of the clinical trial will be held in July 2020 [40].
- The health ministry of India on 12th March announced within 2 years will develop vaccines on 11 isolates of COVID-19 [41].
- German biotech company, CureVac, received an €80 million grant from the EU for developing an mRNA vaccine on 16th March [42].
- Pfizer, Pharmaceutical giant on 17th March announced a collaboration with the German BioNTech company to develop a vaccine, which is currently on pre-clinical stage, and clinical trials will start by May 2020 [43].
- French CEPI (Coalition for Epidemic Preparedness Innovations) on 19th March announced that they invest US$4.9 for COVID-19 vaccine research by institute Pasteur, University of Pittsburgh, and Austrian-based Themis Bioscience. The total amount of investment will be around US$ 29 million; which including developing partners like Curevac, Novavax, Moderna, Inovio, university of Oxford, the University of Queensland, and the University of Hong Kong [44].
- On 20th March Health ministry of Russia announced that six different vaccines of COVID-19 started animal testing [45].

One of the major setbacks for vaccine production is that unlike other viruses, SARS-CoV-2 cannot be injected into chicken eggs for mass-production like the flu vaccine, as it cannot replicate inside the chicken egg [46].

11. Successful trial and hopeful landscape of COVID-19 vaccines development

As of date, 10 vaccine candidates made it to the 2nd and 3rd phase of trials. They belong to different families of vaccines such as Non-replicating viral vector, RNA-based, inactivated form of virus, and DNA-based. Based on WHO factsheet which is published by 9th June 2020, the only vaccine so far could make it into the 2b/3rd phase of clinical trials is the university of Oxford-AstraZeneca candidate by the name of ChAdOx1-S which is a Non-replicative viral vector vaccine. The other candidate could successfully make it into is from the Chinese giant's CanSino biologicals vaccine candidate named Adenovirus Type 5 vector. Moderna's RNA-based vaccine candidate named LNP-encapsulated mRNA successfully passed the 2nd face of the clinical trial. The other candidates at 1/2 and 1st phase of clinical trials including inactivated-form vaccine from Wuhan institute of biological products, Beijing institute of biological products, and Sinovac respectively. the other nominated vaccine is protein subunit-based product from Novavax which is like Pfizer's RNA-based vaccine are at 1/2 phase. And the last two vaccine candidate at the preliminary phase of clinical trials are from the Chinese Academy of medical sciences and Inovio pharmaceuticals, respectively [47].

12. Prevention guidelines in approach to Iranian population and health care workers

Patients and families should receive instruction to:

- Elude coming close to confirmed cases of COVID-19.
- Wash hands for 20 times per day and a minimum of 20 seconds each time.
- Refrain any sort of contact with wild or farm animals.
- Individuals with signs of ARDS keep their distance, cover cough, or sneeze with disposable tissues or clothes, and wash their hands.
- Patients with impaired or weakened immune systems should avoid going to public places. If the immunocompromised person had to be a somewhere closed area or hall like in a meeting should be geared by personal hygiene, masks, and gloves. More importantly, such rooms and conference halls should be disinfected by antiseptic or 70% alcohol. However, the cloud meeting and online conferences such as webinars are still the best choices.
- Strict personal hygiene measures are necessary for the prevention and control of this infection.

13. Conclusions

The COVID-19 disease is the first of its kind in modern history which caused the pandemic. Researchers so far made great achievements in terms of genomic analysis of SARS-Cov-2 transcriptome analysis and identifying its novel mutations and working 24 × 7 to develop a vaccine and to discover safe and effective drugs against this dreadful virus. In this latest succinct rapid-review, we tried to cover all the basics along with the latest findings and trials to help researchers, scientists, and graduate students especially in the fields of biology and medicine. With the current status of the disease, we should new lifestyle and great changes in every aspect of life in the near future which nobody knows how it will look like; only time can say.

Conflict of interest

The authors confirm that there is no conflict of interest.

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