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A Systematic Review on COVID-19 Pandemic and Possible Management Strategy

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ABSTRACT

The World Health Organization (WHO) utilized the term novel COVID-2019 to allude to an infection that influences the lower respiratory tract of patients who are suffering from pneumonia. On 29th December 2019, it was first turn up in the city of China named Wuhan. At present it is also referred as Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus2 (SARS-CoV-2). Coronavirus is a RNA enveloped virus that is found in humans and wildlife. The base of virus was connected to a seafood market in Wuhan city. An aggregate of six animal categories has been distinguished to cause infection in humans. They are known to contaminate the neurological, respiratory, enteric, and hepatic frameworks. The flare-up was pronounced a public health emergency of international concern on 30th January 2020. It has been declared a pandemic by WHO on 11th March 2020 by WHO director general and is seen as a global emergency. There are no specific therapies approved by the U.S. Food and Drug Administration (FDA) yet, but several combinations of existing drugs are used as a supportive therapy. The objective of this review article is to provide key points related to clinical features, etiology, diagnosis, prevention, and treatment of COVID-19.

Keywords: COVID-19; Corona virus; Respiratory tract infection; Supportive therapy

INTRODUCTION

COVID-19 is an emerging deadly infectious disease that occurs due to novel coronavirus. The virus was named COVID-19 by WHO. It is found to be a large family of positive sense, single-stranded RNA viruses and belong to the order of *Nidovirales*. It is the seventh member of the *Coronaviridae* known to infect humans. They can also be isolated from different animal species which include birds, livestock, and mammals such as camels, bats, masked palm civets, mice, dogs, and cats. In December 2019, novel Coronavirus (nCoV) has emerged in the Wuhan seafood market, where livestock animals are also traded, which was seen as a public health problem and it is seen as global attention due to a pneumonia epidemic with unknown cause and then finally the market was closed on 1st January 2020. The indications were extending from those like the regular virus to more serious respiratory, even the enteric, hepatic, and neurological side effects. The fatality rate due to this virus differs from 1% to 12%, but the transmission rate is very high and recently, the WHO declared COVID-19 outbreak a pandemic. Till date, the patients with COVID-19 are being treated with supportive care and there are no therapeutics available. Drug repositioning could be one of the best ways to respond immediately to these infectious diseases as we know that new drug development often takes more than 10 years. One of the best alternative ways is to look for FDA approved drugs but only in the case where at least modest antiviral activity can be achieved. Accordingly, several drugs are being tested in numerous clinical trials [1].

LITERATURE REVIEW

Epidemiology

The first four cases of an acute respiratory syndrome of unknown etiology were reported in Wuhan city on 29 December 2019, in China. They were mostly reported to be the primary contact of the original sea food market and then it took no longer time to see a secondary source of infection due to human-to-human transmission *via* close contact. Later it was found that the COVID-19 infection occurs through exposure to the virus, and mostly the immunosuppressed and normal people appear susceptible. It is also found that the age group between 25 and 89 years old are more susceptible. It was discovered that individuals with a helpless invulnerable capacity, for example, more established individuals and those with renal and hepatic

brokenness might be at higher danger.

Etiology

Coronaviruses (CoV) belongs to the genus Coronavirus. They are single abandoned RNA viruses and belong to the family of *Nidovirales*. Their order includes *Coronaviridae, Roniviridae, Arteriviridae* families. These *Coronaviridae* families are additionally partitioned into *Torovirinae* and *Coronavirinae* subfamilies. Alpha-, beta-, gamma- and delta- CoVs are their further division. The different manifestations due to infections shift from those like the basic virus to more extreme respiratory and furthermore incorporate enteric, hepatic, and neurological side effects. Their viral RNA genome ranges from 26 kilo bases to 32 kilo bases in length. Other than SARS-CoV-2, there are six known COVID in people: They are HCoV-NL63, HCoV-229E, HCoV-OC43, SARS-CoV, HCoV-HKU1, and MERS-CoV.

