Review Article

SARS-CoV-2 – present therapeutics scenario: a review

Jagadish Das[1]*, Devdip Dutta[1], Debarun Ghosh[1] and Sushruta Chakraborty[1]

[1]Dr. B. C. Roy College of Pharmacy & AHS, Durgapur, West Bengal, India

Abstract

The COVID-19 pandemic is considered as the most crucial global health calamity of the century and the greatest challenge that the humankind faced. Although several clinical trials are now underway to test possible therapies, the worldwide response to the COVID-19 outbreak has been largely limited to monitoring/containment. Taxonomically SARS CoV 2 belongs to the family Coronaviridae, subfamily Coronavirinae and the order Nidovirrales. Subfamily Coronavirinae is divided into four genera- α, β, γ and δ. RBD is a fundamental peptide domain as it represents a binding site for the human angiotensin converting enzyme 2 (ACE2). In the course of treatment of SARS-CoV-2 there are hetergeous response was observed in trials and case studies. The major therapeutic agent was used was immunosuppressants like prednisolone assisted by other drugs which are mainly used other infective disorders but principal was those drug came from drug repurposing. Therapy was segregated in 2 objectives. First objective was to reduce and control the inflammatory responses and second objective was to reduce the viral load which is mainly focuses on the antivirals. Vaccine was also implanted as preventive measures but not proven to be fully prophylactic, in addition the vaccine was proven to control the disease severity that finally reduce the morbidity and mortality. Further research is mandatory specially encompasses on the epidemiological and epigenetical approaches.

Keywords: Ivermectin, Repurposing, SARS CoV 2 variants

Introduction

The COVID-19 pandemic is considered as the most crucial global health calamity of the century and the greatest challenge that the humankind faced since the 2nd World War [1]. In late December 2019, a novel coronavirus (nCoV) named as "SARS-CoV-2" was identified in China. A cluster of pneumonia cases with an unidentified cause emerged out suddenly in Wuhan, a city in the Hubei Province of China. Through the analysis of sequence, it was confirmed that the novel coronavirus (nCoV) was responsible for those unidentified pneumonia [2]. From Wuhan it spread rapidly across the mainland China, followed by an increasing number of cases throughout the world. In early March of 2020, the World Health Organization (WHO) announced the COVID-19 (Coronavirus Disease 2019) as a global pandemic. The virus that causes the disease COVID-19 is termed as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [3]. The occurrence of the SARS-CoV (Severe Acute Respiratory Syndrome- Coronavirus) in 2002 and 2003 and MERS-CoV (Middle East Respiratory Syndrome - Coronavirus) in 2012 showed the potential for transmission of newly rising coronavirus from animal to human and human to human. In those epidemics the mortality rates were approximately 9.5% and 34.4%, respectively. In case of COVID-19, as of 15 June, 2021 approximately 176 million cases with 3.8 million deaths globally have been registered by World Health Organization (WHO). Alone India has reported approximately 29.6 million cases with 3.77 lakh death cases [4]. COVID-19 is the third highly epidemic disease detected, with the higher transmission rate and lower mortality rate than the previous epidemics SARS-CoV and MERS. Though there is no suitable medicine for COVID-19 till now, many antibiotics as well other drugs are used in the treatment of COVID-19 [5]. More recently, trial outcomes of ivermectin, a broadly used antiparasitic medicinal drug with recognized antiviral and anti-inflammatory properties, were displaying blessings in a couple of critical medical and virologic outcomes, which include mortality. Although developing numbers of the research helping this end have surpassed thru peer evaluate, about 1/2 of the last trials records are from

