

Review Article

Current Trend in Treatments and Vaccines Development of Novel COVID 19

Farouk S Nas¹, Muhammad Ali^{2*}, Lurwan Mu'azu³, Muhammad S. Abdallah⁴ and Abdullahi Yahaya⁵

¹Department of Biological Sciences, Bayero University Kano, Nigeria

²Department of Microbiology, Federal University Gusau, Nigeria

³Department of Biological Sciences, Federal University Gusau, Nigeria

⁴Desert Research Monitoring and Control Centre, Yobe State University Damaturu, Nigeria

⁵Department of Biological Sciences, Kano University of Science and Technology, Wudil, Nigeria

***Corresponding Author**

Muhammad Ali

Article History

Received: 21.06.2020

Accepted: 01.07.2020

Published: 12.07.2020

Abstract: A novel (new) corona virus (SARS-CoV-2), causing an emerging corona virus disease called COVID-19 was first detected in Wuhan City, Hubei Province, China. The disease outbreak in China which has taken a catastrophic turn with high toll rates in China and subsequently spreading across the globe which resulted in a pandemic situation in the world. The rapid spread of this virus to more than 213 countries and territories affecting nearly 9,504,264 persons with at least 5,161,054 have recovered while causing more than 483,681 human deaths. The SARS-CoV-2 virus belongs to the genus Beta corona virus, like MERS-CoV and SARS-CoV, all of which originated in bats. It is highly contagious, causing symptoms like fever, dyspnea, asthenia and pneumonia, thrombocytopenia and the severely infected patients succumb to the disease. Till date, no clinically proclaimed, proven therapeutic antibodies or specific drugs and therapeutics, and vaccines have turned up. In this review article, we describe the vaccine development and developing potential therapeutic options that can be explored to manage this pandemic virus infection, which would help in valid countering of COVID-19.

Keywords: Coronavirus, Covid 19, treatment, vaccine development.

INTRODUCTION

Coronaviruses are positive-sense, single-stranded RNA viruses belonging to the family Coronaviridae (subfamily Coronavirinae) that infect a wide range of host to produce diseases ranging from common cold to severe/fatal illnesses. The novel virus was initially named “2019-nCoV” which was changed to “SARS-CoV-2” by the Coronavirus Study Group of International Committee on Taxonomy of Viruses, since it was found to be the sister virus of severe acute respiratory syndrome coronavirus (SARS-CoV) [1]. The ongoing coronavirus threat that emerged in China has rapidly spread to other countries and has been declared as a global health emergency by the World Health Organization (WHO). Many nations are diverting their best efforts for the implementation of appropriate preventive and control strategies. Neither vaccines nor direct-acting antiviral drugs are available for the treatment of human and animal coronavirus infections [2-4]. Many efforts have been directed to develop vaccines against human CoV infections in recent decades, but a limiting factor is the degree of cross-protection rendered by these vaccines due to their extensive sequence diversity [5]. Various vaccines, immunotherapeutics, and drug options have been explored during the recent threats of Zika, Ebola, and Nipah viruses [6,7,8] as well as against previous CoVs including SARS- and MERS-CoVs [3, 5, 9, 10]. These valuable options can be exploited for their potency, efficacy, and safety along with expediting other ongoing research [2, 4, 11] so as to discover valuable modalities for tackling the emerging COVID-19, but as yet there is no effective vaccine or therapeutic, for which intense efforts are ongoing. Most of the therapeutic options that are available for managing COVID-19 are based on previous experiences in treating SARS- and MERS-CoV.

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According to WHO guidelines, infected patients will receive supportive care including oxygen therapy, fluid therapy, and antibiotics for treating secondary bacterial infections. The WHO also recommends the isolation of patients suspected or confirmed for COVID-19 [12]. The major therapeutic drugs that might be effective in managing COVID-19 include remdesivir, lopinavir/ritonavir alone or in combination with interferon- β , convalescent plasma, and mAbs [13]. Nevertheless, before utilizing these drugs for COVID-19 pneumonia patients, clinical efficacy, and safety studies should be conducted.

