



Received on 05 December 2021; received in revised form, 20 January 2022; accepted, 28 April 2022; published 01 August 2022

INVESTIGATIONAL TREATMENT OF COVID-19

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Keywords:

COVID-19, Treatment, Diagnosis, Complications, Remdesivir

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ABSTRACT: The novel coronavirus disorder 2019 (COVID-19) outbreak commenced in early December 2019 in the capital metropolis of Wuhan, Hubei province, People's Republic of China and precipitated a world pandemic on march 11, 2020. Though some the international locations have succeeded in slowing down the price of the unfold of this pandemic, most the international locations throughout the globe are nevertheless persevering with To journey and growing vogue in the increase and unfold of this lethal disease. Hence, in the present day scenario, it has grown to be necessary to manipulate and eventually irradiate this lethal sickness using a nice vaccine. An RNA-based vaccine would possibly be greater superb than ordinary as vaccines to deal with a pandemic treatment. However, administration of acute seizures in sufferers with COVID19 as properly as administration of PWE and COVID19 wishes to think about doable drug-drug interactions between antiseizure capsules and candidate tablets presently assessed as therapeutic preferences for COVID-19. In this paper, we look at moral troubles and public conversation challenges associated with the improvement of cell-based therapeutics for COVID19.

INTRODUCTION: Since the first described contamination with extreme acute respiratory Syndrome coronavirus two (SARS-CoV-in December 2019, Coronavirus sickness 2019 (COVID-19) has developed into a Pandemic, the signs of which vary from asymptomatic course to pneumonia, acute lung and/or multiorgan failure and Death ¹. This virus has a greater diploma of lethality than different endemic viruses. It is also greater deadly to humans in contrast to the previously rising outbreaks of SARS-CoV-1 in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 ⁴. Currently, there are no therapeutics accepted with the aid of the US Food and Drug Administration (FDA) for the therapy of COVID-19 ⁷.

Treating sufferers early in a sickness path has constantly been Crucial in treating probably life-threatening infectious diseases. We consequently evaluated the first-rate of each posted and now not yet peer-reviewed trial on remdesivir and spotlight pitfalls ¹. An perfect oral drug is one that is hastily and absolutely absorbed from the alimentary canal, explicitly dispensed to its web site of motion in the body, metabolized in a way that does now not right away eliminate its activity and eradicated suitably, besides inflicting any damage ². It is estimated that almost half of of the pills in the improvement fail to make it to the market due to terrible protection. An best drug additionally has a sturdy security profile and excessive organic endeavor.

The usage of Pharmacokinetics typically decides the security profile through analyzing the motion of the drug in the physique, including in the tactics of absorption, distribution, metabolism, and Excretion of drugs. Laboratory strategies robotically used in assessing the security Profiles of tablets are the most important motive for a slowdown in the comparison Process ².

QUICK RESPONSE CODE 	DOI: 10.13040/IJPSR.0975-8232.13(8).3137-45
	This article can be accessed online on www.ijpsr.com
DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(8).3137-45	

These strategies consist of enzyme assays, phone culture, trans-Location, immunoblotting and phosphor-protein immunoassay on mobile phone Lines, amongst others. They have to be constrained to as Small a variety as feasible of promising drugs. Acknowledging the staggering Translational procedure that resulted in the improvement of multiple Vaccine products, the search for COVID 19 treatments has Been fraught with hyperbolic claims, miscommunication of lookup findings, poorly designed and underpowered clinical studies, science-by- press release and business Efforts to

take advantage of for income the public's fears and anxietie ³. Several coronavirus disease 2019 (COVID-19) vaccines are currently in human trials. In June 2020, we surveyed 13, 426 People in 19 countries to determine potential acceptance Rates and factors influencing acceptance of a COVID-19 vaccine. Of these, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine, and 61.4% reported that they would accept their employer's recommendation to do so ¹⁹.