***Mail id for correspondence**
Sahebdas93250@gmail.com

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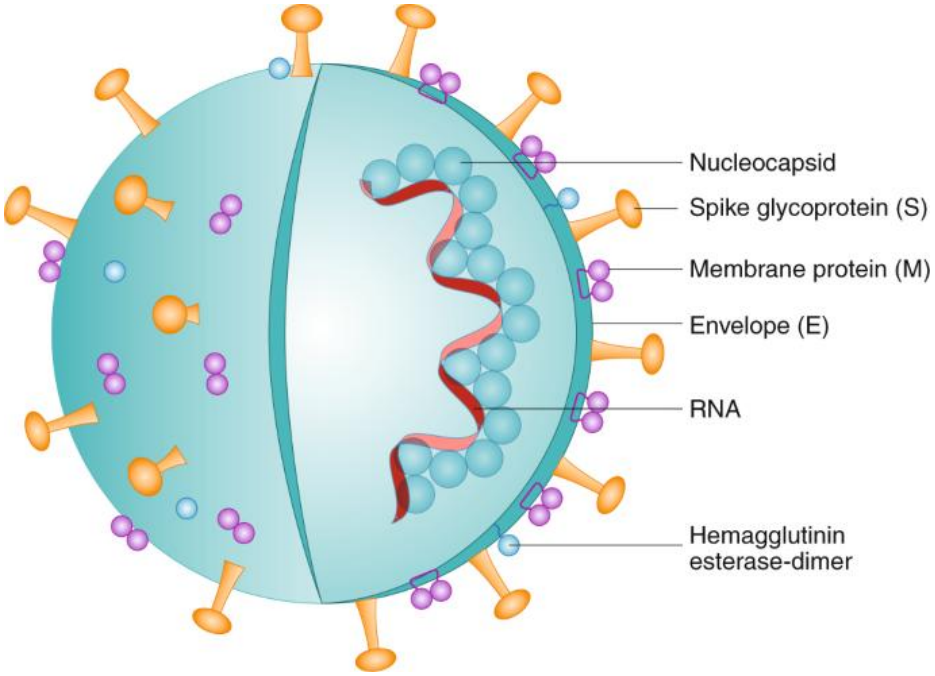

Fig 1: Structure of SARS-CoV-2 virus

manuscripts uploaded to scientific preprint servers, a now widespread exercise for each speedy dissemination and adoption of recent therapeutics in the course of the pandemic [6]. Following is a complete evaluate of the to be had efficacy records as of December 12, 2020, taken from in vitro, animal, medical, and real-international research all displaying the above effects of ivermectin in COVID-19. But due to the complex morphological, immunological and incompletely understood underlying pathophysiological spectrum of this virus, it is the biggest challenge for us to eradicate this pandemic.

History

In 1965, Tyrrell and Bynoe found a virus B814 from a boy with a cold. Then the Pathogen was described as "virtually unrelated to any other known virus of the human respiratory tract" [7]
In 1966, at University of Chicago, Dorothy Hamre and Jhon Procknow grew a unusual virus in kidney tissue culture from the sample obtained from medical students with cold. They named the virus 229E. Both this and B814 was found to be ether sensitive virus and were not related to any myxo- or paramyxovirus [8].
In 1967, McIntosh et al, in the laboratory of Robert Chanock at the National Institute of Health, recovered a group of strains of ether sensitive agents from human respiratory tract and named one of them OC43 (OC for as grown in organ cultures) [9]. In the same time period at St. Thomas Hospital in London, June Almeida along with the founders of B814, 229E and OC43 performed electron microscopy on the samples and that all these are medium sized (80-150nm) particle, pleomorphic, lipid membrane coated and they said the viruses have a "characteristic 'fringe' of projections 200Å long, which are rounded or petal shaped" [10]. In late 1960s some other strains of animal viruses also found to having the same morphological structure. This new group of viruses termed as Cotonavirus (corona designated the crown like appearance of the surface projections) and later it was officially accepted as a new genus of viruses. In 2002, a human coronavirus SARS-CoV caused severe acute respiratory syndrome (SARS), which was emerged in southern China and quickly spread over 28 countries. According to WHO from November2002 to July 2003, 8098 people were infected of which 774 was died. By late July 2003 no new cases were reported worldwide. This had mortality rate of 9.5% [11]. In 2004, at Erasmus Medical Centre in Netherlands, a human coronavirus strain, NL63 was found from a child with pneumonia [12]. In 2005, a group of researchers at University of Hong Kong isolated another human coronavirus, HKU1, from two patients with pneumonia [13]. In 2012, another human coronavirus outbreak emerged in Saudi Arabia, which is known as Middle East Respiratory Syndrome (MERS). It also spread in several countries and most of the patients who infected with MERS CoV, developed severe respiratory illness including fever and had the mortality rate of approximately 34.4% [14]. In late December 2019, in Wuhan, China, a new type of pneumonia has been observed in people which is also caused by a type of novel Coronavirus (nCoV). WHO termed this nCoV as SARS CoV 2 and the disease COVID19. Due to the high transmission capacity, SARS-CoV-2 spread over the globe and infected 177,487,674 people and has climed 9,840,272 lives worldwide till 16th June 2021 (count continues) [15].