Coronaviruses

Coronaviruses, members of the family *Coronaviridae* are enveloped, positive-stranded RNA viruses which appear to demonstrate spikes of glycoproteins protruding from their viral envelopes, thus exhibit a corona or halo-like appearance [14, 15]. Earlier coronaviruses were found to be the causative agents for a broad spectrum of respiratory and gastrointestinal diseases in both wild and domestic animals, including birds, pigs, and rodents, among others [16]. Previous studies have found that six strains of CoVs are capable of infecting human, among which four strains circulate yearly to cause the common cold, and other two strains which are the source for severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS-CoV), respectively [15-18]. Coronaviruses, among all known RNA viruses, have the largest genomes ranging from 26 to 32 kb in length [19, 20]. In addition to encoding structural proteins, a significant chunk of the coronavirus genome is transcribed and translated into a polypeptide, which encodes proteins essential for viral replication and gene expression [21]. The ~306 a long main protease (Mpro), which is a highly conserved sequence, is a crucial enzyme for coronavirus replication [21]. Mpro has been utilized for developing anti-coronaviral drugs [22]. Nevertheless, in the past two decades, a massive amount of research has been done to understand the replication, molecular basis of the coronavirus infection and evolution, develop effective therapy in forms of both vaccines and antiviral drugs, and propose efficient measures for viral detection and prevention [16, 17, 23].

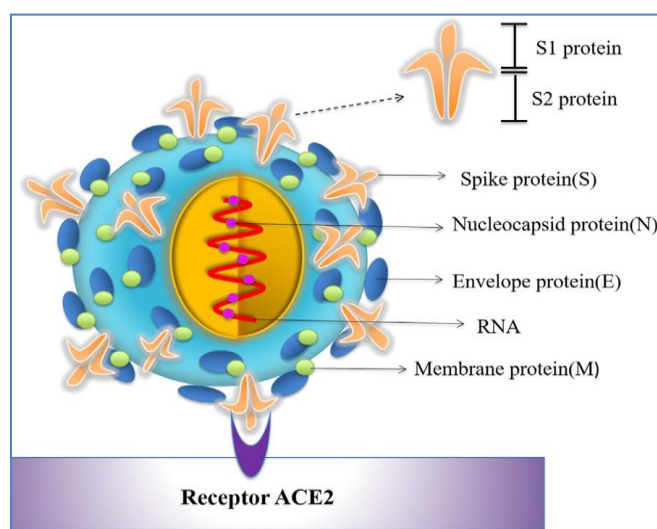


Fig-1: Schematic diagram of SARS-CoV-2 structure and ACE2 receptor on the host cell surface [24]

Clinical Pathology of COVID-19

The coronavirus claimed its first life on January 10th, 2019, and since then the death toll has climbed at an alarming and accelerating rate. The virus seems lethal, causing severe acute respiratory symptoms, including fever, dyspnea, asthenia and pneumonia, thrombocytopenia, and increased C-reactive protein and lactate dehydrogenase levels among people in Wuhan, China [25]. As per reports, mild COVID-19 cases revealed higher levels of pro-inflammatory cytokines and chemokines like IFN- α , IL-1 β , MCP-1 and IP-10 whereas individuals with severe COVID-19 had upregulation of IP-10, IL-8, IL-10, TNF- α , G-CSF, MCP-1 and MIP-1A [26,27] resulting into cytokine storm syndrome followed by severe pulmonary damage and death due to respiratory failure. Additionally, all the blood cells except neutrophils were reported to be decreased with fall in lymphocytes subsets like T cells, B cells and NK cells in severe COVID-19 cases [27]. Chest radiographs show invasive lesions in both lungs with flaws of a variable degree in the lungs. Additionally, bilateral multilobular subsegmental consolidation, ground glass opacity with many mottling was also reported in the COVID-19 patients [26, 28]. Recently, myalgia and fatigue are found associated with rhabdomyolysis in a COVID-19 patient in Wuhan, China suggesting the need of rapid clinical diagnosis followed by favourable hydration treatment to reduce the risk of severe outcomes as a result of rhabdomyolysis [29].

