

Recent Treatment Methods and their Efficacy for Corona Pandemic Situation

Ayman Bin Abdul Mannan and Halima Habib

Student at Department of Microbiology
University of Dhaka, Bangladesh



Abstract – The world is going through a pandemic situation after 100 years. This situation is created by Corona virus SARS-CoV- 2. Its homology is quite similar to MERS-CoV and SARS-CoV. All of these viruses are responsible for respiratory illness. Till now, no licensed treatment or diagnosis method has been discovered against these viruses. Though the age of this disease is only nine months, many scientists working day and night to save the world from this pandemic situation. But the virus is changing itself by the time, seasons and area and making it difficult for the scientists to invent vaccine or treatment. The purpose of this article is to compile the major recent treatments which are being used to subside the adverse condition of the patient. Among the prominent methods that have been operated, obstructing the viral activity, mimicking the immune system, controlling immune hyperactivity are creating either prominent responses or a combination of positive and negative impact which varies from patient to patient. Some of them are widely used in almost all hospitalized patient in some of the countries. But none of the treatments are globally approved yet. Either The most impactful or the least one, each and every treatment is going through further studies.

Keywords – SARS-CoV-2, treatment, respiratory illness, viral activity, inflammatory.

I. INTRODUCTION

In 1965, corona virus was first identified to infect human. No severe symptoms appeared without common cold. Later, on 2002, it reappeared in Southern china which spread very rapidly to cause a small outbreak in 2004 resulting thousands of death. It was named as SARS(Severe Acute Respiratory syndrome) , one of the strains of corona virus .In 2012, another outbreak caused by MERS(Middle East Respiratory Syndrome) which is another strain but less contagious than SARS. Till now, scientists invented that seven strain of corona virus can infect human. The latest and the most impactful strain novel corona virus, SARS-CoV-2 was found in Wuhan of China which subsequently spread globally. Research evidence suggests that forerunner of SARS-CoV-2, the SARS-CoV and MERS-CoV emerged from bat and it is predicted that SARS-CoV-2 did the same [84][85]. Except

from severe breathing difficulties, other symptoms of these disease are very much similar to common respiratory illness. Coronavirus first get attached to the cell surface receptor, and then to endosome where the spike protein of the virus fuse with the membrane and deliver the RNA of the virus. The virus multiplies there and lyses out. It causes a severe cytokine storm and inflammatory response in the body. This hyperinflammation causes shortness of breathing, organ failure and other complications, even may cause death [86]. Though it was discovered in china, but it transmitted throughout the world in such a rate that it caused a pandemic situation, meaning that people are unwittingly catching and passing on the corona virus.

II. METHOD

As the virus is changing its genomic morphology frequently, the scientists could not invent any promising treatment yet. but the scientists are working day and night. Some treatment methods are in hope to get a good result and some are not. LitCovid, EMBase, PubMed and google scholar and some leading news portal were studied to know about the latest treatment methods for corona infected patient. Using the search strategy limited articles which were available upto 30 September related to treatment methods were included here.

III. RESULT AND DISCUSSION

1. Inhibiting viral activity

• Remdesivir

Remdesivir was originally tested as an antiviral against Ebola and Hepatitis C [1]. It is the first drug to get emergency use authorization for the treatment of CoVid-19 patient with severe disease. It has shown the most prominent evidence so far. It is a nucleoside analogue which blocks RNA dependent RNA polymerase (RdRps) by challenging against ATP to incorporate genuine nucleoside into nascent viral RNA. Eventually, premature termination of viral RNA transcription occurs. Thus, the replication of viral genome is delayed. It can be concluded that this chain termination method could be a general mechanism of anti-viral activity of this particular substrate to a broad spectrum of different viral infection.

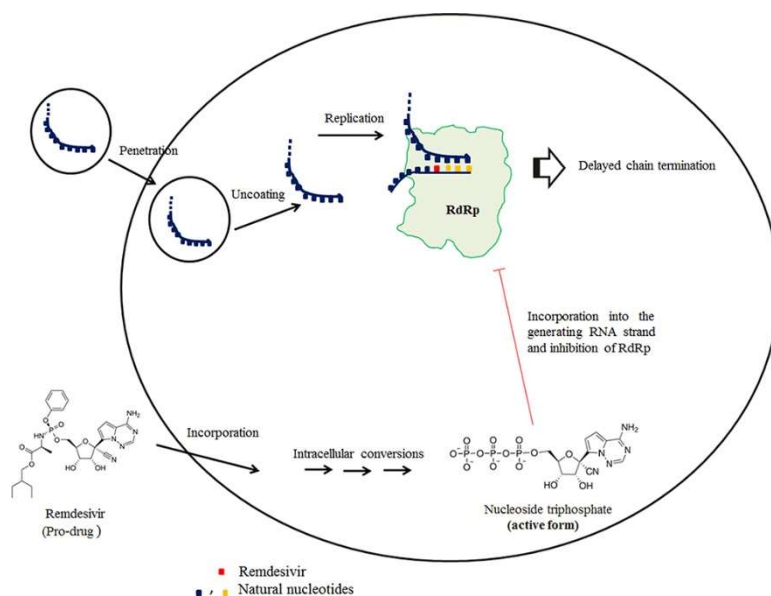


Figure: In the above, Nucleoside analogues of Remdesivir is blocking the RNA dependent RNA polymerase (RdRps) to incorporate genuine nucleoside into nascent RNA. This leads to delayed chain termination and delayed replication of genome [72].