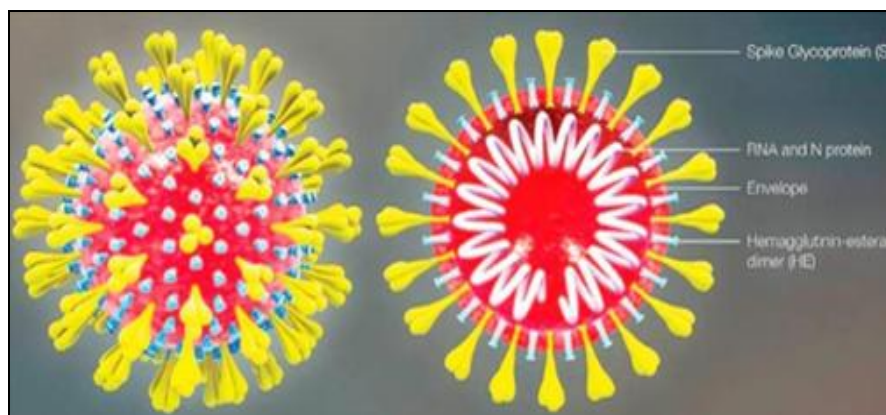


FIG. 1: STRUCTURE OF NCOVID-19 REF ⁹

Physical Examination and History of Treatment for Corona Virus Outbreaks: Middle East respiratory syndrome (MERS) and Severe Acute respiratory syndrome (SARS) are the two historical outbreaks of this coronavirus in the past two decades, and now the world is facing this novel coronavirus disease known as COVID-19 ⁵. History and physical examination are extremely important for the diagnosis of COVID-19 infection. Common related symptoms are fever (in 44% of patients on presentation and up to 88% of admitted patients); dry cough; shortness of breath, which may be severe and progressive, particularly when the patient develops pneumonia; myalgia and tiredness; sore throat; and nausea, vomiting and diarrhoea ⁴. SARS was the first CoV outbreak that appeared between November 2002–July 2003 worldwide. It had a mortality rate of 9.6% and 8098 infected cases; 774 deaths were reported In 29 countries. The disease was cured using broad-spectrum Antibiotics, as no specific and effective antiviral medication was known, though a purine nucleoside analogue, Ribavirin, was tried as a broad-spectrum antiviral agent ⁵. Patients may have neurologically related symptoms, including acute cerebrovascular

disease, headaches, dizziness, seizure, decreased level of consciousness, encephalopathy, agitation, and confusion. Recently, anosmia, hyposmia, and dysgeusia have been reported ⁴. Physical signs include raised body temperature, increased respiratory rate, decreased oxygen saturation, auscultation of the lungs may be normal or show crackles and signs of heart failure, cardiac arrhythmias, myocarditis, acute coronary syndrome, shock, and death may occur ⁴. The COVID-19 pandemic outbreak was once first diagnosed in Wuhan, China, in December, 2019. It affected the fitness and economy of the whole world in a very quick period. There are more than 96.2 million substantiate COVID-19 instances, with about 2.06 million dying stated so some distance throughout the world, with a reported the recovered sufferers 69.8 million from COVID-19. The facts suggested is in approximation as there used to be no longer environment-friendly checking out to record the actual morbidity stages ⁵.

Mechanisms of Action of Covid-19 Candidate Drugs: The mechanisms of contamination by the SARS-CoV2 are not clear yet; however, it is

genetically similar to SARS-CoV and different coronaviruses⁵. The current understanding of the life cycle of the novel coronavirus SARS-CoV-2 suggests drug goal candidates for the prevention and treatment of COVID-19. As it is known, the virus contains a single-stranded RNA that upon entering the host phone, unfolds and translates into polypeptides that further mitigate the synthesis of viral RNA strands via RNA-dependent viral RNA polymerase⁶. The mechanism of coronavirus entry and the working of vaccines toward Covid-19 is shown in Fig. 2. The basic shape of coronavirus comprises of structural proteins- Spike protein and M (membrane) protein and a single-stranded RNA.

The coronavirus enters the human body with the spike (S) protein which attaches to angiotensin-converting enzyme two (ACE2) receptors on the surface of human cells.