Virology & Genomics

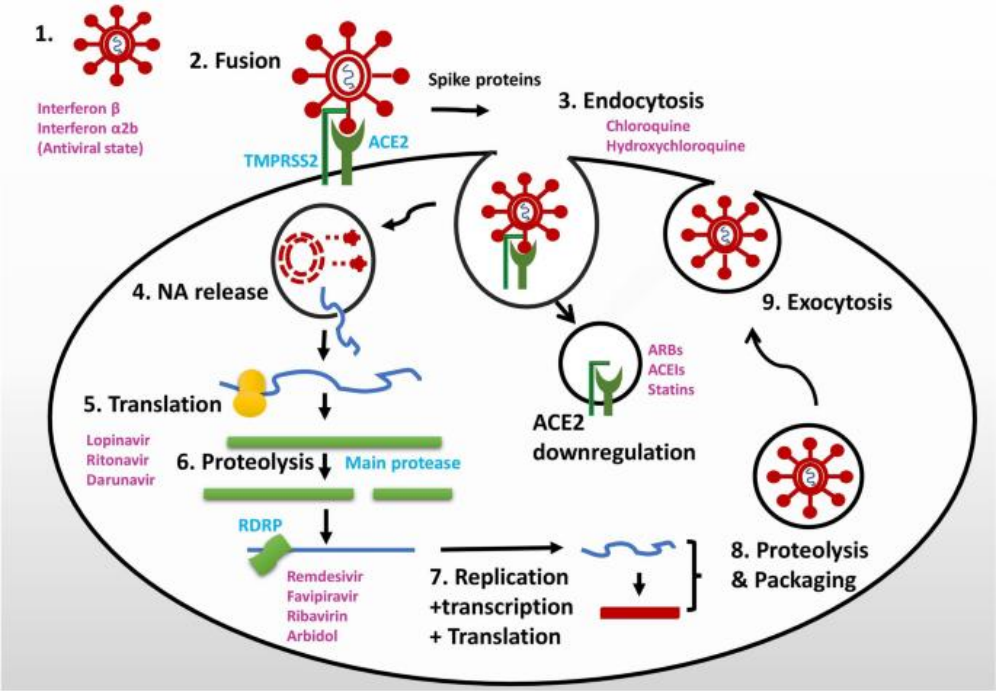

Fig 2: Mechanism of antivirals acting against SARS-CoV-2 virus

To combat the enemy, we must to know it well as how they comes, how they enters, how they attacks, how they effects and what are their weakness. So to fight against coronavirus, the biggest threat to the mankind right now, we have to know its virology.

Taxonomically SARS CoV 2 belongs to the family Coronaviridae, subfamily Coronavirinae and the order Nidovirrales. Subfamily Coronavirinae is divided into four genera- Alfa(α), Beta(β), Gamma(γ) and Delta(δ). α & β coronaviruses infects humans. Bats are the evolutionary hosts for the α & β coronavirus. Complete gene sequencing and phylogenic analysis of this virus indicates that SARS CoV 2 is a β coronavirus as SARS, MERS and several bat coronavirus. SARS CoV 2 is a positive-sense single stranded RNA (+ssRNA) virus, i.e. it can be directly translated into the host protein by the host ribosome. The virions of this virus are spherical or elliptical and often shows pleomorphic form and sizes between 60-140 nm in diameter. The virion surface has characteristic club like projections, made of spike protein (S). SARS CoV 2 is most stable at the temperature of 4°C, for almost 2 weeks. At room temperature it can remain stable for a day bereft of any loss in its infectivity. Like other coronaviruses SARS CoV 2 is also sensitive to UV and high temperature. According to Sabari Nath Neerukonda & Upendra Katneni it can be inactivate by exposing at 56°C for 30 minutes. It is also sensitive to most of the disinfectants like 70-75% ethanol, household bleach, povidone-iodine, chloroform, benzalkonium chloride, chloroxylenol, diethyl ether, chlorine, and chlorhexidine. Vice versa of the high temperature inactivation, it may resist as low temperature as 0°C. SARS CoV 2 is a enveloped virus which consist of four main structural protein: Spike (S) glycoprotein, Envelop (E) glycoprotein, Nucleocapsid (N) and Membrane (M) protein; 16 nonstructural protein and 5-8 accessory protein. The lipid bilayer envelope of the virus is anchored with the membrane, envelope and spike proteins [16].

