Journal of Advances in Biology & Biotechnology

24(1): 12-24, 2021; Article no.JABB.65162
ISSN: 2394-1081

The Coronavirus Disease of 2019: Prevention, Management and Treatment Strategies

Nkechi E. Egbe[1*], Chukwu C. Onyedikachi[1], Ashiru M. Dantata[1], Surajo Jamaliddeen[1] and Amaka M. Awanye[2]

[1]Department of Biotechnology, Nigerian Defence Academy, Kaduna, Nigeria.
[2]Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmaceutical Sciences, University of Port Harcourt, Rivers State, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. Author NEE conceived and designed the study. Authors CCO, AMD and SJ managed literature search and wrote the first draft of the manuscript. Authors NEE, AMA and CCO edited the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JABB/2021/v24i130193
Editor(s):
(1) Dr. Anil Kumar, Devi Ahilya University, India.
(2) Dr. Joana Chiang, China Medical University, Taiwan.
(3) Dr. Fernando José Cebola Lidon, Universidade Nova de Lisboa, Portugal.
(4) Dr. Afroz Alam, Banasthali University, India.
Reviewers:
(1) Ibnu Sina Chandranegara, University of Muhammadiyah Jakarta, Indonesia.
(2) Prashant Patilba Mhase, Krantisinh Nana Patil College of Veterinary Science, India.
(3) S. Puvaneswari, Annamalai University, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/65162

Review Article

Received 14 January 2021
Accepted 10 February 2021
Published 15 February 2021

ABSTRACT

The recent COVID-19 pandemic caused by the novel coronavirus (SARS-CoV2) has taken the world by surprise since its outbreak in 2019, and as on February 2021, the world had experienced a total of 107,643,141 (one hundred and seven million, six hundred and forty-three thousand, one hundred and forty-one) confirmed infection cases and 2,358,244 (two million, three hundred and fifty-eight thousand, two hundred and forty-four) deaths world-wide. This virus, although less lethal than the previous human coronaviruses (SARS-CoV and MERS-CoV), is reported highly infectious and mutable. This has led to a concerted effort by numerous governments and private organisations to try and halt the spread of the virus through the development of highly effective therapeutic drugs or prophylactic therapy. There are various drugs, vaccines and other forms of

**Corresponding author: E-mail: nlegbe@nda.edu.ng;*

therapies currently being developed all over the world, with some at various clinical trial stages, with only one (Remdesivir) being fully approved treatment of the COVID-19 disease. The latest breakthrough with Dexamethasone has currently revealed the efficacy of the drug in treating critically ill and even mechanically ventilated COVID-19 patients, and this has led to the approval of the drug by the United Kingdom and World Health Organization (WHO). The recent development of a protective SARS-CoV-2 vaccine has created hope for life and restoration of normalcy.

Keywords: Covid-19; WHO; pandemic; SARS-CoV-2; Covid-19 vaccine.

1. INTRODUCTION

The emergence of the novel Coronavirus (SARS-CoV-2) has affected the world in ways never seen before. The first case of the disease was officially recorded in December 2019 in Wuhan city, Hubei province of China [1]. Since then, the virus has gone on to infect one hundred and seven million, six hundred and forty-three thousand, one hundred and forty-one (107,643,141) people, causing two million, three hundred and fifty-eight thousand, two hundred and forty-four (2,358,244) deaths across Two Hundred and Twenty (220) countries in world, as at 4th of December 2020 [2]. The genetic makeup of the virus, its high infection rate, long incubation period and the diverse symptom presentations in infected patients have made it difficult for health practitioners and researchers alike to find an effective vaccines or therapeutic agents for treatment of the disease and consequently putting enormous strain on the health systems of countries that are deeply affected.

The emergence of the novel coronavirus (COVID-19) has plunged the scientific community into a spiral as all attempts to find a definitive cure or vaccine to the virus has so far proven abortive. This has led to a concerted effort of various governments, international bodies and many pharmaceutical and biotechnology companies to go into deep research, and so far there are records of numerous therapies and drugs which are currently being repurposed to help improve the clinical status of patients infected with COVID-19, and many vaccines being developed by different companies with some currently undergoing clinical trials at various phases. The clinical trials of some of these therapeutic agents have so far shown pharmaco-therapeutic efficacies in the management of virus infected individuals.

In view of the all-round global effect of the COVID-19 pandemic, there in stems a vital need for an in-depth review of the potential list of repurposed drugs currently being tried for the treatment of COVID-19. This study therefore aims to review some of the latest advances in the development of these therapeutic agents and vaccines against the SARS-CoV-2 virus, with an in-depth look at the achievements of such therapies thus far and their shortcomings. This study looks to keep the academic and research world abreast of recent developments in the fight against the coronavirus and also will serve as a reference point for further research in the near and distant future. Finally, this study will also add to the body of knowledge already present in the scientific and academic community.

2. AN OVERVIEW OF THE SARS-CoV-2

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a novel coronavirus that was recently identified and characterized by scientists. It is a retro-virus that is characterized by crown-like spikes present on its surface (from which it was named), with which it uses to gain access into the cell of the host through the receptors. Afterwards, it goes on to hijack the host cells' machinery and begins making multiple DNA copies of its RNA genome, after which it begins producing viral proteins with the host cell's protein synthesis machinery [3]. The SARS-CoV-2 virus is a single stranded RNA virus which encodes spike S proteins, it binds to the Human Angiotensin Converting Enzyme 2 (ACE2) through its Receptor Binding Domain (RBD), this then creates a fusion which subsequently promotes the uptake of the virus into the host's cell (e.g. Lungs) through endocytosis [4].