Additionally, COVID-19 patients may also manifest neurological signs such as headache, nausea and sometimes vomiting, but even dysgeusia and anosmia. Moreover, SARS-CoV infection has been reported in nervous tissue of experimental animals and patients with heavy involvement of brainstem. In this context, acute respiratory failure

in COVID-19 patients suggests the probable invasion of the brain by SARS-CoV-2 [3]. Recently, a study supported the neurotropic potential of the SARS-CoV-2 virus as 36.4% of involved COVID-19 patients manifested neurological signs [30]. Those who developed severe pneumonia, pulmonary oedema, hypoxemic respiratory failure, gastrointestinal infection, multiple system failure or Acute Respiratory Distress Syndrome (ARDS) succumb to the disease. The threat is still looming high on the event of this deadly virus created a pandemic situation [31, 32].

Treatment strategies for Covid 19

Due to the absence of a specific antiviral therapeutics and vaccine, main treatment strategy for COVID-19 is supportive care, which is supplemented by the combination of broad-spectrum antibiotics, antivirals, corticosteroids and convalescent plasma [33] (Table 1). HIV protease inhibitors ritonavir and lopinavir have been used, typically in combination with appropriate antibiotics or with IFN α -2b, in the treatment of SARS-CoV-2 infected patients [34, 35]. Nucleoside analogs such as ribavirin [3] may be potentially beneficial for the treatment of COVID-19, since ribavirin was approved for treating respiratory syncytial virus (RSV) infection [36] and used extensively during the SARS and MERS outbreak [37]. However, ribavirin had severe side effects such as anemia [36] and whether it had sufficient antiviral activity against SARS-CoV-2 is unclear. Nucleoside analogs favipiravir (T-705) can effectively inhibit the activity of RNA polymerase of RNA viruses such as influenza [38]. A recent *in vitro* study found that it had the anti-SARS-CoV-2 activity [39], but the *in vivo* effect remains elusive. Remdesivir may be the most promising antiviral drug for treating COVID-19. It has *in vitro* and *in vivo* antiviral activity against a wide array of RNA viruses including SARS and MERS [40], and could decrease viral loads and pathology of lungs in animal models [4]. A study showed remdesivir markedly inhibited the infection of SARS-CoV-2 in Vero E6 cells [39], and most symptoms of the first US patient infected with SARS-CoV-2 had resolved swiftly after intravenous administration with remdesivir [41]. Currently, it is under clinical trial to evaluate the safety and efficacy of intravenous remdesivir for patients with SARS-CoV-2 infection [42]. Oral oseltamivir has been used for the treatment of the cases with SARS-CoV-2 [34], while its efficacy currently remains uncertain.

Table-1: Conventional treatment of patients with SARS-CoV-2 infection

Type of treatment	Therapeutic agent	References
Oxygen therapy	Non-invasive mechanical ventilation	[33]
	Invasive mechanical ventilation	
	Nasal cannula	
	Extracorporeal Membrane Oxygenation	
Antibiotic combination	Azithromycin	[33]
	Amoxicillin	
	Fluroquinolones	
Antiviral drugs	Lopinavir/ ritonavir	[33,35]
	Ribavirin	[33,36]
	Favipiravir (T-705)	[38,39]
	Remdesivir	[4,39,40]
	Oseltamivir	[35]
Antimalarial drugs	Chloroquine	[39,43]
	Hydroxychloroquine	[44]
Immunomodulators	Interferon	[34,35,44]
	Sarilumab	[44]
	Tocilizumab	[44]
Corticosteroids	Methylprednisolone	[34]
Convalescent plasma	Convalescent plasma	[4]