- The spike (S) glycoprotein makes the crown like structure on the surface. S protein cleaved into amino (N) terminal S1 subunit, which incorporate the virus into the host cell and a carboxyl (C) terminal S2 subunit which forms the stem which anchors the spike in the viral envelope. S1 subunit consists of two domains N-terminal domain (S1-NTD) and C-terminal domain (S1-CTD). Both these domains of S1 perform as receptor binding domain (RBD). S1-NTD is responsible for the recognizing and binding the sugars on the surface of the host cells whereas the S1-CTD is responsible for recognizing the different protein receptors like angiotensin-converting enzyme 2 (ACE 2), aminopeptidase N (APN) and dipeptidyl peptidase 4 (DPP-4). SARS Cov 2 contain a polybasic furin cleavage site insertion (residues PRRA) at the junction of S1 and S2, probably which is the cause of enhanced infectivity of the SARS-CoV-2. This PRRA is not present in any other Coronavirus [17].
- The M protein, having three domains a short N-terminal ectodomain, a triple-spanning transmembrane domain and a C-terminal endodomain, is the major structural protein of envelope that promotes the assembly and budding of the viral particles.
- The E protein is the minor structural protein, embedded in the lipid bilayer of the envelope. They have two domains, a transmembrane domain and an extramembrane C-terminal domain.
- The N protein is the major structural protein that involves in the RNA replication and virion formation.