Once it enters the cell, it fuses with the vesicle, and then the viral genetic material, RNA, is fully released into the cytoplasm. Following, the viral RNA genome is translated to generate replicase proteins. In the cytoplasm, encapsidation of these replicase proteins result in the self-assembly of new virions. Finally, virions are launched from the infected cells⁵.

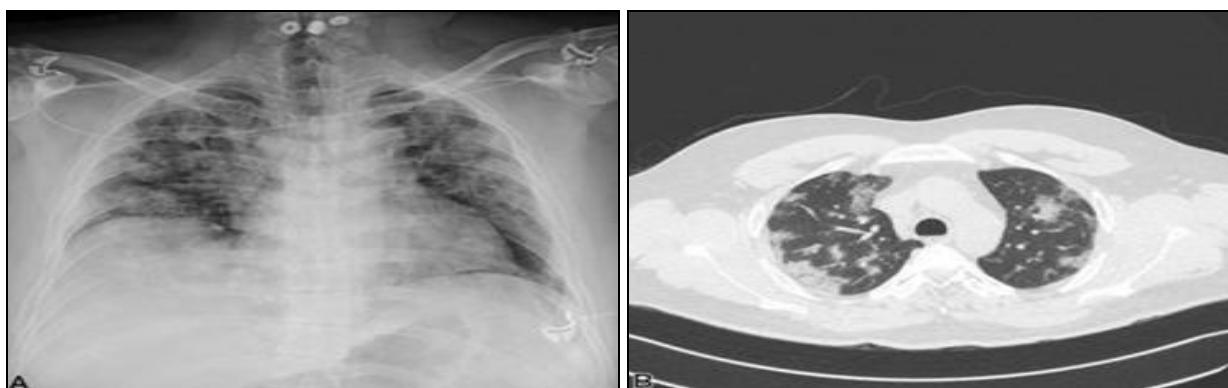


FIG. 2: A CHEST X-RAY DISPLAYING DIFFUSE BILATERAL OPACITIES IN A AFFECTED PERSON WITH CORONAVIRUS DISORDER 2019 AND ACUTE RESPIRATORY MISERY SYNDROME. B, COMPUTED TOMOGRAPHY SCAN OF THE CHEST DISPLAYING PERIPHERALLY PRIMARILY BASED GROUND-GLASS OPACITIES AND PULMONARY INFILTRATES⁸

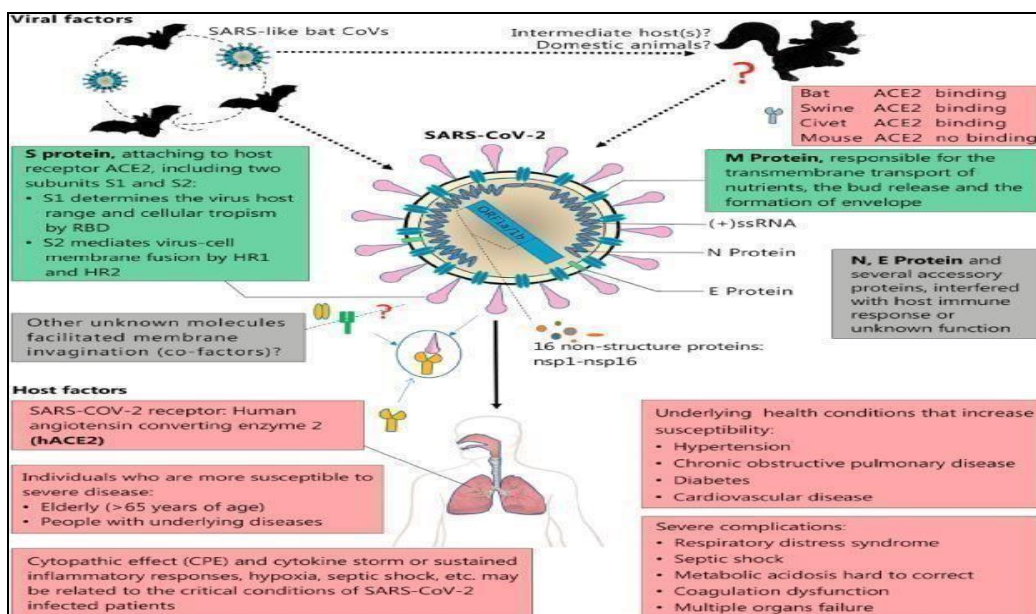


FIG. 3: ORIGIN AND TRANSMISSION OF CORONA VIRUS REF⁹

Evaluation Test:

1. Real-time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR): Real-time RT-PCR

tests are the most widely used laboratory tests for detecting RNA viruses¹⁴. Viral testing is performed by the RT-qPCR test, used for the

qualitative detection of the nucleic acid for SARS-CoV-2. Swabs are usually taken from nasal, nasopharyngeal, pharyngeal, sputum, or lower respiratory tract aspirates or washed. Positive tests indicate the presence of SARS-CoV-2 RNA, and the clinical picture supports the diagnosis. Negative test results do not preclude SARS-CoV-2 infection and shall be interpreted in light of the clinical picture and epidemiologic information⁴.

RT-PCR is currently considered the gold standard for diagnosing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection because of its easy methodology, extensively validated standard operating procedure, and high sensitivity and specificity. It is especially useful in detecting the virus in the setting of an acute illness¹⁴.



FIG. 4: RT-PCR TESTING²¹

2. Antibody-Based Tests / Serology: These tests evaluate the presence of IgM / IgG antibodies against SARS-CoV-2 viral antigen proteins. The specimen for testing is serum, plasma, or whole blood.

These tests are extremely useful for epidemiologic surveillance and indicate past exposure to the virus even in asymptomatic individuals¹⁴. The serology test is particularly useful (i) when the viral test is unavailable. Using the serology test together with the clinical picture could guide in decision-making. (ii) Patients with late disease complications and their physicians need to make immediate decisions (the viral test takes more time to get the results). (iii) In some patients, virus shedding is reduced, making RT-qPCR results falsely negative. The serology test can detect IgM and IgG antibodies against SARS CoV-2 in serum, plasma, and whole blood⁴.



FIG. 5: SEROLOGY TESTING²¹

3. Rapid Antigen Testing: Rapid antigen testing is a monoclonal antibody test against the SARS-CoV-2 nucleocapsid protein (N). This protein is abnormally expressed in infected cells⁴. Test further reduces turnaround time by simplifying the test to an immunochromatographic assay that detects the SARS-CoV-2 antigen in the sample. The preferred specimen for this test is a nasopharyngeal swab.

The test involves the insertion of the collected nasopharyngeal swab into an extraction buffer followed by application of the extracted solution to a specimen well on the test device¹⁴. The test has a reported sensitivity of 84.1% and a specificity of 98.5%. No cross-reaction with human and animal coronaviruses in the assay was reported.



FIG. 6: RAPID ANTIGEN TEST SET TO BE KEY TO COVID STRATEGY NOW²²

Ayurveda Treatment: Ayurveda, being the science of life, propagates the gifts of nature in maintaining healthy and happy living by improving the quality

of standard care. There is no highly potential drug or medication in the market that can unroot the cause of the COVID-19 disease completely. In these critical times, it will be bet-better to take ayurvedic

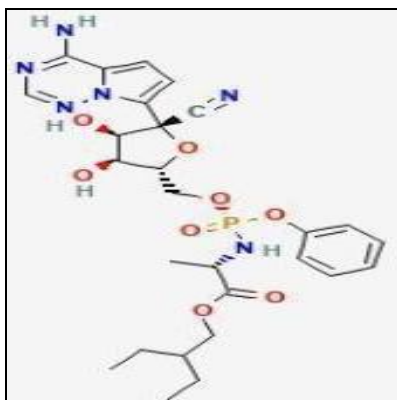
medicines and preventive measures to boost immunity to stop the coronavirus from entering your body⁵.