Host-targeted small molecules approved for other human diseases may modulate the virus-host interactions of SARS-CoV-2. Chloroquine, a potential broad-spectrum antiviral drug [45, 46], was shown by a recent study had anti-SARS-CoV-2 activity [39]. Its clinical efficacy is under study in an open-label trial (ChiCTR2000029609) [3]. IFN α (5 million U) atomization inhalation was recommended as antiviral therapy to treat SARS-CoV-2 [33]. A trial testing IFN α -2b combination of the approved anti-HCV inhibitors has been initiated [35], however, whether it could act synergistically against SARS-CoV-2 is unclear. Corticosteroids were frequently used to suppress the elevated cytokine levels in patients with SARS-CoV [47, 48] and MERS-CoV [49, 50]. However, there are no evidences showing that the mortality of SARS and MERS patients was reduced by the treatment with corticosteroids, while the clearance of viral was delayed by /such treatment [51, 52, 53]. Consequently, corticosteroids are not suggested to systemically use in SARS-CoV-2 infected patients [54]. Previously, it was shown that, either in severe influenza or SARS-CoV infection, convalescent plasma treatment could significantly decrease viral load and reduce the mortality [43, 51]. Convalescent plasma has been used for severe SARS-CoV-2 infection in China [4], although promising, the efficacy and safety need to be carefully further

evaluated. WHO also concluded "to date, there is no specific medicine recommended to prevent or treat SARS-CoV-2" [55].

Development of vaccines against COVID-19

Vaccine development is the most effective strategy to prevent and eliminate infectious disease. By learning from the vaccine development path of MERS and SARS, several platforms, including DNA, mRNA, recombinant protein, and adenoviral vector, are being investigated. Since S protein and its fragments, such as S1, S2, RBD, and N protein, are prime targets for developing MERS and SARS vaccines, it is expected that similar regions of SARS-CoV-2 could also be considered as critical targets for COVID-19 vaccines [2,39]. Since the genetic sequence of SARS-CoV-2 has been released on 11 January 2020, more than 140 pharmaceutical companies and academic institutions from many countries have engaged in actively developing COVID-19 vaccines. According to World Health Organization (WHO), as of 10th June 2020, there are about 13 candidate vaccines in clinical evaluation (Table 2) and about 128 candidate vaccines in pre-clinical evaluation [56].

Table-2: Candidate vaccines in clinical evaluation as of 10th June 2020

Platform	Type of candidate vaccine	Developer	Current stage/regulatory status
Non replicating viral vector	ChAdOx1-S	University of Oxford/AstraZeneca	Phase 2b/3 2020-001228-32 Phase ½ 2020-001072-15
Non replicating viral vector	Adenovirus Type 5 vector	CanSino Biological Inc./Beijing institute of Biotechnology	Phase 2 ChiTR2000031781 Phase 1 ChiTR2000030906
RNA	LNP-encapsulated mRNA	Moderna/NIAID	Phase 2 NCT04405076 Phase 1 NCT04283461
Inactivated	Inactivated	Wuhan Institute of Biological Products/Sinopharm	Phase ½ ChiTR2000031809
Inactivated	Inactivated	Beijing Institute of Biological Products/Sinopharm	Phase ½ ChiTR2000032459
Inactivated	Inactivated + alum	Sinovac	Phase ½ NCT04383574 NCT04352608
Protein Subunit	Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with matrix M	Novavax	Phase ½ NCT04368988
RNA	3 LNP-mRNAs	BioNTech/Fosun Pharma/Pfizer	Phase ½ 2020-001038-36 NCT04368728
Inactivated	Inactivated	Institute of Medical Biology, Chinese Academy of Medical Sciences	Phase 1 NCT04412538
DNA	DNA plasmid vaccine with electroporation	Inovio Pharmaceutical	Phase 1 NCT04336410
Non repl. viral vector	Adeno-based	Gamaleya Research Institute	Phase 1
RNA	saRNA	Imperial College London	Phase 1
RNA	mRNA	Curevac	Phase 1

Nucleic acid vaccines

Several major biotechnology companies have advanced nucleic acid platforms for COVID-19 vaccine development. The Innovation and Value Initiative (IVI), Inovio and the Korea National Institute of Health (KNIH) are collaborating with the Coalition for Epidemic Preparedness Innovations (CEPI) to test the safety and immunogenicity of a DNA vaccine named INO-4800 in Phase 1/2 clinical trial in South Korea (Inovio Pharmaceuticals, 2020). Both Moderna/NIH and CureVac are focusing on mRNA vaccine development, and a safety clinical trial of Moderna's candidate vaccine mRNA-1273 with a sample size of 45 volunteers was performed in March 2020 [57].