China CDC gathered 585 samples from people in an around Wuhan in the middle of first January and twelfth January 2020. Accordingly, they discovered 33 examples containing SARS-CoV-2 and demonstrated that it is started from wild creatures that are being sold in the Wuhan market. Further, scientists conduct the tests of 15 patients by gathering the blood, lung liquid, and throat swab tests [2]. Through these lab tests, they found that the infection explicit nucleic corrosive successions in the test are unique in relation to those of known human COVID species. Research facility results additionally showed that SARS-CoV-2 is similar to the beta (β) COVIDs genera recognized in bats, which is arranged in a gathering of SARS/SARS-like CoV. The coronavirus virion is an enveloped particle containing the Spike (S), Membrane (M), and envelope protein. Besides, some strains of virus express a Hemagglutinin protein (HE) which is absent in the case of SCoV.

DISCUSSION

Pathogenesis

Once the virus enters the body, it needs a special receptor to help it enter the cell. This receptor is called (Angiotensin Converting Enzymes-2) ACE-2. The ACE-2 is present on the surface of alveolar cells in the lungs. There are three types of alveolar cells:
Type-I: Responsible for gas exchange
Type-II: Responsible for producing proteins
Type III: Dust cells, which are macrophages

The ACE2 is found on type 2. Coronavirus envelope contains Spikes (S) that help the virus to bind to ACE2. When the above association occurs, the genetic materials of the virus enters the cells and the cell harnessed to produce viral protein, thus the virus multiplies and the cell dies, when type II alveolar cells die, they release substances called specific inflammatory mediators. These substances stimulate the existing immune cells "macrophages" and when they stimulate the macrophages, they secrete three immune substances called "cytokines" which are: Interleukin 1 (IL-1), Interleukin-6 (IL-6), Tumour Necrosis Factor (TNF-α). These substances, when they reach the bloodstream, causes the symptom associated with infection with the coronavirus, cause the symptoms associated with infection with corona virus (Figure 1).

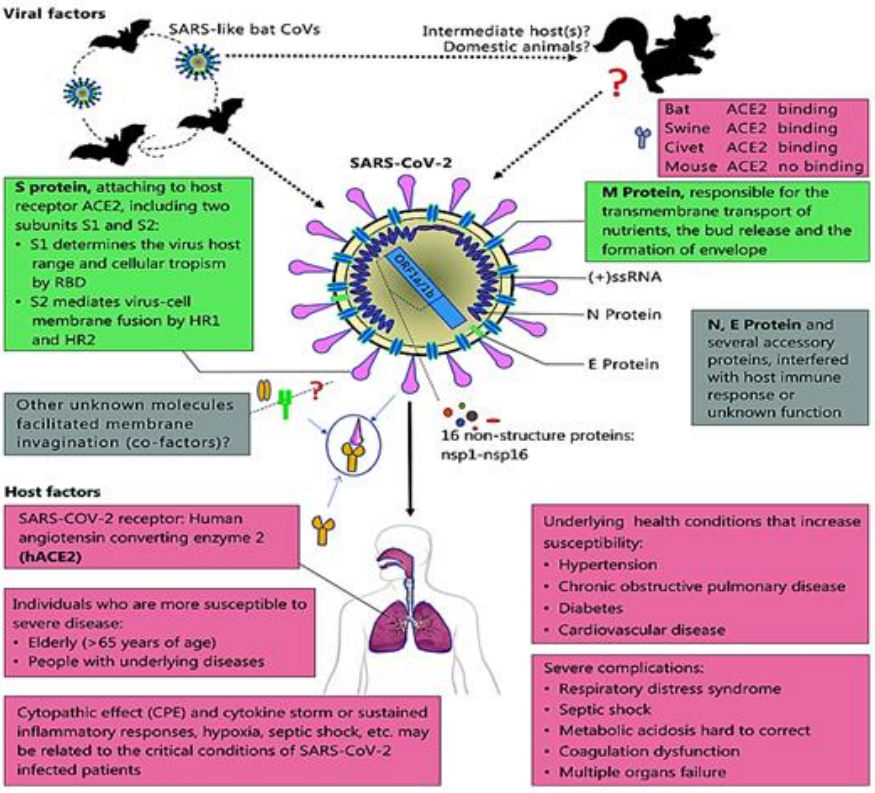

Figure 1: Pathogenesis of virus and its effect on human host.