TABLE 1: THERAPEUTIC INTERVENTION²³

	Stage 1: Jwara Day 1-13	Stage 2: Jwara Mukti Day 14-30
Medicines	Sudarsana Churna -4 tablets (2 gm) in room temperature water Tid; Talisadi Churna Chikitsa Sthana, 1tsp with honey Tid; Dhanwantara	Vidaryadi Ghritame Chikitsa Sthana, 15 ml Bid Include milk, ghee, Chikitsa Sthana,
Diet Regimen	Gutika -2 tablets Tid Rice porridge, Yusha and Bhakta Avoid sleeping during the day (Divaswapna) and keeping awake at night (Ratri jagarana)	Avoid sleeping during the day (Divaswapna) and keeping awake at night (Ratri jagarana)

Antiviral Drugs:

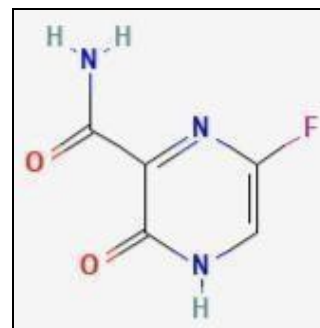
Remdesivir: Remdesivir is a prodrug before being acknowledged as GS 5734. It is a monophosphate that is metabolized to an adenosine nucleoside triphosphate analogue, which is built into the viral RNA prior to its replication⁶. Its structure is comparable to tenofovir alafenamide, which is Active in opposition to HIV and hepatitis B virus. It was developed using Gilead Sciences (Foster City, CA) for cure of Ebola in the course of the 2013e 2016 outbreak. The use of remdesivir in the rhesus monkey model showed that Once-daily intravenous administration Resulted in the suppression of Ebola viral replication and covered animals from deadly disease⁸.



Early research of remdesivir in COVID-19 have been inconclusive due to the fact of non-RCT designs and incapability to Achieve goal enrollment. On February 21, 2020, The National Institutes of Health launched the Adaptive COVID-19 Treatment Trial (ACTT – NCT04280705), a doubleblind randomized, placebo-controlled trial⁷. An antiviral drug for ‘EBOLA’, has been in the beginning declared to deal with COVID-19 sufferers “under emergency use” with the aid of Emergency Use Authorization (EUA) of the Food

and Drug Administration (FDA), United States of America. Remdesivir has verified the mechanism to overcome genetic mutations and drug resistance in coronavirus⁵.

Favilavir: Favilavir, an oral anti-viral drug, has been approved as a treatment for coronavirus by The National Medical Products Administration of China. The drug was originally manufactured by Fujifilm Toyama Chemical Ltd., Japan, for the treatment of influenza. Studies have revealed that favilavir gets activated on getting inside the cell and then finally gets incorporated into the virus's RNA, as the novel coronavirus is an RNA virus⁵. Favipiravir is a broad-spectrum anti-viral drug that inhibits the replication of virus⁶. These are limited published studies regarding *in-vitro* and clinical data on the use of favipiravir in coronavirus infections⁸. Favipiravir has also shown its effectiveness against various other RNA viruses that cause hemorrhagic fever, including arenavirus bunyavirus, flavivirus, and filoviruses (Du and Chen, 2020). Hence, in clinical trials, favipiravir is being investigated globally as a potential therapeutic agent against SARS-CoV-2⁶.



Lopinavir / Ritonavir: Lopinavir and Ritonavir are anti-retroviral agents used against the human immunodeficiency virus. They inhibit the enzyme

protease responsible for cleaving viral polypeptides, which are essential for viral replication⁶. Lopinavir (LPV) is a protease inhibitor approved for use, in a fixed-dose combination with ritonavir, as part of antiretroviral therapy for HIV infection. LPV/r was used for the treatment of SARS-CoV during the 2003 outbreak⁸. The use of lopinavir/ritonavir has been discouraged recently and has also been recommended against by the NIH expert panel in their COVID-19 Treatment Guidelines due to the adverse pharmacodynamics and no clinically

beneficial outcome reported in COVID-19 patients⁶.