Subunit vaccines

Subunit vaccines based on recombinant S or S1 protein of SARSCoV and MERS-CoV have been demonstrated to be efficacious in many studies [58,59,60]. Clover Biopharmaceuticals is developing a vaccine consisting of a trimerized SARS-CoV-2 S protein using their patented Trimer-Tag technology [61]. The receptor-binding domain (RBD)

in SARS-CoV-2 S protein was identified, and it was further demonstrated that SARS-CoV-2 RBD exhibited significantly higher binding affinity to ACE2 receptor compared to binding between SARS-CoV RBD and ACE2 [62], suggesting that the RBD-based SARS-CoV vaccines have the potential to be developed for prevention of SARS-CoV-2 infections. RBD-based vaccines are now under development by several organizations through international collaborations [34]. The pulmonary surfactant-biomimetic nanoparticles used to potentiate heterosubtypic influenza immunity can be used as adjuvant to enhance the immunogenicity of SARS-CoV-2 subunit vaccines [39].

Inactivated or live-attenuated virus vaccines

Whole inactivated or live-attenuated virus vaccines represent a traditional vaccine strategy. Researchers at the University of Hong Kong have developed a live influenza vaccine that expresses SARS-CoV-2 proteins [63]. Codagenix has developed a “codon deoptimization” technology to attenuate viruses, and the company is exploring COVID-19 vaccine strategies [64].

Virus vector-based vaccines

Vaccines based on viral vectors offer a high level of protein expression and long-term stability, and induce strong immune responses [65]. Johnson & Johnson is developing an adenovirus vectored vaccine using AdVac®/PER.C6® vaccine platforms [66]. The first COVID-19 vaccine candidate based on adenovirus vectored vaccine developed by Chen Wei group entered human clinical testing (NCT04313127) with unprecedented rapidity early on 16 March 2020. Another phase I safety trial of a recombinant adenovirus vaccine candidate (Cansino Biologics Inc., Tianjin, China), Ad5-nCoV, recruited 108 healthy adults in Wuhan, China in March 2020 [67]. Apart from adenovirus vector-based vaccine, two lentivirus vector-based vaccine candidates, COVID-19/aAPC and LVSMENP-DC have been developed by Shenzhen Geno-Immune Medical Institute. The COVID-19/aAPC vaccine was developed by applying lentivirus modification including the SARS-CoV-2 minigenes and immune modulatory genes, to the artificial antigen presenting cells (aAPCs). The Phase I clinical trial consisting of 100 participants started on February 15, 2020 and the estimated study completion date was December 31, 2024 (NCT04299724). The LVSMENP DC vaccine was developed by modifying DC with lentivirus vectors expressing SARS-CoV-2 minigene SMENP and immune modulatory genes. The Phase I clinical trial involving 100 patients was conducted on March 24, 2020 and the estimated study completion date was also December 31, 2024 (NCT04276896)[65]. As we all know that adjuvants play a critical role by enhancing immunogenicity of the vaccine candidates and make dose viable in some vaccine platforms. So far, there are at least 10 developers have engaged into developing adjuvanted COVID-19 vaccines. Vaccine developers Dynavax, Seqirus and GlaxoSmithKline have committed to making some licensed adjuvants including MF59, AS03 and CpG 1018 available for use [65]. No matter which platform we take to develop the COVID-19 vaccines, researchers need to carefully evaluate the effectiveness and safety of the candidate vaccine at each step. In this situation, SARS-CoV-2 specific animal models seem quite essential. Until now, some different animal models are under developed, including hamsters, ferrets, ACE2-transgenic mice and non-human primates [65].

CONCLUSION

Currently, SARS-CoV-2 outbreak has taken a disastrous turn with high toll rates worldwide. There are no licensed vaccines or therapeutic agents (i.e., antivirals and monoclonal antibodies) indicated for this coronavirus prevention or treatment. However, researchers are working to develop countermeasures. Several vaccine candidates for both SARS-CoV-2 are in early clinical trials. It is recommended that validated and clinically proven therapeutic measures are in great need at this time of crisis to ensure global safety against this pandemic infection.

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