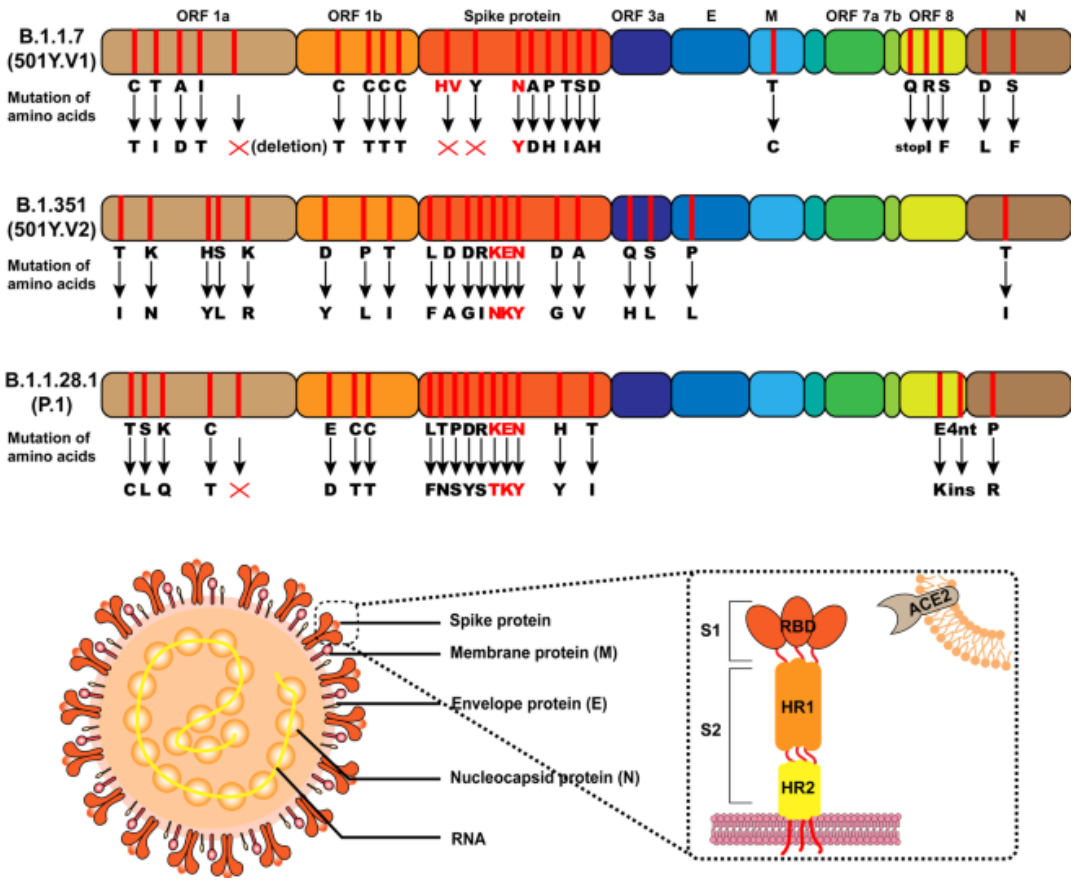

Fig 3: variants of SARS-Cov 19 proteins

The +ssRNA of SARS-CoV-2 virus has a 5' methylated cap and a 3' polyadenylated tail. The range of the genome size of the coronaviruses varies from 26.4 to 31.7 kilobases which makes this virus one of the largest RNA virus. All coronaviruses have the similar genome organisation for coding. The genome order is 5'-untranslated region- replicase (ORF1a & ORF1b), spike(S), envelope(E), membrane(M), nucleocapsid(N) -3'UTR, several unidentified non-structural ORFs and poly(A) tail. ORF1a locates at 5' end, followed by the ORF1b which encodes polyprotein pp1a and polyprotein pp1ab respectively. There are 14 open reading frames (ORFs) in the viral genome. About 66% of the viral genome are occupied by the first two ORFs (ORF 1a and 1b). The polyprotein cleaves to form 16 non-structural protein (NSP1 to 16). Other reading frames encode the structural protein (spike protein, envelope protein, membrane protein and nucleocapsid) and accessory proteins whereas the accessory proteins are almost nonessential for viral replication [18].

As per study RBD is a fundamental peptide domain as it represents a binding site for the human angiotensin converting enzyme 2 (ACE2). ACE2 is a type I membrane glycoprotein expressed in lungs, heart, intestines, and kidneys. SARS CoV2 enters into the host cell by binding the S protein (S1) to the ACE2 receptors on the respiratory epithelium. This process is followed by priming the spike protein S2 subunit by the host transmembrane serine protease 2 (TMPRSS2) that facilitates cell entry and subsequent viral replication endocytosis with the assembly of virions. Inhibition of renin angiotensin aldosterone system (RAAS) [19].

Like other RNA viruses, SARS CoV 2 is prone to genetic evaluation, which develops mutation over time. These mutations results in variants that may have different characters than its previous strains. Several strains have been described during COVID 19 pandemic. At the beginning of the pandemic genetic evaluation was minimal. D614G, having increased transmissibility and less ability of causing severe illness, was the dominant variant globally. Among all the described variants few are considered as Variants of Concern (VOCs), which have shown their impact on public health. WHO and CDC independently classified all these variants into-

1. Variant of concern (VOCS)- VOC202012/01 (B.1.1.7 lineage), 501Y.V2(B.1.351 lineage), P1 (B.11.1.28.1 lineage).

2. SARS COV 2 Variant of interest (VOIs)- "A SARS-CoV-2 isolate is a variant of interest (VOI) if it is phenotypically changed compared to a reference isolate or has a genome with mutations that lead to amino acid changes associated with established or suspected phenotypic implications.". By 13th April 2021, WHO described seven VOIs, which are B.1.427, B.1.429, B.1.525, B.1.526, B.1.1.28.2 (P2), B.1.1.28.3 (P3) and B.1.616. CDC has also described three- B.1.525, B.1.526 and B.1.1.28.2 [20].

Mode of Transmission:

In general virus can be transmitted through various way as- Respiratory tract, gastrointestinal tract, genital tract, direct contact to the skin, through Placenta, Eye, and even through transplantation of an organ or blood.

As COVID 19 is a respiratory infection primarily SARS CoV 2 is transmitted via respiratory droplets carrying the virus from close contact or droplet transmission from individual harboring the virus. According to WHO, an individual can be infected when droplets containing the virus are inhaled or come directly into contact with the eyes, nose, or mouth. WHO also said the virus can be transmitted in a poorly ventilated and/or crowded indoor situation where aerosol containing the virus can be suspended in air. According to study report it also can transmitted through air and from contaminated surfaces (porous or nonporous). It can stay stable and viable up to 28 days at 20°C from inoculation on the nonporous surfaces like stainless steel, glass etc. whereas on porous surfaces it found to be less stable than nonporous surfaces. Presence of viable virus in the feces of infected individual implying possible fecal-oral transmission. In minor number of cases vertical transmission is possible from mother with COVID19 to the neonates [21].