In a mouse model of SARS-CoV-1, by prophylactic and therapeutic (at early stage) administration of remdesivir significantly reduced pulmonary viral load and improved respiratory function and other clinical signs of the disease. Likewise, both prophylactic and therapeutic remdesivir has shown improvement on the pulmonary function and reduced lung viral loads and severe lung pathology in MERS-COV strains in mice model. In the rhesus macaque model of MERS-CoV infection, remdesivir reduced virus replication, the severity of the disease, and lung damage when administered in animals infected with MERS-CoV [56][5].

Despite having an *in-vitro* antiviral activity against SARS-CoV-2, there are no published studies justifying the activity of remdesivir in animal models of SARS-CoV-2 *in vivo* until the time of this review. After successful trial result in animal model scientists approached towards human trial, it has given a sign of positivity on treatment of novel corona patient on rudimentary level.

Preliminary results from the ACTT1 trial in 1059 patients (538 assigned to remdesivir and 521 to placebo) with data available after randomization indicated that those who received remdesivir had a median recovery time of 11 days

(95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo [3].

Though it is showing prominent result in most cases but it has shown some major faults and flaws on human body as well. The most common adverse effects reported after intravenous infusion include elevated aminotransferase and bilirubin levels and other liver function tests. Diarrhea, rash, renal impairment and hypotension have also been reported [6].

Avigan (favipiravir)

Favipiravir is a modified pyrazine analog. Favipiravir-ribofuranosyl-5' triphosphate-(favipiravir-RTP) is the active form of favipiravir which is achieved by ribosylation and phosphorylation. The active form of favipiravir (favipiravir-RTP) inhibits the action of RNA Dependent RNA Polymerase (RdRp) [7]. This inhibition results in termination of the transcription and translation of the virus [7].

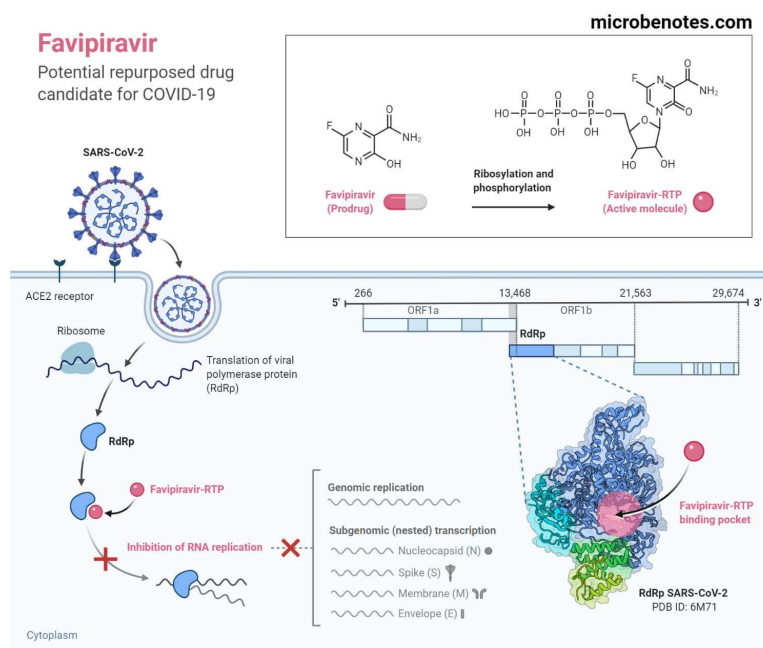


Figure: In the above, favipiravir-RMP, the inactive form becomes active by phosphorylation and converts to favipiravir-RTP which acts as a nucleoside analogue and inhibits RNA dependent RNA polymerase (RdRps). The inhibition causes hampers it's replication [73].

In Japan, it is approved for use against novel influenza virus and is hoped to be an effective drug for severe acute respiratory syndrome corona virus 2. As of recent, favipiravir was one of the experimental drugs on trial for Covid-19. The drug has shown an 80% efficacy so far and it is undergoing through the third phase of the trial against CoVid-19. In February, 2020, The initial study was done in Japan and China and found the evidence of reduced time of viral clearance. In particular, 80 patients demonstrated better chest improvement who were treated with favipiravir in a clinical trial performed in Shenzhen in China, [57]. China, Japan, Italy, and Russia have given it their verdict for emergency use on June 11, 2020.

Apart from having these positive impacts, it has shown some adverse side effects also. For instance, decreased production of RBC, and increased liver function, vomiting,

reduced body weight, increased vacuolization in hepatocytes [7].

It has teratogenic effect, that means it may cause congenital defects. So pregnant women should avoid it. Nevertheless, it may cause them embryonic deaths and teratogenicity [7].

Combining with other drugs like acyclovir, aminophenazone may reduce or increase the effect of favipiravir by some extent. Such as change in metabolism, excitation and serum concentration have been reported [7].

Recombinant Human angiotensin- converting-enzyme-2

To enter a cell, the corona virus first must unlock them- fiat accomplishes by getting onto a human protein called ACE 2. Scientists have created artificial ACE-2 proteins

which might be able to act as decoys, luring the corona virus away from vulnerable cells [1].

APNO1 is the recombinant form of the human angiotensin-converting enzyme-2 (rhACE-2) and has potential to block the infection of cells by the novel SARS-CoV-2. It works by two ways. First method is by acting as a copy of human ACE-2 enzyme. It remains soluble in the fluid

of the body. Virus binds to those ACE instead of the ACE on the cell surface. So the virus loses infectivity to the cell. The second method is by converting angiotensin2 (ang1-8) to angiotensin (ang1-7) which improves the immune function [59]. It can play role in anti-inflammatory, anti-fibrosis and anti-hypertension activity. It protects the lungs from over inflammatory responses and thus, from severe acute injury or from acute respiratory distress syndrome. (ARDS) [8][58].