Transmission

The first cases were seen at a seafood market in Wuhan, China that occurs due to direct exposure to infected animals *i.e.,* (animal-to-human transmission). However, various clinical cases were seen which were having contact history with a virus affected patient. This proves further that there is also the possibility of human-to-human transmission. Hence, human-to-human transmission is now considered as the main reason for transmission [3]. Numerous cases were seen where people may stay asymptomatic and could likewise communicate the infection to others. Notwithstanding, the most widely recognized wellspring of contamination is suggestive individuals. Through hacking or wheezing transmission happens from the spread of respiratory beads. Some information likewise presume that nearby contact between people can likewise bring about transmission. This additionally shows conceivable transmission in shut spaces because of raised airborne focuses (Figure 2).

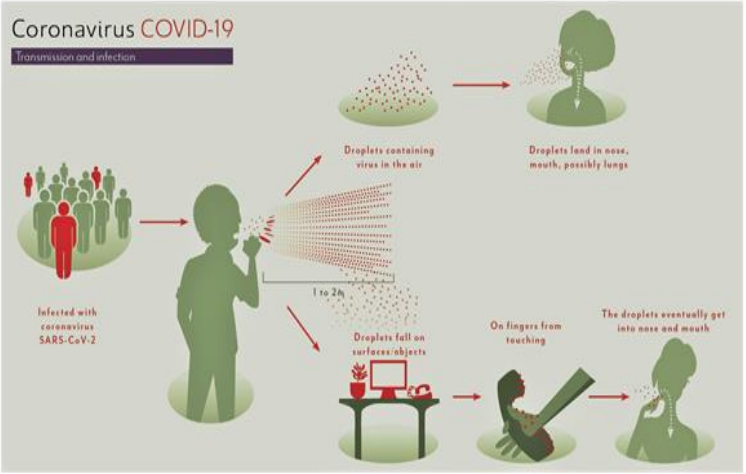

Figure 2: Transmission and spread of COVID-19 infection.

Clinical features

Initially, it was seen that the symptoms of COVID-19 were a cold like upper respiratory infection and self limiting lower respiratory infection. The first death due to corona virus has been reported by the isolation of SARS-CoV from a patient with pneumonia in China. As in other respiratory infected viruses and previous beta-CoV, similarities present in the clinical aspects of COVID-19 infections, later seen that clinical symptoms vary from simple respiratory infection findings to septic shock. The infection might be arranged into gentle, moderate, serious, and basic. The most well-known indications of patients incorporate fever (98.6%), exhaustion (69.6%), dry hack, windedness and the runs.

Diagnosis

The lab test which is performed to test coronavirus is raised prothrombin time, ALT, LDH (Lactate Dehydrogenase), D-dimer, C-responsive protein (CRP) and creatine kinase. There will be a lessening in CD4 and CD8 lymphocytes in beginning days. Patients who are seriously affected demonstrated more elevated levels of interleukin IL-2, IL-7, IL-10, GCSF (Granulocyte Colony Stimulating Factor), IP10 (Interferon gamma-induced Protein 10), MCP1 (Monocyte Chemotactic Protein 1), MIP1A (Macrophage Inflammatory Protein Alpha), and TNF-α (Tumour Necrosis Factor-α). There might be different ordinary changes, for example, coagulation actuation, cell safe inadequacy, heart related problem, disturbance in renal function, liver injury. In basic patients, amylase and D-dimer levels are increases. Nonetheless, blood lymphocyte tallies are discovered to be diminished [4]. In case of non-survivors, ascends in ferritin, neutrophil count, D-dimer, blood urea and creatinine levels are watched. Heights in procalcitonin levels are not seen in coronavirus. Thus, a patient with a raised degree of procalcitonin might be recommended as bacterial pneumonia. Those patients who are seriously influenced need to perform following procedures, for example Performing Continuous Fluorescence (RT-PCR) to identify the positive nucleic acid of SARS-CoV-2 in throat swabs, sputum, and emissions of the lower respiratory tract tests.