There are four major sub-groups of coronaviruses, which are alpha, beta, gamma and delta. The SARS-CoV-2 virus belongs to the beta sub-group of coronaviruses and is one of the seven coronaviruses which is known to infect humans [5]. The Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and the Severe Acute Respiratory

Syndrome Coronavirus 2 (SARS-CoV-2) are known to cause severe diseases in humans, while the 229E Alpha Coronavirus, OC43 Beta Coronavirus, NL63 Alpha Coronavirus and HKU1 Beta Coronaviruses cause mild clinical symptoms in infected human patients [6].

Once inside the host's cell, the virus then triggers responses in the host's system, which could include stress response, autophagy, cell apoptosis and the activation of host's innate and adaptive immunity [7]. Upon infection, individuals with compromised immune systems or underlying health conditions will display symptoms of severe diseases characterized by significant respiratory symptoms leading to Acute Respiratory Distress Syndrome (ARDS) and Acute Lung Injury (ALI), which may ultimately end up in the death of the patient [8]. Transcriptomic RNA-sequence analysis of infected COVID-19 individuals showed several immune pathways and pro-inflammatory cytokines (CXCL, CCL2 and CCL3L1) in the Broncho-Alveolar Lavage Fluid (BALF) and TNFSF10, CXCL10, and NRG1 in Peripheral Blood Mononuclear Cells (PBMC), resulting in a sustained inflammation and cytokine storm [9].

3. CURRENT THERAPUTIC AGENTS IN PREVENTING AND TREATING COVID-19

Although the fight against the novel coronavirus is still ongoing, but as of the month of February 2021, the Federal Drug Administration (FDA) approved treatment for the virus has been Remdesivir (an antiviral agent) only. It is approved for the treatment of children (with minimum 40kg body weight and 12 years and above) and adults. Other than that, there are many other strategies currently deployed for the management of patients with the COVID-19 namely; timely reporting, early diagnosis, supportive treatment and isolation. These are important lines of action in the fight against the virus. Even though various other therapeutic agents are currently being developed and under investigation, the scientific community currently believes that the best way to developing new treatments is by repurposing the available therapeutic drugs which have already been approved for human use by the Federal Drug Administration (FDA) and corresponding health agencies in other countries, based on the symptomatic conditions of infected individuals. Along with the various therapeutic agents being developed, there also have been great efforts and strides in the development of a largely effective and clinically safe vaccine against the SARS-CoV-2. However, some of the lessons learned from the efforts made in creating effective therapies for the MERS-CoV and SARS-CoV is that, numerous compounds which were found to be effective in the treatment of the virus *in vitro* and in animal models, do not always translate to efficacy in humans [10].

In this study, various therapeutic and prophylactic agents are discussed that are divided into five major categories, as follows;

1. Antiviral Agents
2. Immune Based Therapy
3. Vaccines and Preventive Therapies.
4. Supporting Agents
5. Traditional/Herbal Therapy

4. ANTIVIRAL AGENTS

Antivirals are a class of medications which are used in the treatment of viral infections. The aim of antiviral therapy is to minimize symptoms, infectivity and shorten the duration of illness in the infected individual. These drugs act by arresting the viral replication cycle at various stages. Some of the antiviral drugs currently being used for the treatment of COVID-19 include:

4.1 Remdesivir

This is a novel chemical compound developed by Gilead Sciences, an American biopharmaceutical company. It is the first drug to be fully approved for the treatment of the COVID-19 by the FDA. Remdesivir is a phosphoramidate prodrug of an adenosine nucleoside triphosphate analog with broad-spectrum antiviral agent. When administered by intravenous route, it acts by diffusing into the cells where it subsequently metabolizes into its active form of GS-441524 mono-phosphate. Although the *in-vivo* method of action of Remdesivir in the treatment of COVID-19 is yet to be fully understood, but from *in-vitro* studies, Remdesivir has been found to function by obscuring/blocking the viral RNA-dependent RNA polymerase (RdRp) and this in turn results in the reduction of viral replication [11].

Prior to the full approval of Remdesivir for COVID-19 treatment, the United States Food and Drug Administration (USFDA) issued an Emergency Use Authorisation (EUA) on the 1st of May, 2020 [12]. The EUA allowed the

prescription of Remdesivir for the treatment of confirmed cases of COVID-19 [12]. Holshue et al. [13] reported that intra-venous administration of Remdesivir to COVID-19 patients recovering from pneumonia in the USA yielded promising results.

The National Institute of Allergy and Infectious Diseases (NIAID) in the United States of America started a series of phase 3 clinical trials with Remdesivir on COVID-19 patients, with the aim of determining its efficacy for the treatment of COVID-19 (this trial was known as Adaptive COVID-19 Treatment Trial – ACTT). At the end of the trial, NIAID reported that recovery time in patients given Remdesivir was significantly shorter than those given placebo. In China, a randomized double-blind placebo controlled clinical trial was conducted in 10 hospitals in Hubei province, and the scientists reported that the drug did not result in any statistically significant clinical improvement. But rather, more adverse effects were reported in patients that received Remdesivir, than in those who received the placebo [14].

In summary, evidences from few trials in the USA on Remdesivir showed that 70% of patients treated had improvements in terms of oxygen requirements, and some patients who were experiencing extreme respiratory distress and were mechanically ventilated, were extubated after treatment [15].

4.2 Hydroxychloroquine and Chloroquine

Hydroxychloroquine and Chloroquine are oral prescription drugs with similar chemical structures and a long history of clinical use [16]. Over the years, it has been used for the treatment of diseases like malaria, lupus erythematosus and rheumatoid arthritis. In contrast to chloroquine, hydroxychloroquine contains a hydroxyl group which makes it less toxic while maintaining a similar potency [17]. The FDA issued an EUA for the use of both chloroquine and hydroxychloroquine on the 30th of March 2020.