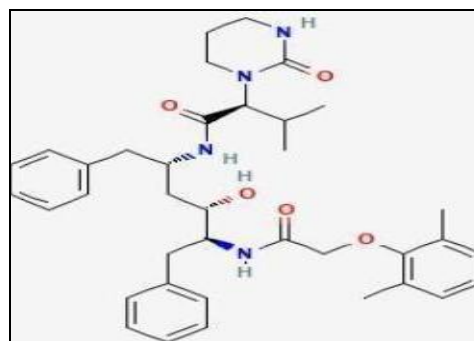


TABLE 2: INVESTIGATIONAL CURES VIEWED FOR TREATMENT OF COVID-19¹⁰

Therapy	Mechanism of action/rationale
(Hydroxo) chloroquine*	Blocks viral entry in endosome. Negative learn about outcomes so far; further results pending
Remdesivir	Blocks RNA structured polymerase
Lopinavir/ritonavir	Protease Inhibitor, first find out about with Disappointing results
Tocilizumab	Anti-IL-6 (anti-inflammatory)
Corticosteroids	T-cell inhibition (anti-inflammatory)
Favipiravir	Selectively inhibits viral RNA dependent RNA polymerase (RdRp)
Ribavirin	Guanosine analog that interferes with The viral replication
Vaccination	Half-life of antibodies seems to be Short

RNA = Ribosomic nucleic acid; IL = interleukin; TNF = tumor necrosis Factor; IFN =interferon

Immune-Based Therapy:

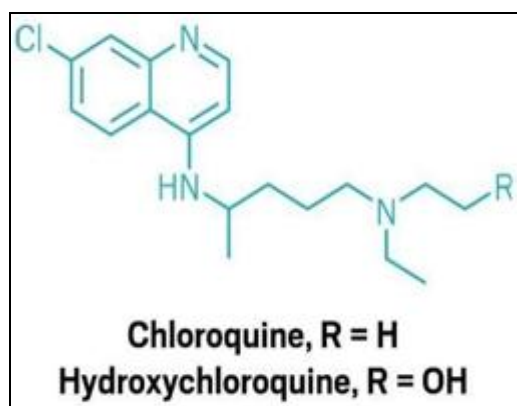
Convalescent Plasma: Convalescent plasma (CP) contains antibodies directed against specific pathogens and is used for passive immunization in the treatment of infections. CP has been used since the 19th century in infectious disease outbreaks, including diphtheria, influenza, SARS, MERS and Ebola⁷. The US FDA has approved the emergency investigational use of convalescent plasma to treat critically ill patients with COVID-19. 70 convalescent plasma is collected from COVID-19 recovered individuals eligible for blood donation. The traditional screening protocol for blood donation should be satisfied.

In addition, the plasma should be collected from people with a prior confirmed diagnosis of COVID-19 who have resolved their symptoms at least 14 days before donation⁸. People with severe risk of cytokine storm, Pneumonitis in extreme cases, and breathlessness are on priority for the therapy. It is an already used procedure for numerous diseases, but the potency for SARS-CoV-2 is still not known and is under investigation. (ClinicalTrials.gov Identifier: NCT04425915 and NCT04372979)⁵. As of August 3 2020, a total of 132 studies evaluating the role of Convalescent

plasma in COVID19 are registered on Clinical Trials.gov. The first randomized trial of convalescent plasma therapy for COVID-19 patients was conducted in China¹². A retrospective controlled study on SARS-CoV showed no Deaths in 19 patients who received CP therapy and there was a statistically significant difference in the case fatality ratio (CFR) Compared with the control group (0% vs. 23.8%; 95% CI 6– 42; P = 0.049)¹¹.