Prevention

As it is an infectious disease so preventive measures should aim to infection control. Guidelines have been issued by WHO on the proper use of face masks in the community, during care at home, and in the health care settings of COVID-19. Infection Preventive and Control (IPC) measures which help in the decrease of presentation or transmission incorporate the following: Utilization offace veils; covering hacks and wheezes with tissues that are then securely discarded (or, if no tissues are accessible, utilize a flexed elbow to cover the hack or sniffle); shirking of contact with tainted individuals and keeping up a fitting separation however much as could reasonably be expected.

Management

Isolation is the prior and first step for prevention of COVID-19 as there are no particular medicine available against virus. Hence, currently we mainly focus on supportive therapy and symptomatic care for treatment. Patients who are not severely infected need various supportive management. These are being done with the use of analgesics, oxygen therapy, external cooling, balanced diet, and using antibacterial. Whereas those patients who are severely ill and in critical condition should be given supply of oxygen, antibodies from recovered patient, Extracorporeal Membrane Oxygenation (ECMO) or use of glucocorticoid [5]. The use of systemic corticoid is not favourable. People should not unnecessarily use

antibiotics. Treatment of septic shock requires the administration of vasopressor's support with the hemodynamic. Organ function support is necessary in patient with organ failure alpha-interferon (5 million units twice daily) as aerosol can be therapeutically administered, Lopinavir/Ritonavir and Chloroquine phosphate, have also been suggested. Some others also suggested anti-viral drugs such as Ribavirin and Abidor. One shouldn't use three or more antiviral drug simultaneously. Various clinical report suggests that Remdesivir (GS5734) can also be used for prophylaxis. A fusion inhibitor which targets the HR1 domain of spike protein of virus is reported to use against COVID-19.

Selected COVID-19 drug therapy-potential options

As, there are no particular therapies which are confirmed by FDA for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 COVID-19. Currently, various clinical trial and protocols are being performed on limited clinical experience.

Chloroquine

Category: Antimalarial, amoebicides (Figure 3).

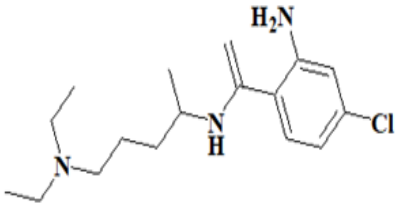

Figure 3: Choroquine.

Mechanism of action

MWCE gave MIC of 1.000 mg/mL and 0.250 mg/mL for *E. coli* and *K. pneumoniae* respectively, CCE gave MIC of 32.000 mg/mL for both *E. coli* and *S. typhi*. JTR1 showed no MIC at coverage concentration for all bacteria analyzed while MCE, HCE and MWCE were 16.000 mg/mL for *S. typhi*. MCE had MIC for *E. coli, K. pneumoniae, S. typhi, S. pneumoniae* and *S. aureus* at 2.000 mg/mL, 2.000 mg/mL, 16.000 mg/mL, 4.000 mg/mL and 0.250 mg/0 mL respectively [6]. Excluding JTR1 both the crude and pure extracts had appreciable MIC when compared to ampicillin. They block the entry of virus into the cell by inhibiting the glycosylation of host receptor and acidification of endosome. They can inhibit the autophagy and liposomal activity in host cells and also can module the immune system by attenuation of production of cytokine. It can also act by processes such as viral protein glycosylation, viral DNA and RNA polymerase, new virus particle transport, and virus release. They inhibit virus *in vitro* with a half maximal Effective Concentration (EC50) in the low micro molarrange. Dosing of chloroquine to treat COVID-19 has consisted of 500 mg orally once or twice daily.