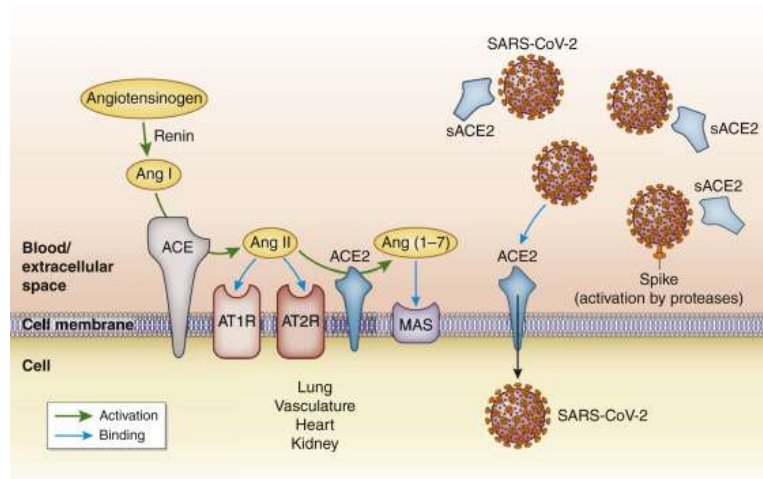


Figure: Recombinant Human ACE-2 works by 2 ways. The soluble ACE prevents the virus to get attached to the ACE receptor on the surface of cell. Again, it converts Ang 2 to Ang (1-7) which plays role in regulating inflammatory response [80].

Phase 1 and 2 trials have been completed until now following all the safety and security. All the patients were between 18 to 80 years. After completing the trials, the health measures were taken, almost all patients were sound and healthy. Moreover the angiotensin 2 level was decreased, added by an increase in number of ang1-7 and ang1-5 which have an eminent role in immune function [58][59]. Phase 3 trial is going on and the result is soon to be published. In case of phase 2 trial, a total of 89 patients were tested with APNO1. Among them, some were healthy volunteers and some were patients having pulmonary arterial hypertension (PAH) and ARDS as patients with PAH and ARDS are more vulnerable to CoVid-19. Recombinant ACE2 proteins have shown promising results in experiments not only on cell, but also people [9].

• Ivermectin

Ivermectin is an anti-helminthic drug. That means, it can eject parasites like helminths by stunning or killing but not damaging the host. It causes stimulation of gamma amino butyric acid (GABA)-gated-Cl⁻ channels, leading to hyperpolarization, and resulting in immobility of the infecting organism. Besides it also has some

immunomodulation effect on host that has been attained by the neutrophil activation, increase in the levels of C-reactive protein and interleukin-6 [10].

Till 1st October, 2020 many trials have been done in different countries, incase Australian experiment, ivermectin was experimented on petri dish. Ivermectin produced a 5,000-fold reduction in COVID-19 viruses in the petri dish, implies that it killed all the virus particles. In another study, which took place in Bangladesh, found that 100 patients took part in the study and all of them tested negative after 72 hours. Another retroactive review states that among 248 patients, 115 patients who received ivermectin, were hardly in need of oxygen or intensive care or to die from corona virus infection. Dominican Republic declared 99 percent cure ratio after treating with ivermectin and aythromycin together where 1,300 COVID patients were treated and evaluated. In Egypt, to protect family members of COVID patients, ivermectin was provided to 203 person which engender a great result in which 7 percent of treated people became infected with the virus compared to nearly 60 percent who were not treated [11]. Apart from showing prominent evidence in different trial this treatment method has shown

some adverse effects too. Among them, adverse effects like skin rash and redness, loss of appetite, swelling and bleeding from eye are significant.

- **Disulfiram**

Disulfiram is a safe and easily dosed drug. Initially, FDA approved the drug for the treatment of alcohol dependence. Later on, it has been identified as a potential therapeutic agent for SARS-CoV-2 infection. Disulfiram has two types of

activity on SARS-CoV-2. First one is antiviral activity. It blocks Mpro protease which has an important role in replication of the virus. Eventually, replication of the virus. It also ejects zinc which causes metabolic disbalance. And another one anti-inflammatory activity. It inhibits NF-kB and NLRP induced cytokine which results in reduction of severe inflammatory responses. It also prevents pyroptosis which causes fever by releasing different cytokine [13]

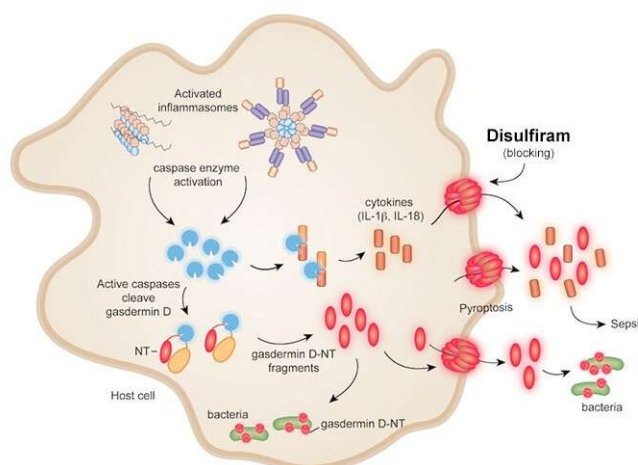


Figure: Pyroptosis is an inflammatory cell death in which cell membrane almost explodes and releases different inflammatory substance. disulfiram quiets pyroptosis [71].