One of the mechanisms of action of Hydroxychloroquine and chloroquine is its activity as a protease inhibitor. Once in the body system, chloroquine and hydroxychloroquine functions by targeting the lysosomes in the cells, and subsequently increases their pH (from 4 to 6) after its accumulation in the lysosome. This alteration in pH causes the inhibition of acidic proteases of the lysosome which then affects the degradation of proteins and glycosaminoglycan [18]. Chloroquine has been reported inhibiting the entry of the SARS-CoV-2 into host cells preventing virus-cell fusion by interfering with the glycosylation of the ACE2 receptors and its binding with the spike protein.

According to scientific analysis, one of the main causes of death in COVID-19 infected patients is the triggering of the cytokine storm by an infected individual's immune system, which then leads to an Acute Respiratory Distress Syndrome (ARDS) [19]. Hydroxychloroquine possesses anti-inflammatory effect on Th17-related cytokines (IL-6, IL-17, and IL-22) in healthy individuals, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) patients, and there is also evidence that chloroquine and hydroxychloroquine help reduce cytokine storm [16]. There are evidences that zinc enhances chloroquine intracellular uptake, so combining zinc with chloroquine or hydroxychloroquine is intriguing and is under investigation [20]. Zinc inhibits retrovirus RNA (including SARS-CoV-2) polymerase activity *in vitro* and zinc ionophores block the replication of these viruses in cell culture [21]. A study by Tang et al. [22] showed that negative conversion rates were observed with hydroxychloroquine, rather, clinical symptoms were observed to be improving through its anti-inflammatory properties and recovery in lymphopenia.

Hydroxychloroquine and chloroquine have been reported to cause abnormal heart rhythms such as QT interval prolongation and a dangerously rapid heart rate called ventricular tachycardia [23]. These risks may increase when these medicines are combined with other medicines known to prolong the QT interval. Also, it has been reported that high doses of chloroquine (600 mg twice daily for 10 days or total dose of 12 g) may be closely associated with significant cardiac risks and resultant high mortality rate, and should not be recommended for treating COVID-19 [23].

FDA issued an EUA for the use of both chloroquine and hydroxychloroquine for the treatment of hospitalized COVID-19 patients on the 30th of March 2020, and on the 5th of June, 2020, revoked its EUA status [24]. This reversal was due to analysis leading to the conclusion that chloroquine and hydroxychloroquine were unlikely to be effective in the treatment of COVID-19. Also, the side effect of possible serious cardiac problems further led to the

decision for the withdrawal of the EUA, as the potential risks outweighed the potential benefits.

In summary, there is still a significant lack of evidence with regards to the safety and efficacy of Chloroquine and Hydroxychloroquine for therapeutic use in the treatment of COVID-19.

4.3 Lopinavir-Ritonavir

Lopinavir is a protease inhibitor with high specificity for HIV-1 protease. It is orally administered and combined exclusively with ritonavir. Lopinavir has low bioavailability and an extensive biotransformation in the human system, because of which, it is usually co-formulated with ritonavir to improve its exposure. Ritonavir is a potent enzyme inhibitor, which inhibits the enzymes that are responsible for lopinavir metabolism, and its co-administration subsequently "boosts" lopinavir exposure and improves its antiviral activity [25].

Lopinavir-Ritonavir formulation was investigated in a recent clinical study in an open-label, individually randomized, controlled trial, where infected COVID-19 patients were treated with either lopinavir-ritonavir 400 mg/100 mg, orally twice daily plus standard care, or standard care alone. The result of the study showed that there were no observed benefits in patients treated with lopinavir-ritonavir treatment beyond standard care. Rather, adverse effects of nausea, diarrhea and asthenia were recorded in patients receiving the lopinavir-ritonavir combination treatment [26]. A study in Taiwan also reported that it did not shorten the duration of SARS-CoV-2 shedding *in-vivo* [3].

The use of lopinavir-ritonavir for the treatment of COVID-19 was strongly opposed by the National Institute of Health (NIH) panel for COVID-19, because of its negative pharmacodynamics *in vivo* and also due to the fact that the drug failed to prove its clinical benefits in patients with the SARS-CoV-2 virus [27].

5. IMMUNE-BASED THERAPY

Medical therapy which aims at improving a patient's clinical condition by the activation or suppression of the patient's active immune system. Therapies which are designed to elicit or amplify immune responses are called activation immunotherapy, while those that reduce or suppress immune responses are called suppression immunotherapy.

5.1 Convalescent Plasma

Convalescent plasmas are purified plasmas obtained from the blood of a formerly infected COVID-19 patient who has achieved complete recovery. Such purified blood plasma contains antibodies which are fully developed to fight the COVID-19 virus, and when injected into the critically ill patients, offers passive immunity against virus by opsonizing the virus particles [28]. This method offers short-term protection in infected patients. The mechanism of action of convalescent plasma is through the binding of the transfused antibodies to the pathogen, resulting in cellular cytotoxicity, phagocytosis, or direct neutralization of the opsonized pathogen [28].

The use of convalescent plasma for therapeutic treatment was investigated during the SARS, Ebola, MERS and influenza A H1N1 outbreaks with some promising results, including reduced mortality and shorter hospital stays [29]. A study published in China which involved 10 patients reported that all patients treated with convalescent plasma had diminution or elimination of COVID-19 symptoms after treatment with convalescent plasma [30].

In the United States of America, Johns Hopkins Institute is at the fore front of efforts to develop plasma-based treatment along with researchers at Mayo Clinic, Minnesota, Stanford University Medical Center in California and Albert Einstein College of Medicine in New York have joined the effort [31]. Results from the Mayo clinic trials which involved the use of 35000 hospitalized COVID-19 individuals, suggested that treatment with covalescent plasma helped in the treatment of the disease, but was more effective in those who received the treatment at early stages of their disease and had higher levels of antibodies already present in their body systems. An EUA was issued for the use of covalescent plasma for treatment of hospitalized COVID-19 individuals by the FDA, on th 23rd of August 2020, even though the National Institute of Health (NIH) panel was strongly opposed to the FDA's decision [32].