Hydroxychloroquine

Category: Antimalarial (Figure 4).

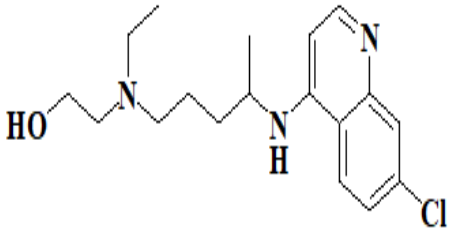

Figure 4: Hydroxychloroquine.

Mechanism of action

Same as chloroquine, hydroxychloroquine act on various pathways of virus entry into and exit from cells and then cause disruption of the essential viral protein synthesis. The *in-vitro* activities of chloroquine and hydroxychloroquineseems to have an inhibitory effect on virus mRNA production, with showing greater efficacy by hydroxychloroquine thanchloroquine. Asymptomatic health workers involved in the care of suspected or confirmed cases of COVID-19:400 mg twice a day on day 1, followed by 400 mg once weakly for the next 7 weeks to be taken with a meal. Asymptomatic household contacts of laboratory confirmed cases: 400 mg twice a day on day 1, followed by 400 mg once weakly for the next 3 weeks to be taken with a meal [7].

Lopinavir and Ritonavir

Category: HIV protease inhibitor (Figures 5 and 6).

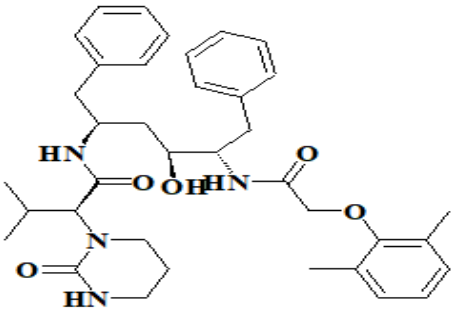

Figure 5: Lopinavir.

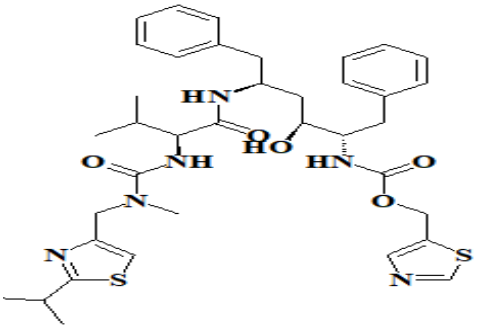

Figure 6: Ritonavir.

Mechanism of action

They act by binding to a specific enzyme known as M Pro, as it is essential for replication of the coronavirus as a result the action of the virus is suppressed. It works on the principle that chloroquine shows a synergistic anti-viral effect with Lopinavir, due to which two drugs when administered together block some pumps such as P-glycoprotein, which cross the cell membrane and extrude Lopinavir from the cell. This allows very good penetration of the drug into the tissues [8]. Since these membrane pumps are ubiquitous in tissues, it was assumed that this effect could also exist in the cells that are targeted by coronaviruses. Adverse effects includes gastrointestinal distress such as nausea and diarrhea (up to 28%) and hepatotoxicity (2%-10%). In a ratio of 1:1 ratio patient were given either Lopinavir-Ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care, or standard care alone.

Remdesivir

Category: Antimetabolite, Adenosinetriphosphate (ATP) analogue (Figure 7).

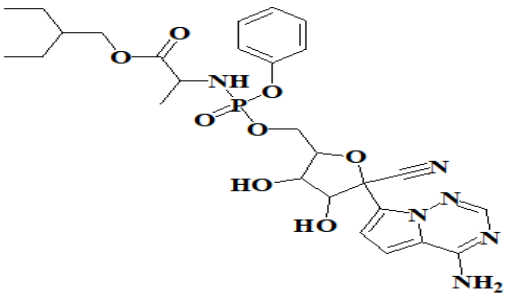

Figure 7: Remdesivir.