As FDA has approved disulfiram, many CoVid dedicated hospitals are using it for treating CoVid infected patients . Except from drowsiness, headache and allergic reaction no other major adverse effect has been identified against this drug. Though it has positive sign, but the trials that are going on are yet to publish and confirm the effectivity [14].

- **EIDD-2801(β -D-N4-hydroxycytidine-5'-isopropyl ester)**

MK-4482, commonly known as EIDD-2801, is an antiviral prodrug which is a nucleoside derivative of N4-hydroxycytidine. Initially, it was developed for the treatment of influenza [15][60]. MK-4482 and remdesivir work in a similar way; both the drugs mimic or act as a copy ribonucleosides which is a primary component of RNA molecules. This duplication causes replication errors when the drugs are incorporated into viral RNA during replication, resulting in an incompetent RNA which is non-functional as genome. Consequently, the spreading of the virus gets stopped [16].

However, scientists suggest EIDD-2801 may have some advantages over remdesivir. Till now, the drugs on which the world kept hope the most and thinking to have the most prominent result to treat the CoVid-19 patients is remdesivir. But according to the latest sources and trials going on all over the world, another drug which is in highlight alongside remdesivir is EIDD-2801. In some cases, EIDD may offer better therapeutic advantages over remdesivir because it can be taken orally. In University of North Carolina, researchers have evaluated the drug in human lung cell infected with SARS CoV-2 and in mice infected with different species of novel corona SARS and MERS. They have reported that the drug showing prospectus evidence that it may stop CoVid-19 if given before or early after the infection [17]. It has also shown improvement in pulmonary function, decrease weight loss, reduce the viral loads in mice[16]. This drug has a lot of advantages but it will be a foolishness to think that it does not have disadvantages. Proficient Clinical trials is still going on and result is yet to be come. It is difficult for one to get idea about disadvantages of this drug before the result of the trials are published.

2. Mimicking the immune system

✓ Convalescent plasma

The use of convalescent plasma collected from previously infected individuals to passively transfer antibodies in order to protect or treat humans from early twentieth century. Plasma is the yellow fluid if the blood cells are removed from blood. Plasma comprises 55 percent of the blood. It contains water, salt, enzyme and proteins like albumin, globulin etc. Those who lacks these components can undergo plasma infusion [19]. To prevent viral infection plasma derived immunoglobulin can be used. It can be used both as post-exposure prophylaxis as well as treatment for

diverse infectious diseases. Specially outbreaks like polio, measles, mumps, influenza and pandemics like Spanish flu and now CoVid-19[19]. passive immunity can be provided to the CoVid-19 patient by convalescent plasma. The immunity is found in the form of neutralizing antibodies or possibly other immune mediators. Various antibody subclasses (immunoglobulin [Ig] G, IgM, and IgA) are there to provide different role in boosting immunity against the pathogens. These Antibodies binds to the viruses and inhibits viral entry into cells and increases antibody-dependent phagocytosis or antibody-dependent cellular toxicity to clear the viruses.

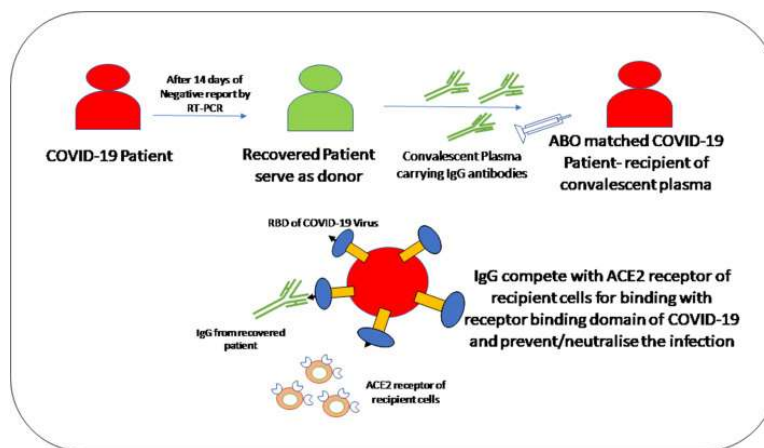


Figure: Immunoglobulin produced in recovered patient helps to recover another covid 19 patient [79].

FDA has given emergency approval to treat CoVid-19 patient with Convalescent plasma on August 23 [61]. The convalescent plasma is plausibly healthy and safe. In two reports published by Chinese physician on convalescent plasma therapy which were done on very severe cases of CoVid-19 patients on ventilators. There were 5 patients in 1 report and 10 in the other. All of them showed rapid improvement where fever came down and viral load diminished [19]. Immuno compromised patients get more benefit from convalescent plasma because it replenishes the scarcity of B and T cell in their body. Moreover, it is free from the adverse effects created by different chemical drugs. In another report, Four immuno compromised patients comprising two kidney transplant recipients, one lung transplant recipient, and one chronic myelogenous leukemia patient improved after administration of plasma from immunized post CoVid-19 patient [20]. In another experiment, sample tested by positive SARS-CoV-2 IgG with negative SARS-CoV-2 PCR suggests that using convalescent plasma therapy can be safe. These preliminary trials are showing a prospectus result but we need further evaluation of

the therapy by adequate trials and study. Some limitation like transfusion related complicity, allergic reaction, risk of aggravating hyper immune attacks are to be analyzed and elevated [21].