Chloroquine / Hydroxychloroquine: The US Food and Drug Administration (FDA), WHO and NIH have warned and recommended against the use of chloroquine or hydroxychloroquine except for emergency use in hospitalized COVID-19 patients or in a clinical trial to avoid the risk of ventricular tachycardia and prolonged QT interval⁶. Chloroquine, a quinoline derivative, was introduced into drugs and medicine in the 1940s. It is an antimalarial agent. It avoids virus-cell fusion by intruding with glycosylation of ACE2 receptor, and on merging with spike protein, it can impede the entry of nCoV-2. This mechanism of chloroquine suggests its efficiency as a therapeutic usage in the initial stage of infection only. Hydroxychloroquine (HCQ) falls into the class of medication of Disease-Modifying Ant Rheumatic

Drug. The drug helps diminish the pain and swelling in patients suffering from arthritis. It was initially synthesized in India for the treatment of malaria ⁵. In assessing its activity against SARS-CoV-2, Wang et al ⁸ showed, in in-vitro studies on Vero cells, chloroquine affected the entry and post-entry stages of contamination. They suggested that a daily dose of 500 mg of chloroquine would achieve the half-maximal effective concentration (EC50) in clinical scenarios. Subsequently, Gao *et al* ¹¹ reported their preliminary finding on the use of chloroquine in 100 patients in Wuhan, China, which concluded that chloroquine prevented pneumonia exacerbating pneumonia and improved lung imaging findings. However, this clinical trial's full, peer-reviewed publication is not available ⁸.



IL-6 Inhibitors: Similar to the previous coronavirus, the systemic organ damage seen in COVID19 is due to a “cytokine storm”, the release of proinflammatory cytokines including IL-6 ⁷. Although it is not clear whether elevation in IL-6 has a causal association with pro-inflammatory damage of the lungs or is just a consequence of the lung infection, attempts at blocking IL-6 by using monoclonal antibodies directed against IL-6 receptors have garnered interested as a potential therapeutic option ⁸. Tocilizumab, a monoclonal antibody that blocks the IL-6 receptor, is FDA approved for the treatment of cytokine release syndrome (CRS). An early retrospective report on 21 patients with severe or critical COVID-19 showed significant improvement in CRS symptoms, including resolution of fever and decreased oxygen requirements after treatment with tocilizumab. Although case series were promising, recommendations included the need for RCTs ⁷. Blocking IL-6 receptors may curb fever and inflammation, but this approach also blunts the

host's defense against infection. IL-6 inhibition is associated with an increased risk of infections, albeit this is more common after chronic use and in combination with other immunosuppressive drugs. Ongoing clinical trials are excluding patients with active or untreated tuberculosis and systemic bacterial and fungal infections ⁸.

Investigational Vaccines for Combating Covid-19:

Covi-shield: Neutralizing Antibody Cocktail is developed by Sorrento to get merged with different epitopes on Spike protein (SARS-CoV-2). The antibody cocktail efficiently develops a high barrier to the emanation of resistant modifications in perfectly cured individuals ⁵. The Covishield vaccine is a vaccine that aims to protect against COVID-19. Manufacturer/developer: AstraZeneca, Serum Institute of India. Research name: AZD1222 (ChAdOx1) Vaccine type: Non-Replicating Viral Vector. Route of Administration method: Intramuscular injection it's Also known as Oxford, AstraZeneca vaccine ¹⁶.

Covaxin: Covaxin is developed by Bharat Biotech in association With NIV (National Institute of Virology) at ICMR, Indian Council of Medical Research. This is India's native vaccine for combating COVID-19. Covaxin, an immobilized vaccine candidate, has been Developed using SARS-CoV-2 particles that were eliminated and Made it unable to multiply in the people having the dosages of vaccine and hence avoid the chances of infection in them ⁵. The Covaxin vaccine is a vaccine that aims to protect against COVID19. Manufacturer/developer: Bharat biotech, Research name: BBV152, Vaccination type: Inactivated, route of Administration is Intramuscular ¹⁵.