Mechanism of action

Remdesivir is a prodrug and has potential antiviral activity. It was earlier indicated for the treatment against Ebola virus infection and now it's a potential weapon against SARS CoV-2 virus. As it's a prodrug, upon administration it undergoes metabolism and form active GS-441524. It's an ATP analogue so it competes with ATP and interferes with viral RNA dependent RNA polymerase which in turn decreases viral RNA production. It

may also inhibit viral nucleotide synthesis to prevent viral replication. Current dose is 200 mg loading single dose followed by 100 mg daily infusion. It is not recommended during pregnancy as safety data's are not available [9].

Azithromycin

Category: Macrolide antibiotic (Figure 8).

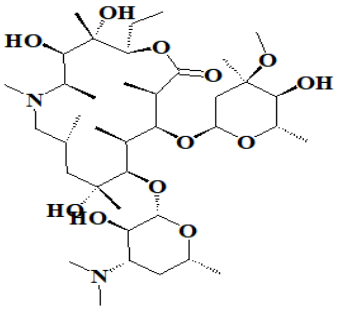

Figure 8: Azithromycin.

Mechanism of action

Azithromycin has immune modulating property in case of various inflammatory disease. They act by reducing the increased cytokine production and downregulate inflammatory response which is associated with respiratory problems; while, the effects of azithromycin on viral clearance are not found [10]. Immuno modulating mechanism occurs by inhibiting cytokines which take place by reducing chemotaxis of neutrophils in the lungs by (*i.e.*, IL-8), increasing neutrophil apoptosis, decreasing secretion of mucus, decreased production of free radical, and blocking the activation of nuclear transcription factors.

Safety concerns

There may be the risk of QT prolongation or cardiac arrythimia. Olina et al assessed virologic and clinical outcomes of 11 consecutive hospitalized patients who received hydroxychloroquine (600 mg/day for 10 days) and azithromycin (500 mg on day 1, then 250 mg days 2-5) 500 mg on day 1, then 250 mg days 2-5) [11].

Tocilizumab

Category: Immunosuppressive (Figure 9).

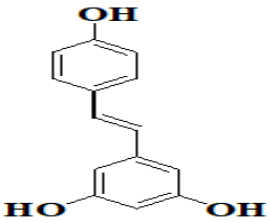

Figure 9: Tocilizumab.

Mechanism of action

IL-6 is one of the pro-inflammatory cytokines which are responsible for various physiological processes in our body such as T-cell activation, immunoglobulin secretion induction, and a precursor for cell proliferation and differentiation stimulation. IL-6 are formed. By various cells, including T- and B- cells, various lymphocytes, monocytes, and fibroblasts [12]. They act by inhibiting IL-6 mediated signalling by competitively binding to both membrane-bound and soluble IL-6 receptors. Side effects which are observed in patients who are treated with tocilizumab are:
Upper respiratory tract infections.

- Headache
- Hypertension
- Injection site reactions

At times different type of side effects occur, which include:

- Tears of the stomach or intestines
- Hepatotoxicity
- Nervous problem

Immunomodulators

Various immune modulating agents such as (e.g., alfa-interferon, sarilumab (Kevzara) are thought to be used as adjunctive for the treatment.

Convalescent plasma for COVID-19

Convalescent plasma therapy uses the blood from SARS-CoV-2 recovered patient to help other infected person to recover. Various health professional says that human convalescent serum is the best option for treating the virus. This serum can be very easily and rapidly available from the various person who have successfully recovered from virus. They can donate their immunoglobulin containing serum. In this therapy-The antibodies are given to patient against a virus to treat them (Figure 10).