✓ Monoclonal antibody

Monoclonal antibodies are antibodies that are made by identical immune cells which are clones of a particular parent cell and have monovalent affinity: that is, they bind to the same epitope. Neutralizing antibodies can bind right to the portions of viruses that is used to attach and enter into cells. This halts them from promoting the infection cycle. Monoclonal antibodies can be administered to the non-infected person as a preventive measure. The antibodies if they are long lasting and potent enough may provide protection for week to several months. Moreover, it takes less time to produce monoclonal antibodies than vaccines or a new targeted small molecule antiviral [62]. So, monoclonal antibodies may provide short-term protection until reliable vaccine is installed [22].

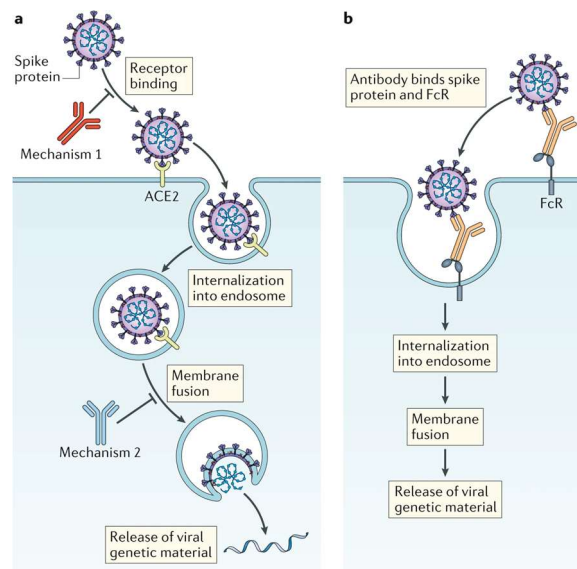


Figure: Monoclonal antibody prevents the infection of virus and induces phagocytosis [78].

Eli Lilly published a report which states that 5 of 302 patients had to be hospitalized among those who received the drug that is only 1.7% patient was found to have severe symptoms. On the other hand, 9 of the 150 placebo patients had to go for hospital, that comprises 6% of the patient. This implies that the risk of being hospitalized reduced upto 72% by receiving antibody than placebo. Besides no side effects was reported by the company [23][24].

It has a favorable edge that same quality of antibody can be maintained and it is highly reproducible. On the contrary, this method may have some barrier like its cost and effort, chance of contamination and small change in the antigen may drive it ineffective. Different trials are going on to test the efficacy of monoclonal antibodies in treating CoVid-19. For instance, The trial, called NCT04507256, will evaluate the safety, tolerability, and pharmacokinetics of AZD7442 which is a combination of two monoclonal antibodies derived from previously SARS-CoV-2 infected patients. This trial will include up to 48 healthy participants in the UK aged between 18 to 55 years [25]. Scientists are having a ray of hope that the monoclonal antibodies will be the “magic bullet” they are looking for.

✓ Interferon

Interferons are cytokines with strong antiviral properties, released from host cells in response to the abnormal nucleic acids which is a sign of viral infections. It acts through toll-like receptors (TLRs) and other pattern-recognition receptors of host cells that are responsive to viral RNA or DNA [26]. Some viruses including corona viruses are weak interferon inducers and hence they can evade natural defense of the body by hardly activating them. The importance of this interferon evasion strategy can be evaluated by cell culture and animal experiments in which interferons can strongly inhibit the replication of corona viruses. Beside this antiviral properties, interferons performs anti proliferative activities of different cells they regulates cell a variety of humoral and cellular immune functions. Interferon can be divided into three types Based on their protein structures and cell-surface receptors. They are, type I interferons (interferon alpha, interferon beta, interferon epsilon, interferon kappa, interferon omega), type II interferons (interferon gamma) and type III interferons (interferon lambda). Interferon beta has a stronger hydrophobicity alpha and gamma. So, it has a much higher tissue affinity compared to other interferon [27]. Applying this property, interferon beta can be used to reduce the viral multiplication.

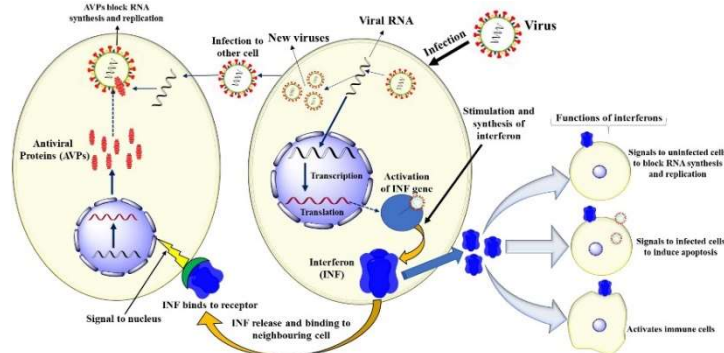


Figure: Interferon is secreted by the infected cell to protect adjacent cell. But SARS-Cov-2 can evade interferon by hardly inducing the interferon secretion. So, interferon is applied to treat covid 19 patient [81].

In a placebo control trial by United Kingdom, 50 person were given placebo, and 48 were given interferon beta. The patients receiving interferon were more like to recover without any severe symptoms. In Hongkong, 76 people were given triple drug therapy which included interferon beta, Ritonavir and Ribavirin and 51 people were given only Ritonavir and Ribavirin. The recovery time of the triple drug therapy were 7 days which were less than the double drug therapy which was 12 days. Interferon alpha maybe also used as antiviral drugs. In a study in china, 77 adults with moderate CoVid-19 were treated with nebulized interferon alfa-2b, nebulized interferon alfa-2b with umifenovir, or umifenovir only. The participants who were given interferon alpha 2 took less time for viral clearance in the upper respiratory tract and to reduce the systemic inflammation[28].