On the 1st of October 2020, it was reported that the president of the United States (Donald Trump), First lady (Melania Trump) and some other officials of the white house tested positive for COVID-19. The treatment given to him was a mix of two monoclonal antibodies from Regeneron (although it was medically developed

for non-hospitalized patients), and other drugs used for his treatment included Remdesivir and Dexamethasone [33].

5.2 Sarilumab

Sarilumab is a humanized monoclonal antibody (mAb) which was originally developed for the treatment rheumatoid arthritis (RA), it works by damping down an overactive immune system. It also is an antibody for the pro-inflammatory cytokine IL-6.

A phase 2 and 3 randomized double-blind placebo-controlled clinical trial was setup by Regeneron Pharmaceuticals and Sanofi, in partnership with Northwell Health's Feinstein Institutes for Medical Research. The study enrolled 400 COVID-19 patients, measuring percent change in C-protein (Phase 2 only) and time to improvement on a 7-point scale in patients with serum IL-6 level above a threshold as primary endpoints [34]. Unfortunately, as of the time of this study, the result of the research hasn't been made public.

5.3 Tocilizumab

Tocilizumab is a humanized monoclonal antibody used for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis in patients. Tocilizumab has been approved by the United States Food and Drugs Administration (FDA) for the treatment of cytokine release syndrome (cytokine storm). Cytokine storms follow some infections and are believed to be one of the factors in many fatal and critical cases of COVID-19.

There are currently over 35 interventional clinical trials which are investigating the therapeutic effect of Tocilizumab in the treatment of COVID-19 disease [35]. A published study in China reported that 21 severe to critically ill COVID-19 patients were treated with the Tocilizumab, 20 of the infected patients recovered with one still in recovery state Fu et al. [36].

Positive results so far from initial trials of COVID-19 treatment with Tocilizumab have resulted in a larger multicenter clinical trial (ChiCTR2000029765), which was launched with about 500 patients treated with Tocilizumab. The trials are over, but the results are yet to be published [37].

6. VACCINES AND PREVENTIVE THERAPIES

Vaccines are biological preparations that provides active acquired immunity to a particular infectious disease. It helps the body's immune system to recognize and fight specific pathogens. Different from most medicines which treat or cure diseases, vaccines prevent an immunized individual from getting sick with that particular disease in the first place. The vaccine contains an agent which closely resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins. Vaccines are the most common form of prophylactic therapy but can sometimes act as therapeutic agents.

Since the start of the global pandemic, various governments, pharmaceutical, biopharmaceutical and biotechnology companies have been in a race to get an effective vaccine against the SARS-CoV-2. According to the World Health Organisation, there are currently over 110 vaccines in different stages of development in the world, but only 8 vaccines are currently at the stage of clinical trials.
Following vaccines are currently undergoing clinical trials (listed according to the name of the companies/organisations carrying out the research).

6.1 Moderna Inc. Vaccine

Moderna Inc. is a US based biotechnology company currently working on the development of an mRNA-1273 vaccine which is currently being produced against the SARS-CoV-2. Moderna Inc. undertook clinical trials for the vaccine in March 2020, in collaboration with the U.S. National Institute of Allergy and Infectious Diseases (NIAID). The first phase human trial enrolled 845 volunteers testing the vaccine for prevention of COVID-19, with all participants of 18 and above age group. The trial phase showed some mild to moderate vaccination effects.

The Moderna Inc vaccines are mRNA vaccines which are genetically engineered to produce viral proteins of the SARS-CoV-2 called "spikes" once delivered intramuscularly into the subject. Vaccine will be given in two doses after which subjects will be closely monitored [38]. An interim analysis from an independent monitoring board on the 3rd (and final) phase of the Moderna Inc vaccine clinical trial showed a 95% efficacy in the

analysis from the trial conducted on 45,000 people. At the end of the trial, a total of 170 cases of COVID-19 infections were recorded (with 10 severe cases) [39].

6.2 Inovio Pharmaceuticals

Inovio is an American biotechnology company focused on the discovery, development, and commercialization of synthetic DNA products for treating cancers and various infectious diseases. The INO-800 is a synthetic DNA vaccine which has been engineered to target SARS-CoV-2 spike (S) protein. Immunization with INO-4800 resulted in a robust expression of the S protein and a subsequent production of antigen-specific T-cell and concomitant antibodies which neutralizes SARS-CoV-2 and block S protein binding to the ACE2 receptors [40]. The vaccine is made from optimized DNA plasmids, which are delivered intramuscularly to the cells or intradermally.

Inovio began its early-stage clinical trials for a potential COVID-19 vaccine candidate on the 6th of April 2020, making it the second potential Covid-19 vaccine to undergo human testing after Moderna. In June 2020, results from phase 1 clinical trial showed that this vaccine triggered human immune response in 34 of 36 participants with little or no adverse effects. But in early September 2020, the clinical trial of the INO-4800 was put on hold by the FDA and is yet to be resumed as at the time of publication of this paper.

6.3 Oxford and Astrazeneca

COVID-19 vaccine developed by researchers at Oxford University in collaboration with AstraZeneca plc began phase 1 human trials in April 2020. The experimental vaccine currently called ChAdOx1 nCoV-19 is made from an attenuated Adenovirus which infects chimpanzees. The viral vector is engineered to express the SARS-CoV-2 spike protein [41].

The phase 1 and then phase 2 clinical trials started in April 2020, and enrolled a total of 1077 adult participants aged between 18-55 years. The results from this trial showed an acceptable safety profile and a significantly increased antibody response [42]. The phase 3 clinical trial of the ChAdOx1 nCoV-19 vaccine showed a 70.4% average efficacy with a two-dose regimen. But researchers claim that the efficacy can reach as high as 90% if administered with a half first-dose and followed by a full second dose [43].