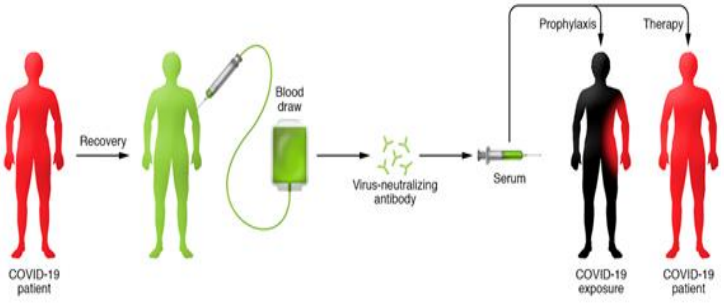

Figure 10: Convalescent plasma therapy.

Rationale for use

We need to remember that it is not use for preventing oneself from infection. Various clinical trials are being conducted for treating COVID infected patient by the use of convalescent plasma [13]. For taking part in clinical trials with plasma one should submit an application requesting to FDA. These can be done by single patient emergency Investigational New Drug applications (eINDs). Only licensed physicians are eligible to obtain COVID-19 convalescent plasma for an individual patient.

Facts associated with routine BCG vaccination

It is a vaccine which is given to children is seen to have protection of respiratory infections. BCG is utilized generally over the world as an immunization for Tuberculosis (TB). It is a live lessened strain isolated from a seclude of *Mycobacterium bovis*. To support the above statement they analysed the enormous number of nations BCG immunization approaches with the bleakness and mortality for COVID-19. With these data, they found that countries having no universal policies of BCG vaccination like (Italy, Nederland, USA) are more affected as compared to countries having universal and long-standing BCG policies [14]. As it has been seen that there is reduced morbidity and mortality in countries having BCG policies, BCG vaccination is seen as a potential new tool to fight against COVID-19. A few antibodies including the BCG inoculation have been appeared to create vague safe or positive heterologous impacts prompting improved reaction against other non-mycobacterial microorganisms.

For example, BCG inoculated mice infected with the virus infection were shielded by expanded IFN-Y creation from $CD4^+$ cells. This marvel was named prepared resistance and is proposed to be brought about by metabolic and epigenetic changes prompting the advancement of hereditary districts encoding for favourable to pro-inflammatory cytokines [15]. It has been discovered that BCG immunization essentially elevates the secretion of pro-inflammatory cytokines, explicitly IL-1B, which has an incredible task to carry out in antiviral invulnerability (Figure 11).

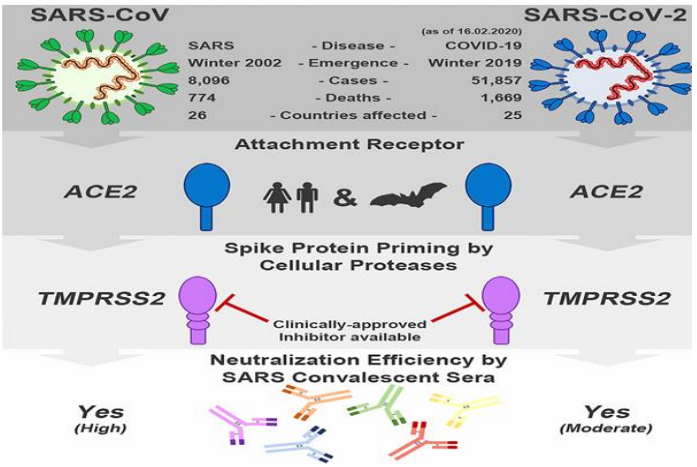

Figure 11: SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor.

CONCLUSION

We have discussed here the recent research in response to the pandemic of COVID-19. As we are going through pandemic disease we saw the causes, epidemiology, clinical development, diagnosis, prevention, and control of the virus corona. Further, we have focussed on treatment prevention and control measures. The entire world is suffering and drug repositioning is seen to be the option useful to minimize the effect of the virus. Government authorities have been showing the effort to look for various scientific findings in the community, regional, and national levels to slow down and/or prevent the further spread of the COVID-19. Various newer ideas and approaches are showing up to cope with the virus every day and even many vaccines are in the different stages of clinical trial. Furthermore, research and clinical trials are needed as our aim should be not just managing the disease but to permanently cure it.

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