Interferon therapy has a major advantage over the nucleoside analogs is that it has no risk of getting resistance [29]. But, still it needs further experimentation and analysis. Some adverse effects of interferon alfa include flu-like

symptoms, nausea, fatigue, weight loss, hematological toxicities, elevated transaminases, and psychiatric problems are sometimes reported which can be a insurmountable obstacle [28].

3. Reducing inflammatory response

❖ Cytokine inhibitor (Tocilizumab, Sarilumab, Siltuximab)

The novel corona virus SARS-CoV-2 not only causes direct cytopathogenic effect but also invokes a hyper inflammatory state; that is, inappropriate immune responses that causes organ dysfunction like respiratory difficulties. The exaggerated immune response is driven by multiple cells and mediators like interleukin (IL)-1, IL-6, IL-12, and IL-18, tumor necrosis factor alpha (TNF α), etc. IL-6 is the key factor in stimulation the cytokine dysregulation that causes hyper inflammation in lungs [33][34]. So IL-6 inhibiting drugs could be an effective way to fight against CoVid-19. Tocilizumab, Sarilumab, Siltuximab are the prominent drugs that inhibits IL-6 hyper inflammatory function.

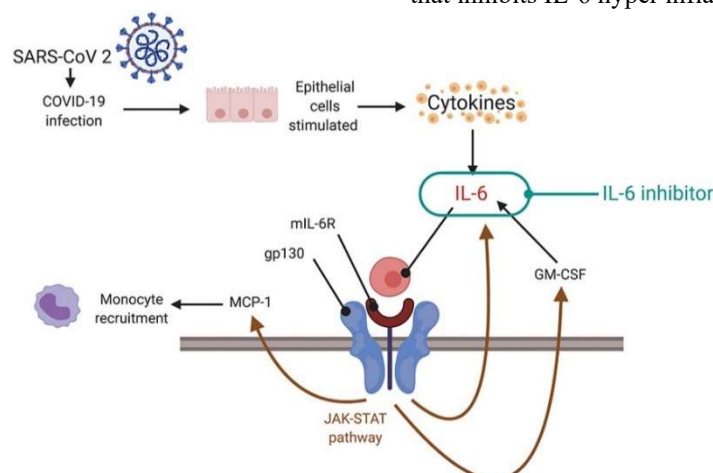


Figure: Interleukin-6 (IL-6) can promote different inflammatory response. Inhibiting IL-6 may subside hyperinflammatory response. Most of the cytokine inhibitor inhibits IL-6 from mediating signals [76].

Tocilizumab can bind to both soluble and membrane-bound IL-6 receptors [30]. This interaction will block IL-6 from performing the downstream signaling pathways or pro-inflammatory effects. As tocilizumab recognizes binding sites on both receptor forms a combative inhibition of IL-6 functions occurs. Different trials are going on to identify whether only inhibition of IL-6 is enough to reduce the hyper inflammatory response. In France, random 65 patients were given tocilizumab 8 mg/kg along with standard of care, and 64 were given standard of care only. The number of people hospitalized in need of ventilation and number of deaths were significantly reduced among those patients who were given tocilizumab and standard care [33].

Siltuximab binds to human interleukin-6 (IL-6) and prevents the binding of IL-6 to its receptors [31]. For Siltuximab a Phase II, randomized, open-label trial is going on to compare the efficacy and safety of Siltuximab in hospitalized patients with CoVid-19 symptoms in Spain [33].

Sarilumab is another drug which contains monoclonal antibody that binds to human interleukin-6 (IL-6) receptors. Consequently, it inhibits IL-6-mediated signaling [32]. FDA has given approval to Sarilumab from data collected from 3 clinical trials of phase 2 in which 1197 patients were tested by receiving Sarilumab with methotrexate, and the test shown rapid improvement. In March 2020, Sanofi and Regeneron began another Phase II or III trial of the intravenous formulation on hospitalized patients with severe CoVid-19. The result of the trial is not published yet [33].

The immune response and the resulting inflammatory reaction against a pathogen are usually regulated by a flock of cytokines, and therefore blocking of just one of the many is not predicted to make the process slower, because the absence of function of one cytokine may show redundancy and counterbalanced by other pro-inflammatory mediators. So there remains a theoretical complexity on these therapies [34].

❖ Blood Purification

FDA has approved for several extracorporeal blood purification filters like CytoSorb, oXiris, Seraph 100 Microbind, Spectra Optia Apheresis for emergency use to

treat severe CoVid-19 pneumonia in patients with respiratory failure. The devices reduce the cytokine levels to diminish hyper inflammatory response created by the SARS-CoV-2 which may cause damage of different organs or tissue [36].

There are different ways blood purification may help to fight against the CoVid-19. Some of them are removing metabolic waste products, removing various inflammatory mediators by convection or absorption or plasma replacement, regulating volume and correcting fluid overload, correcting electrolyte and acid-base balance, controlling high fever and replenish oxygen by extracorporeal multiple organ support [35].

In a clinical trial, five men and five women of age range from 26 to 83 years were enrolled and six of them have improved significantly on three sessions of extracorporeal hemo adsorption. Peripheral capillary oxygen saturation increased from an average 89.6 to 92.13 after the hemo adsorption which indicates considerable improvement [37]. It has some disadvantages like cell damage, expensive equipments.