Although ChAdOx1 nCoV-19 vaccine showed significantly lower efficacy when compared to the vaccines of Moderna and Pfizer, it still retains great promise as the vaccine can be stored in temperatures of 2-8 degrees Celsius (36 to 46 degrees Fahrenheit) for at least six months, while Moderna vaccine should be stored at a temperature of -20^{o}C (-4F) which can remain active for 30 days, and Pfizer/BioNTech vaccine needs to be stored at -75^{o}C (-103^{o}F) and can only be kept for 5 days if stored at a higher temperature [44]. These extremely low temperature requirement for storage and transport may prove to be an added advantage for the Oxford vaccine over that of Moderna and Pfizer/BioNTech in the long run.

6.4 Pfizer and BioNTech

The US pharmaceutical giant Pfizer are working alongside German drug makers BioNTech for the production of an experimental vaccine to help combat SARS-CoV-2. The experimental vaccine, BNT162 uses mRNA technology similar to that of Moderna Inc, but this is combined with lipid nanoparticles (LNP) formulation used as adjuvants [45]. The vaccine requires 2 doses, with the second taken 21 days after the first.

Results from phase 1 trial which began in May, 2020 showed that the vaccine was able to create dose dependent immunogenicity that was well tolerated by the body system. The vaccine was administered in 2-dose series, with its immunogenicity measured by RBD-binding IgG concentrations and SARS-CoV-2 neutralizing antibody titers. Also, this trial phase showed that all subjects in the prime-boost cohorts had CD4+ T-cell responses, except for two at the lowest dose level [46].

Phase 2 trial started in July 2020, while phase 3 trial was kicked off in early October 2020. In mid-October, the FDA allowed the expansion of the phase 3 trials which allowed the inclusion of adolescents from 12 years and above. Phase 3 trial enrolled about 38,000, with close to 31,000 volunteers receiving two vaccination shots.

On the 2nd of December 2020, UK granted the Pfizer/BioNTech vaccine an emergency authorization, making it first mRNA vaccine to be approved for human use. The first set of immunization kicked-off in the UK by the second week of December 2020, making it also the fastest vaccine to be developed in history which followed the mandatory stages (the Russian and

Chinese vaccines were approved prior to Phase III trials).

6.5 Russian Vaccines

Two main vaccines from Russia had drawn a lot of attention as well as criticism from the scientific community, and they are the EpiVacCorona produced by the Vector Institute and Sputnik V produced by The Gamaleya National Center of Epidemiology and Microbiology.

The Sputnik V is a viral vector vaccine which makes use of attenuated adenoviruses to illicit immune responses in vaccinated individuals. The vaccine is administered in two doses, with the second (boost dose) coming 21 days after the first. The results of the phase 1 and 2 clinical trial showed that the vaccine was able to produce antibodies and also illicit some reaction from the T cells. In August 2020, Sputnik V was approved by the Russian government and was tagged the first registered COVID-19 vaccine, even though the phase 3 trial was yet to begin. On the 11th of November, Gamaleya announced 92% efficacy of its vaccine [47].

The EpiVacCorona prepared by Vektor State Research Center of Virology and Biotechnology Russia, is a peptide vaccine that makes use of small fragments of the coronavirus antigen to illicit immune response from the immunized patient. On the 14th of October, the vaccine was granted approval by the Russian government even though the vaccine was yet to enter the phase 3 clinical trial and was yet to publish any results from the first and second trial phases, making it the second COVID-19 vaccine to be approved by Russia [48].

6.6 Sinopharm

Sinopharm is state owned pharmaceutical company in China which developed a COVID-19 vaccine in collaboration with Wuhan Institute of Biological Product. The COVID-19 vaccine was developed from an inactivated coronavirus (SARS-CoV-2). Preliminary results from a randomized trial showed the ability of the vaccine to illicit immune responses with little or no adverse effects (though the T cell-mediated immune response was not measured) [49].

6.7 Covaxin

Though India is a world vaccine powerhouse producing about 60% of the world's vaccines, Covaxin is the first Indian indigenous COVID-19 vaccine produced by Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR). It is an inactivated vaccine, made from killed coronaviruses along with adjuvants used to increase its immunogenicity. The virus samples used in the production of the vaccine was isolated by India's National Institute of Virology. The vaccine is administered in two doses with the second administered four weeks (28 days) after the first, and stored at temperatures ranging from 2-8^{o}C.

The phase 1 and 2 clinical trials for Covaxin have been concluded, with results showing enhanced humoral and cell-mediated responses [50]. The phase 3 clinical trial is currently ongoing with participants having received the first dose, and the second dose still ongoing. The interim efficacy estimate will be made available by the end of February 2021 [51].

Though the vaccine is yet to conclude its clinical trials, it was approved for emergency restricted use in India by DCGI-CDSCO on 03 January, 2021. This approval has raised various concerns by the scientific community in India, with the major concern being the approval of an incompletely studied vaccine [52].

7. SUPPORTING AGENTS

Many adjunctive therapies are currently used as supportive care for managing COVID-19 infected patients. With some of them being discussed as follows;

7.1 Dexamethasone

Dexamethasone is a type of corticosteroid medication used in the treatment of many conditions, including rheumatic problems, skin diseases, allergies, asthma and many other respiratory related diseases. It is the latest breakthrough drug currently leading in the fight against COVID-19. It is a low-cost drug and widely available around the world. Dexamethasone has recently been approved by the United Kingdom for treatment of critically ill COVID-19 patients.

In March 2020, the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial was established by the University of Oxford as a randomized clinical trial to evaluate a range of potential treatments for COVID-19, including low-dose dexamethasone. A total of 2,104 patients

were randomly selected to receive 6mg of dexamethasone once per day, intravenously for 10 days [53].