Treatment

On the onset of this epidemic all the governments, health providers and institutions began to continuously review the rapidly emerging basic science, translational and clinical data to identify potentially effective treatment for COVID 19. Different strategies at different time period has been suggested by the authorities. Several drugs are clinically tried and repurposed for the treatment of COVID 19. Here we will discuss about the various treatment strategies.
The all of a sudden out brake of SARS CoV2 forced the global health care system to repurposing the already existing drugs which have activity against HIV, MERS and SARS CoV1.

Anti-viral treatment

There is much similarity (about 80-90%) in genome sequence and enzymes of SARS COV 2 and preexisted beta coronavirus like SARS COV1 and MERS COV. So the preexisting anti-viral drugs, which are already used to treat these pathogens, may be effective to reduce the viral load and treat COVID 19 infection. On the other hand protease inhibitors also possess inhibitory effect on RNA viruses. On this account some preexisted antiviral drugs, like Remdesivir, Favipiravir, Ribavirin, has been clinically tried to treat the COVID19 infection. Among all these drugs Remdesivir found to possess significant effect on the infection. Currently it is the only antiviral drug which can be used in the patients with low oxygen saturation and in critical condition. Study data also demonstrate that use Remdesivir lowers the mortality rate among hospitalized patients. But in mild symptomatic patients it is not recommended to use.
In addition to that another antiviral drug Arbidol and a prodrug N-hydroxycytidine also found to possess prominent anti-SARS CoV2 activity. A randomised control trial conducted in China comparing the cure rate and 7-day recovery rates in patients randomly allocated to two groups, one receiving Favipiravir and the other receiving Arbidol treatment [22].

Treatment with anti-malarials

To counter SARS CoV 2, an renowned anti-malarial and anti-rheumatic drug, Chloroquine has been found to exhibit substantial snit-SARS CoV2 activity at a low effective concentration i.e. EC50 1.13μM. The results of the controlled clinical trial, conducted in 10 hospitals of China, was found to be promising in terms of reducing the viral load, disease duration and even preventing the exacerbation of COVID19 pneumonia. Chloroquine inhibits the viral fusion and entry into the host cell. The major drawback of Chloroquine is its toxicity related limitation.
In account of the toxicity of the Chloroquine, Hydroxychloroquine becomes a suitable alternative of its parent drug. It shows approximately 40% less toxicity and almost same anti-SARS CoV 2 activity as Chloroquine. Hydroxychloroquine acts against virus by increasing endosomal pH and prevents the viral entry in the host cell [23].

Treatment with antibiotics

In a study carried out in Michigan, USA, it is found a combination of antibiotic drug Azithromycin with the Hydroxychloroquine shows a significant reduction in viral load in COVID19 patients. But the results were not much practical due to some limitations of the study and NIH recommendations also suggests to avoid the use of this combination [24].

Treartment with anti-SARS Cov2 Neutralizing Antibody

A SARS CoV2 infected individual develops neutralizing antibodies against the virus while the recovering stage. The role of these neutralising antibodies has an extensive role as therapeutic agent in the management of COVID 19.

- Convalescent Plasma therapy was introduced during SARS, MERS and Ebola epidemics. But due to lack of trials, its efficacy is unknown. In the early period of COVID 19 pandemic FDA approves the use of convalescent plasma therapy for the patients with severe life threatening condition. Though this came out to be promising, but the data from multiple studies has generated a mixed results.

- REGN-CoV2 (Casirivimab & Imdevimab): this is an antibody cocktail which contains two noncompeting IgG1 antibodies. This targets the RBD on SARS COV2 spike protein. This show the decrease in the viral load in vivo. But another in vitro data regarding two SARS COV 2 variants, which are variants of concern (B.1.1.7 & B.1.351), reveal the retention of the activity.

- Bamlanivimab & Etesevimab are potent spike neutralizing monoclonal antibodies. Both these are derived from convalescent plasma of COVID 19 positive patient. Like REGN-CoV2 it also targets the RBD on the spike protein.

- FDA approves the clinical use of REGN-CoV2 and Bamlanivimab/Etesevimab in in nonhospitalized patients (aged more than 12 years & weighing more than 40 kg) with

laboratory-confirmed SARS-CoV-2 infection and mild to moderate COVID-19 patients who are at high risk for progressing to severe stage and hospitalization [25].