❖ Stem cell

Stem cells are either completely undifferentiated or limited differentiated cells that can proliferate for infinite times to produce more cells of the same type and can differentiate into different types of cells when needed. Hematopoietic stem cells (HSCs) are usually found in bone marrow and Mesenchymal stem cells (MSCs) usually found in bone marrow and different other tissues. Both of the stem cells can play an important role in tissue repairing as they can divide infinitely remaining in undifferentiated state and differentiate into other types of cells if necessary. Since MSCs can perform activities like immuno modulation, anti-apoptosis, supporting the growth and differentiation of local stem and progenitor cells, anti-scarring, and chemo-attraction, it can boost up different biological processes and that why MSC is used for various therapy in lung diseases. Specially, immuno modulatory properties of MSCs can be utilized in the process of lung repair and regeneration in many pathological conditions of respiratory tract [38].

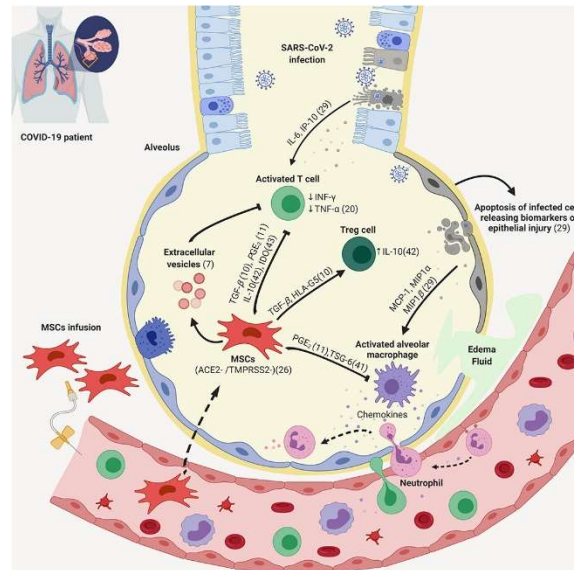


Figure: Stem cell can proliferate infinitely and can differentiate into different types of cell. So, it can boost up the immunity by producing more WBC and platelets to fight the virus and repair the damage [75].

In China, a study with 18 CoVid-19 patients were carried out. In which 9 patients were given three cycles of MSC treatment and other 9 were given standard care. In both the group 5 patient were moderately ill and other 4 were severely ill. Only 1 patient needed ventilation for 1 day and 1 patient had shortness of breath among the group in which MSC treatment is provided. On the contrary, 4 patient required ventilation and 5 patient had dyspnea [64].

in Beijing's YouAn Hospital, another study with seven CoVid-19 patients of different 1 critically severe, 4 severe and 2 common type were conducted. Everyone was given a single dose of MSCs and standard care for 14 days. After 14 days, No adverse effects were reported and pulmonary function and symptoms improved significantly in all the patients only 2 days after MSC injection. increase in number of peripheral lymphocytes, decrease in levels in C-reactive protein (CRP), and reduction in numbers of over activated cytokine secreting immune cells were reckoned in the experiment [39]. Though these small trial showed prospectus result it needs to be evaluated more to know any possible adverse effect of the therapy. Besides, the production of relevant number of stem cells need a considerable amount of time which is not always possible to produce and supply it in

an emergency situation like the current CoVid-19 emergency [38].

❖ **Dexamethasone and other corticosteroids**

Dexamethasone is a type of corticosteroid medication. Corticosteroids have two sub-classes: glucocorticoids and mineralocorticoids. Dexamethasone falls into glucocorticoids sub type which have anti-inflammatory activity. It binds to the DNA and modifies transcription protein that inhibits leukocyte infiltration to the site of inflammation and interferes with the effect of inflammatory mediator [41].

In CoVid-19 patients, dexamethasone serves to dampen the body's immune response when it becomes too aggressive to control by other means. A trial was done giving Dexamethasone to 2104 patient and giving usual care to 4321 patients. The mortality rate of the group that was given Dexamethasone (22.9%) was less than the other group having only usual care.(25.7%) [65]. In another recovery trial dexamethasone was announced to reduce the numbers of CoVid-19 related deaths by 35% in patients on the intensive care unit (ICU). Hospitalization time was also reduced from Dexamethasone treatment [40].

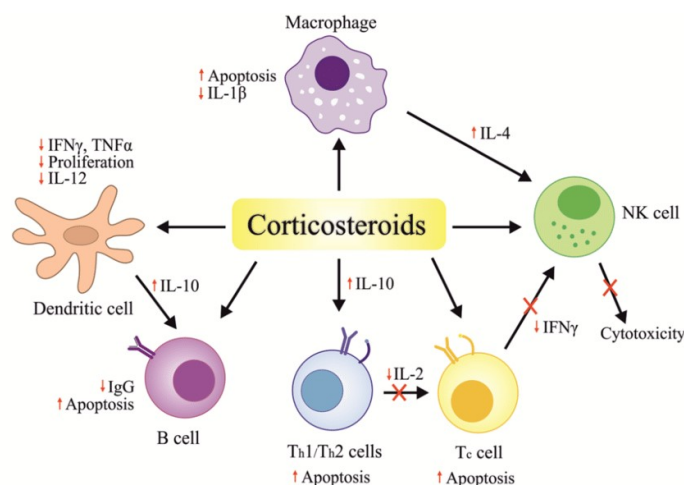


Figure: Anti-inflammatory activity of corticosteroids [77].

Few Side effects from dexamethasone treatments are reported and some of them includes Stomach pain and cramping, headaches, dizziness, change in the menstrual cycle, insomnia, increased appetite, weight gain, acne, drying and thinning of the skin, vision change [42].