The results showed dexamethasone reduced deaths in ventilated patients by one-third, and by one-fifth in patients receiving oxygen only. Benefits among patients who did not require respiratory support was not observed. This means that based on the above result, treatment of COVID-19 infected individuals with dexamethasone will prevent 1 death in 8 ventilated patients, or 1 death in 25 patients requiring oxygen alone [53].

According the World Health Organisation (WHO), Dexamethasone was the first drug showing reduced mortality in patients with COVID-19 requiring oxygen or ventilator support [54].

7.2 Vitamin C

Vitamin C is an essential nutrient needed by the human body system and plays significant roles. It neutralizes free radicals, assists to prevent or reverse cellular damage as a potent antioxidant agent and also is involved in some biological processes, many of which are associated with immunity [55]. Vitamin C has also been shown to be effective as an antiviral agent, especially against influenza viruses [56], and also positively affects the development and maturation of T lymphocytes and NK (natural killer) cells involved in the immune response to viral agents [57].

Vitamin C has recently drawn a lot of attention due to claims by Dr. Andrew G. Weber, a pulmonologist with the Northwell Health system in New York, that COVID-19 patients in China who received Vitamin C did significantly better that those who did not [58]. This phase 2 clinical trial (NCT04264533) was initiated in China to evaluate the effect of administering high-dose intravenous (IV) vitamin C in ICU patients with severe COVID-19-associated pneumonia. Some hospitals have reported giving 1500 mg of vitamin C as supportive treatment in infected patients.

7.3 Azithromycin

Azithromycin is an antibiotic which is currently used for the treatment of different types of bacterial infections like respiratory infections, skin infections, and sexually transmitted diseases. It also has been proven to be effective *in-vitro* against Zika and Ebola viruses, and prevent severe respiratory tract infections in patients suffering from viral infections [59,60].

Azithromycin has been used as an adjunctive therapy to provide antibacterial coverage and potential anti-inflammatory and immunomodulatory effects in some viral respiratory tract infections treatments (e.g., influenza). Many trials are currently conducted for testing the effect of azithromycin in conjunction with hydroxychloroquine and its effects in people with COVID-19. Pfizer recently announced positive data in its research regarding the use of azithromycin, along with hydroxychloroquine, in a COVID-19 clinical trial that was performed in France. Gautret et al. [61] reported a 100% viral clearance in nasopharyngeal swabs in 6 patients after their treatment with hydroxychloroquine and azithromycin. However, the experiment by Molina et al. [62] showed that 8 out of 11 patients had significant viral load in the nasopharynx after this therapeutic combination was administered which stands in direct contrast to the earlier report.

Based on the results, the data presented to date are insufficient to evaluate possible clinical benefits of azithromycin in patients with COVID-19.

8. TRADITIONAL AND HERBAL THERAPY

Traditional/Herbal medicines have been used for treatment of various human and animal ailments for thousands of years, and have contributed greatly to the improvement of the overall human health through their various nutritional properties. They also have been effective in the prevention of illnesses. The outbreak of the COVID-19 disease has also seen various traditional and herbal medicine specialists turning to nature for a cure to this global pandemic.

8.1 Traditional Chinese Medicines (TCM)

Traditional medicine has been used for the treatment of various diseases for decades all over the world, and has also played roles in the control of past epidemic outbreaks such as SARS and H1N1 influenza [63]. China and South Korea currently issued a traditional medicinal treatment guideline on the prevention and treatment of COVID-19 [64]. It has been reported that more than 85% of COVID-19-infected patients in China received some forms of Traditional Chinese Medicine (TCM) treatments, as it appears that some Chinese traditional

medicines (TCM) may have the capacity to target ACE2 receptors and subsequently shows some promise in preventing the COVID-19 [65].

The 10 most commonly used herbal traditional Chinese medicinal products in China to treat COVID-19 patients are extracts from the following plants; *Astragalus membranaceus*, *Glycyrrhiza uralensis*, *Saposhnikoviae divaricata*, *Rhizoma atractylodis macrocephalae*, *Lonicerae japonicae flos*, *Fructus forsythia*, *Atractylodis rhizoma*, *Radix platycodonis*, *Agastache rugosa*, and *Cyrtomium fortunei J. Sm* [66]. Also some traditional chinese medicinal herbal products such as Shen Fu Injection and Re Du Ning Injection, has been shown to manifest potential immunosuppressive effects which resultantly decreases the level of TNF-α, IL-1β, IL-6, IL-8, IL-10, and other cytokines leading to the inhibition of lung inflammation or acute lung injury [67].

8.2 Madagascar's Covid Organic (CVO)

Madagascar officially announced the release of an indigenously developed herbal therapy for the COVID-19 disease in April 2020. The herbal therapy was developed by the Malagasy Institute of Applied Research. It was originally produced as a liquid tonic to be delivered orally, but currently has the intravenous injections being developed [68].

The herbal drug is produced from the plant *Artemisia annua,* from which extracts are derived for the production of artemisinin-based combination therapies (ACTs) which is currently the standard treatment for malaria worldwide [69].

The efficacy of CVO is yet to be clinically proven which has led to the WHO warning clinicians and general public against its use until proven otherwise.

9. CONCLUSION

The COVID-19 pandemic today represents the greatest global public health crisis in the past 100 years, with no fully certified drug, vaccine or treatment regimen against the virus at the moment. This paper therefore, set out to review some of the latest advances in the development of therapeutic agents, prophylactic drugs and vaccines against the SARS-CoV-2 virus, with an in-depth look at the achievements of such therapies, their setbacks and/or shortcomings. Regardless, there are a number of promising therapies currently being developed and clinically tested, with the likes of Remdesivir and Dexamethasone already been given emergency use authorizations. Some vaccines are at the final stage of clinical trials, while emergency authorization have been given to some like the Pfizer-BioNTech, Moderna and Oxford/ Astrazeneca vaccine by the United Kingdom and some other countries. It is all but possible to say that at this rate, the COVID-19 pandemic will soon be a thing of the past.