Immunomodulatory Agents-Host Targeting Strategy

Corticosteroids: dexamethasone is now considered the standard care in the hospitalized patients with inflammation related lung injury, who requires supplemental oxygen or mechanical ventilation. A randomised evolution of COVID 19 therapy trial showed the use of dexamethasone lowers the 28 days mortality in patients who were in intensive mechanical ventilation. Dexamethasone is given either alone or in combination with Remdesivir based on the severity of the illness [26].

Treatment with anti-parasitic agent

Nitazoxanide, previously known an anti-parasitic drug, also exhibits significant SARS CoV2 inhibitory activity. But the efficacy of this drug is inferior to Remdesivir and Chloroquine. Australian researchers, Caly et al., demonstrate the anti-SARS CoV2 activity of another previously known anti-parasitic agent, Ivermectin, which is also active against Human Immunodeficiency Virus (HIV) and dengue virus. It significantly reduces viral RNA levels at a low concentration. The detail mechanism of action, dosage, efficacy, pros and cons of use of Ivermectin will be discussed in the following [27].

Ivermectin for treatment of Covid19

The COVID19 pandemic hit more than 200 countries in less than 4 months and destroyed the entire healthcare system. There is no viable medicine to suppress the spread or infection of the virus. It is not that effective, and the vaccine still has a long way to go, so it is very necessary to use strong evidence to reuse existing drugs. The current situation requires therapeutically effective lenses.

A pre-existing drug, Ivermectin is a US-FDA approved anti-parasitic drug. It is traditionally used for the treatment of flatworm. Regardless the anti-parasitic property, Ivermectin has proven to have a wide range of in vitro antiviral properties. Ivermectin has been proven to be effective against RNA and deoxyribonucleic acid (DNA) viruses in vitro, including human immunodeficiency virus 1 (HIV1), dengue fever virus (DENV), influenza, Venezuelan equine encephalitis virus (VEEV) and Zika virus [28].

The nuclear import of viral proteins plays an important role in the life cycle of many viruses, including RNA viruses that replicate in the cytoplasm. Ivermectin inhibits the interaction between integrase protein and import protein α/β1 mediated nuclear import required for HIV infection, and is the first evidence that nuclear import inhibitors have effective antiviral activity.

In an in vitro study Australian researchers Caly at al. found the effect of Ivermectin on Vero-hsLAM cells infected with SARS-CoV-2 treated with 5μM Ivermectin showed a 93% reduction in the viral RNA load compared to the vehicle Dimethyl sulfoxide in 24 hours duration. In 48 hours duration 5000-fold reduction of viral RNA was observed in the ivermectin-treated samples compared to the control samples. This observation indicated that approximately all viral material was eradicated by ivermectin treatment in 48 hours duration. They also determined the IC50 (half maximal inhibitory concentration) of ivermectin treatment to be 2.5μM under the test conditions.

Mechanism of action of Ivermectin against SARS CoV2:

Ivermectin inhibits and interacts in the binding of S protein of SARS-CoV-2 at the ACE-2 receptors. The green dotted lines in the picture depict activation pathways and the red dotted lines depict the inhibition pathways. The TLR-4 receptors are directly activated by SARS-CoV-2 and also by LPS mediated activation causing activation of NF-Kb pathway and MAP3 Kinases leading to increased intranuclear gene expression for proinflammatory cytokines and chemokines (responsible for cytokine storm) and NO release (responsible for blood vessel dilatation, fluid leak, low blood pressure, ARDS and sepsis). The NF-Kb and STAT-3 pathway activation is central to the pathogenesis and sequelae of COVID-19. STAT-3 physically binds to PAK-1 and increases IL-6 transcription. The annexin A2 at the cell surface converts plasminogen; PLG to plasmin under the presence of t-PA. Plasmin triggers activation and nuclear translocation of STAT-3. An upregulation of STAT-3 stimulates hyaluronan synthase-2 in the lung cells causing hyaluronan deposition leading to diffuse alveolar damage and hypoxia. STAT-3 also directly activates TGF-beta initiating pulmonary fibrosis; a typical characteristic of SARS-COV-2 lung pathology. The damaged type 2 cells express PAI-1 and an already hypoxic state also causes an upregulation of PAI (through Hypoxic inducible factor-1) along with direct stimulation by STAT-3. Simultaneous STAT-3 and PAI-1 activation inhibits t-PA and urokinase-type plasminogen activator leading to thrombi formation. Also, the SARS-CoV-2 spike protein binds to the CD147 on red blood cells and causes clumping. IVM in turn, binds to SARS-CoV-2 Spike protein and hence prevents clumping. T cell lymphopenia in COVID-19 can also be attributed to the direct activation of PD-L1 receptors on endothelial cells by STAT-3. IVM directly inhibits the NF-kb pathway, STAT-3, and indirectly inhibits PAK-1 by increasing its ubiquitin-mediated degradation. The natural antiviral response of a cell is through interferon regulatory genes and viral RNA mediated activation of TLR-3 and TLR7/8- Myd88 activation of transcription of interferon-regulator (IRF) family. For a virus to establish an infection, this antiviral response needs to be inhibited by blocking interferon production. The proteins such as importin and KPNA mediate nuclear transport of viral protein and subsequent IFN signalling. The SARS-CoV-2 proteins (ORF-3a, NSP-1, and ORF-6) directly block IFN signalling causing the surrounding cells to become unsuspecting victims of the infection. IVM inhibits both importin a-b (green) as well as the KPNA-1 receptors (brown) causing natural antiviral IFN release. IVM also inhibits viral RdrP, responsible for viral replication. IVM Ivermectin, ACE-2 angiotensin-converting-enzyme 2, LPS Lipopolysaccharide, TLR Toll-like receptor, t-PA tissue-like plasminogen activator, PLG Plasminogen, IMPab Importin alpha-beta, Rdrp RNA dependant RNA polymerase, KPNA-1 Karyopherin Subunit Alpha 1, NF-kB nuclear factor kappa-light-chain-enhancer of activated B cells, Map3Kinases Mitogen-activated Kinases, PAK-1 P21 Activated Kinase 1, STAT-3 Signal transducer and activator of transcription 3, PAI-1 Plasminogen activator inhibitor-1, HIF-1 Hypoxia-Inducible Factor [29].

Some clinical tails has been conducted to ensure the efficacy of Ivermectin for the treatment of COVID 19 (30].

A case-control study has been conducted among health care professionals (HCPs) at Bhubaneswar AIIMS, India. Out of 186 case-control pairs, 76 controls and 41 cases received 300 µg/kg of ivermectin as prophylaxis, and it showed 73% reduction in SARS CoV2 infection among HCPs.

Another group of researchers from Bangladesh took conducted a study on 72 patients and grouped them in three division. One group has been administered placebo another recived ivermectin + doxycycline therapy and the rest one group got a 5 day ivermectin therapy. In this study they found the viral clearance (95% CI) is fastest among the group with 5 days ivermectin therapy (9.7 days) following the group with ivermectin + doxycycline (11.5 days) and placebo (12.7 days)

According to Asiya Kamber Zaidi & Puya Dehgani-Mobaraki "Considering the urgency of the ongoing COVID-19 pandemic, simultaneous detection of various new mutant strains and future potential re-emergence of novel coronaviruses, repurposing of approved drugs such as Ivermectin could be worthy of attention" [31]

So there is evidence that supports the use of Ivermectin in decreasing mortality figures in patients with SARS-CoV-2 infection. However, the use of ivermectin orally in an outpatient setting also requires strict and well defined guidelines to avoid any form of overdosing that could lead to toxicity. A study by Baudou, et. al described two human ABCB1 nonsense mutations associated with a loss of function in a patient who had an adverse reaction to ivermectin after the administration of a usual dose. This finding warrants caution regarding medical prescriptions of ivermectin and other ABCB1 substrates.

Conclusion

In the course of treatment of SARS-CoV-2 there are hetergeous response was observed in trials and case studies. The major therapeutic agent was used was immunosuppressants like prednisolone assisted by other drugs which are mainly used other infective disorders but principal was those drug came from drug repurposing. Therapy was segregated in 2 objectives. First objective was to reduce and control the inflammatory responses and second objective was to reduce the viral load which is mainly focuses on the antivirals. Vaccine was also implanted as preventive measures but not proven to be fully prophylactic, in addition the vaccine was proven to control the disease severity that finally reduce the morbidity and mortality. Further research is mandatory specially encompasses on the epidemiological and epigenetical approaches.

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