mRNA-1273: The mRNA-1273 vaccine candidate, manufactured by Modern, encodes the S2P antigen, consisting of the SARS-CoV-2 glycoprotein with a transmembrane anchor and an intact S1-S2 cleavage site. S-2P is stabilized in its perfusion confirmation by two consecutive proline substitutions at amino acid positions 986 and 987, at the top of the central helix in the S2 subunit ⁸. The lipid nanoparticle capsule composed of four lipids was formulated in a fixed ratio of mRNA and lipid. The mRNA-1273 vaccine was provided as a sterile liquid for injection at a concentration of 0.5

mg per milliliter. Normal saline was used as a diluent to prepare the doses administered¹⁷. A preliminary report submitted by Jackson *et al.* concluded that anti-SARSCoV-2 immunity boosters were noted, using this vaccine in all the targeted bodies, and the identifications of concerns related to the trial's safety were not studied and reported. This concluding statement further supports the vaccine's development in the future ahead⁵.

mRNA Vaccine BNT162: The serologic responses elicited by BNT162b1 And BNT162b2 were similar. Two serum samples, both from the group of participants 18 to 55 years of age who received 30 µg of BNT162b2, were obtained outside the Time windows (one each at day 28 and day 35) And thus were excluded from the reported immunogenicity analysis. Antigen binding IgG and Virus neutralizing responses to vaccination with 10 µg to 30 µg of BNT162b1 or BNT162b2 were Boosted by the second dose in both the younger Adults 2,5 and the older adults. Both vaccines generally elicited lower antigen-binding IgG and virus-neutralizing responses in participants 65 to 85 years of age than in those 18 to 55 years of age. Higher doses appeared to elicit somewhat Higher antibody responses¹⁸.

Complications: Age and sex have been shown to affect the severity of complications of COVID19. The rates of hospitalization and death are less than 0.1% in children but increase to 10% or more in older patients. Men are more likely to develop severe complications than women due to SARS-CoV-2 infection Drug-induced liver injury (DILI) is one of the major safety concerns⁴. For drug developers, regulators, and clinicians. Chen and others have created a reference drug list with a sufficient number of well-annotated drugs based on their DILI risk in humans². The main complications reported in patients with SARS-CoV-2 may include:

- ❖ Coagulopathy, mainly disseminated intravascular Coagulation, venous thromboembolism, elevated D-dimer, and prolonged prothrombin time.
- ❖ Cardiovascular complications include acute pericarditis, Left ventricular dysfunction, acute

myocardial injury (associated with increased serum troponin), new or worsening arrhythmias and new or worsening heart Plasma, and neutralizing failure.

- ❖ In acute respiratory failure, approximately 5% of COVID-19 Patients require admittance to an intensive care unit because they develop severe disease complicated by acute Respiratory distress syndrome, sepsis, septic shock, and multiple organ failure.
- ❖ Higher risk of death, particularly in male patients with severe⁴.

CONCLUSION: Demonstrated and highly efficacious countermeasures against SARS-CoV-2-induced COVID-19 are currently lacking. There are, however, existing agents that are being repurposed. Current Antiviral Therapies Under Investigation for COVID-19 The COVID-19 pandemic has taken a heavy toll on human life and, on a global scale, caused massive disruption of Social life and economic activities. According to our analysis and predictions, CP has some curative effects and is a safe method for treating infectious diseases early after symptom onset. Considering the urgency associated with the rapid development of the pandemic, these efforts so far focus on repurposing licensed or investigational drugs including compounds with possible antiviral effects and immunomodulators⁶. Due to the persisting global Covid-19 pandemic, researchers worldwide are working rapidly to identify and develop a viable vaccine candidate. At present, more than 200 prophylactic vaccines are in development against Covid-19.

ACKNOWLEDGEMENT: This work was funded by the author at Pratibhatai Pawar College of Pharmacy, Shirampur (413709), under the guidance of MS Thange T. A. (Assistant Professor Pharmaceutical Chemistry).

CONFLICT OF INTEREST: The authors declare no conflicts of interest.

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How to cite this article:

Satpute SA: Investigational treatment of Covid-19. *Int J Pharm Sci & Res* 2022; 13(8): 3137-45. doi: 10.13040/IJPSR.0975-8232.13(8).3137-45.

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