DISCLAIMER

There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. WHO, "World Health Organisation; 2020. Available:https://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/.
   Accessed: 13 June 2020.
2. Worldometer, Worldometer; 2020.. Available:https://www.worldometers.info/coronavirus/?.
3. Chen Y, Liu O, Guo D. Emerging Coronaviruses: Genome, structure, replication and pathogenesis. Journal of Medical Virology. 2020;22:418-23.
4. Wu R, Wang L, Kuo HCD, Shannar A, Peter R, Chou PJ, et al. An update on current therapeutic drugs treating COVID-19. Current Pharmacology Repoort. 2020;15-20.
5. Muhammad AS, Suliman K, Abeer K, Nadia B, Rabeea S. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. Journal of Advanced Research. 2020;91-98.
6. Anderson KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV2. Nature Medicine. 2020; 450-52.

7. Fung TS, Liu DX. Human coronavirus: Host-pathogen interaction. Annual Review of Microbiology. 2019;529-557.
8. Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid-19 does not lead to a “typical” acute respiratory distress syndrome. American Journal of Respiratory and Critical Care Medicine. 2020;10.
9. Xiong Y, Liu Y, Cao L, Wang D, Guo M, Jiang AO, et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. Emerging Microbes and Infections Journal. 2020; 1:761-770.
10. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses - drug discovries and therapeutic options. Nature Reviews Drug Discovery. 2016;327-347.
11. Avadheshkumar RH, Kirtikumar BC, Rahoul Z, Hemant K, Vivek BC. A review of pharmacology, mechanism of action, in-vitro activity and clinical use based on available case studies. Journal of Drug Delivery and Therapeutics. 2020;264-270.
12. Marcia F. FDA authorizes emergency use of remdesivir for COVID-19. Medscape; 2020.
Available:https://www.medscape.com/view article/929836.
Accessed: 2 February 2021.
13. Holshue ML, De Bolt C, Lindquist S, Lofy KH, Wiseman J, Bruce H, et al. First case of 2019 novel Coronavirus in the United States. National Library of Medicine. 2020;250-253.
14. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA. 2020;1843-1844.
15. Grein J, Ohmagari N, Shin D, Diaz G, Asper E, Castagna A, et al. Compassionate use of remdesivir for patients with severe Covid-19. The New England Journal of Medicine. 2020;250.
16. Silva J, Mariz H, Rocha JL, Oliveira P, Dantas A, Duarte A. Hydroxychloroquine decreases Th17-related cytokines in systemic lupus erythematosus and rheumatoid arthritis patients. Clinics. 2013; 766-771.
17. Rynes R. Antimalarial drugs in the treatment of rheumatological diseases. Pub Med. 1997;799-805.
18. Ohkuma S, Chudzik J, Poole B. The effects of basic substances and acidic ionophores on the digestion of exogenous and endogenous proteins in mouse peritoneal macrophages. The Journal of Cell Biology. 1986;959-966.
19. Cao X. Immunopathology and its implications for therapy. Nat Rev Immunol. 2020;1-2.
20. Te Velthuis AJ, Van Den Worm SH, Sims AC, Baric RS, Van Hemert MJ. "Aartjan J. W. te Velthuis,Sjoerd H. E. van den Worm,Amy C. Sims,Ralph S. Baric,Eric J. Snijder," Plos Pathogens 2010;6.
21. Te Velthuis AJ, Van Den Worm SH, Sims AC, Baric RS, Snijder EJ. Zn2+ Inhibits Coronavirus and Arterivirus RNA Polymerase Activity In Vitro and Zinc Ionophores Block the Replication of These Viruses in Cell Culture. Plos Pathogens. 2010;I(1):51-57.
22. Tang et al. Hydroxychloroquine in patients with COVID-19: An open-label, randomized, controlled trial. MedRxiv; 2020.
23. Borba M, Almeida VF, Sampaio V, Alexandre M, Melo G, Brito M. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety result of a randomized, double-blinded clinical study. MedRxiv. 2020;1.
24. USFDA. Coronavirus (COVID-19) update: FDA revokes emergency use authorization for chloroquine and hydroxychloroquine," USFDA. 2020;1.
25. FDA. US department of health and human services; 2019.
Available:https://www.accessdata.fda.gov/ drugsatfda_docs/label/2019/021251s058.
26. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. Ritonavir in adults hospitalized with Severe Covid-19. New England Journal of Medicine. 2020;120-127.
27. NIH. Antiviral drugs that are under evaluation for the treatment of COVID-19. Covid-19 Treatment Guideline. 2020;5.
28. Gunn BM, Yu WH, Karim MM, Brannan JM, Herbert AS. A role for Fc function in therapeutic monoclonal antibody-mediated protection against Ebola virus. Cell Host Microbe. 2018;221-233.
29. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis. 2020;141-149.

30. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. PNAS. 2020;1.
31. Jaroslaw D. [UPDATED] therapies for COVID-19: What is in the pipeline?. DLA Piper. 2020;6.
32. NIH. NIH COVID-19 Treatment Guideline; 2020. [Online]. Available:https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/blood-derived-products/convalescent-plasma/. Accessed: 1 November 2020.
33. BBC, dexamethasone, remdesivir, Regeneron: Trump's Covid treatment explained. USA: BBC; 2020.
34. Regeneron pharmaceuticals. Evaluation of the efficacy and safety of sarilumab in hospitalized patients With COVID-19. US National Library of Medicine. 2020;19.
35. ClinicalTrials. US NAtional Library of Medicine; 2020. Available: https://clinicaltrials.gov/.
36. Fu B, Xiaoling, Wei, Haiming. Why tocilizumab could be an effective treatment for severe COVID-19. Journal of Transitional Medicine. 2020;125.
37. Chineese critical trial registry. Trial Research: CHICTR; 2020. [Online]. Available:http://www.chictr.org.cn/showproj en.aspx?proj=49409.
38. NIAID. Safety and immunogenicity study of 2019-nCoV vaccine (mRNA-1273) for prophylaxis of SARS-CoV-2 infection (COVID-19). US National Library of Medicine. 2020;1.
39. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA Vaccine against SARS-CoV-2 — Preliminary Report. The New England Journal of Medicine. 2020;1.
40. Smith TRF, Broderick KE. Immogenicity of DNA vaciine candidate for COVID-19. Nature. 2020;1.
41. University of Oxford. News and events: University of Oxford; 2020. Available:http://www.ox.ac.uk/news/2020-05-22-oxford-covid-19-vaccine-begin-phase-iiiii-human-trials#.
42. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij Rammerstorfer S. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: A preliminary report of a phase 1/2, single-blind, randomised controlled trial. The Lancelet. 2020;467-478.
43. Oxford University. Press release: Oxford University breakthrough on global COVID-19 vaccine. University of Oxford, Oxford; 2020.
44. CNN. "Why Oxford's Covid-19 vaccine could do more for the world than other shots. CNN Health, USA; 2020.
45. Vaccine Info. Vaccines: Vaccine info; 2020. Available:https://www.precisionvaccinations.com/vaccines/bnt162-sars-cov-2-vaccine.
46. Walsh et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. The New England Journal of Medicine. 2020;3.
47. Logunov DY, Dolzhikova IV, Zubkova OV, Tukhvatullin AI, Shcheblyakov DV, Dzharullaeva AS. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: Two open, non-randomised phase 1/2 studies from Russia. The Lancet. 2020; 112-113.
48. CNBC. Russia approves second Covid-19 vaccine after preliminary trials. CNBC. 2020;5-6.
49. Shengli X, Kai D, Yuntao Z. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: Interim analysis of 2 randomized clinical trials. JAMA Network. 2020;951-960.
50. Bharat biotech, Bharat biotech home. Bharat Biotech; 2020. Available:https://www.bharatbiotech.com/blog/vaccines/covaxin-phase-2-study-results-phase-1-follow-up-data. Accessed: 10 February 2021]
51. Bharat biotech. COVAXIN Bharat Biotech; 2021. Available:https://www.bharatbiotech.com/covaxin.html. Accessed: 10 Frebruary 2021.
52. BBC. BBC NEWS. BBC; 2021. Available:https://www.bbc.com/news/world-asia-india-55748124#:~:text=The%20homegrown%20government%2Dbacked%20vaccine,be%20injected%20into%20the%20body. Accessed: 10 February 2021.
53. University of Oxford. Dexamethasone reduces death in hospitalised patients with severe respiratory complications of

COVID-19. University of Oxford News. 2020;1.
54. WHO. News-Room: WHO; 2020. [Online]. Available:https://www.who.int/news-room/detail/16-06-2020-who-welcomes-preliminary-results-about-dexamethasone-use-in-treating-critically-ill-covid-19-patients.
55. Carr AC, Maggini S. Vitamin C and immune function. MDPI. 2017;1211.
56. Kim Y, Kim H, Bae S, Choi J, Lim SY, Lee N, et al. Vitamin C is an essential factor on the anti-viral immune responses through the production of interferon-alpha/beta at the initial stage of influenza A virus (H3N2) infection. Immune Network. 2013;70-74.
57. Van Gorkom G, Klein Wolterink R, Van Elssen C, Wieten L, Germeraad W, Bos G. Influence of vitamin c on lymphocytes: An overview. MDPI; 2018.
58. New-York Post. New-York Post News; 2020. Available:https://nypost.com/2020/03/24/new-york-hospitals-treating-coronavirus-patients-with-vitamin-c/.
59. Retallack H, Di Lullo E, Arias C, Knopp K, Laurie M, Sandoval-Espinosa C et al. Zika virus cell tropism in the developing human brain and inhibition by azithromycin. PNAS. 2016;14408-14413.
60. Madrid P, Panchal R, Warren T, Shurtleff A, Endsley A, Green C, et al. Evaluation of ebola virus inhibitors for drug repurposing. ACS Publications. 2015;317-326.
61. Gautret P, Lagier J, Parola P, Hoang V, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Intrnational Journal of Antimicrobial Agents. 2020;1.
62. Molina J, Delaugerre C, Le Goff J, Mela-Lima B, Ponscarme D, Goldwirt L. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Médecine et Maladies Infectieuses. 2020;4:384.
63. Chen W, Lim C, Kang H, Liu J. Chinese herbal medicines for the treatment of type A H1N1 influenza: A systematic review of randomized controlled trials. PLOS ONE. 2011;1.
64. Ang L, Lee H, Choi J, Zhang J, Soo L. Herbal medicine and pattern identification for treating COVID-19: a rapid review of guidelines. Science Direct. 2020;407.
65. Zhou S, Li W, Ai Z, Wang L, Ba Y. Investigating mechanism of qingfei Dayuan granules for treatment of COVID-19 based on network pharmacology and molecular docking. Chin Tradit Herb Drugs. 2020;1.
66. Luo H, Tang Q, Shang Y, Liang S, Yang M, Robins N, et al. Can Chinese medicine be used for prevention of corona virus disease 2019 (COVID-19)? A review of historical classics, research evidence and current prevention programs. Chinese Journal of Integrative Medicine. 2020;243-250.
67. Yang Y, Islam M, Wang J, Li Y, Chen X. Traditional Chinese medicine in the treatment of patients infected with 2019-new coronavirus (SARS-CoV-2): A review and perspective. International Journal of Biological Sciences. 2020;1708-1717.
68. Alfa Shaban AR, "COVID-organic: Madagascar launches Africa's first cure for virus. Africanews; 2020.
69. Seeberger PH. MPICI; 2020. Available:https://www.mpg.de/14663263/artemisia-annua-corona-virus.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/65162