4. Other treatment

▪ Prone positioning

When a person is in supine position, the dorsal pleural region gets a increase in pressure as it has to lift up ventral lungs, heart, and abdominal viscera and gravitational force. When inflammation occurs in the lung due to pathogen like

CoVid-19 the mass of the lung increases more as due to phagocytic infiltration to the lung producing more pressure on the dorsal pleural region. This pressure causes compression and decreasing oxygen holding capacity. This phenomenon leads to shortage of oxygen in blood and results in organ failure and inefficient energy supplement to fight against the pathogen. Placing a person in the prone position reduces the pleural pressure gradient due to gravitational effects, conformational changes of the lung which matches to the chest cavity, and loss of weight from the heart. As a result, more homogenous lung aeration is ensured [43].

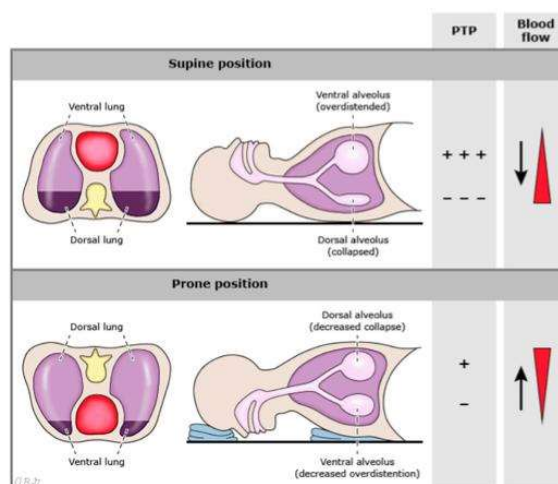


Figure: prone positioning reduces pressure dorsal side and increases blood flow in the lungs [74].

In Singapore, a trial with 100 patients show prospectus result in which 12 patients needed intubation when prone positioning therapy was done early of the disease [66]. In another trial, among 46 patients, 23 received prone positioning treatment and other 23 received usual care. Those who received prone positioning were shown to have lower platelets, higher C reactive proteins and lactate dehydrogenase. These trials give evidence that prone positioning may have positive impact on CoVid-19 patients [44]. However, there may be complications like endotracheal tube obstruction, pressure injuries, bronchial plexus injuries [45].

■ Anti-coagulants

The exact mechanism of hypercoagulation created by the CoVid-19 is still under research. but most scientists believe that SARS-Cov-2 causes severe inflammatory response and cytokine storm by damaging the endothelial cell during entry

which plays an important role in homeostasis regulation. Along with the cytokine storm, platelets adhesion molecule, Von Willebrand factor, Toll-like receptor activation and tissue factor activation occurs which induces thrombin formation. Excess thrombus formation leads to hypercoagulate state which is identified by thrombosis in different area inside blood vessel. The thrombosis is triggered more by chain reaction of thrombin after onset of thrombosis and an increase in D- dimer and fibrin degradation product is found in the blood. This uncontrolled state makes it more risky for cardiac injury, myocarditis and arrhythmic complications. Sometimes, the clot travels in the circulation and enters into lungs which blocks blood circulation in lungs which often can be fatal. Thus, immune cell, platelets and endothelial cell all the three plays its role in the hyper coagulate state formation. Bed rest of the patients may be also a factor of the coagulation [68][47].

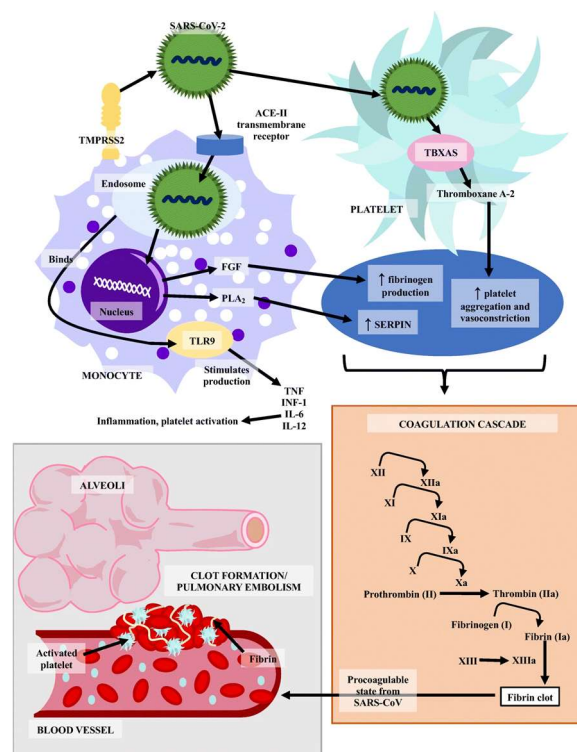


Figure: while entering into the cell by ACE receptor, SARS-CoV-2 damages the cell and induces different inflammation mediator. Some of the mediators enhances thrombin and fibrin production which causes excess coagulation inside the vein. Sometimes the clot breaks free into the blood and enters to alveoli blocking blood flow in lungs [82].

In a recent study with 4389 patients, 900 were provided with a full-treatment dose of anticoagulants. 1,959 patients were provided with a lower, prophylactic dose of anticoagulants and 1,530 were not provided with any blood thinners. the mortality rate

were reduced by 50 percent to the both of the anticoagulants receiving group compared to the non-receiver group of anticoagulants. So, the result depicts a strong relation between blood thinners and mortality of the CoVid-19 patients. Anticoagulants also reduced the number of

intubated patients by 31 percent [46]. However, there are some complications like passing of blood through urine, presence of blood in vomit or cough, prolonged nosebleed, heavy periods in women are reported through the administration of anticoagulant. So the treatment needs adroit hand, proper care and appropriate dose [48].

▪ Vitamins and mineral supplements

Till date, no particular treatment method for CoVid-19 has been approved. That is why boosting immune system can be effective measure against CoVid-19. Taking minerals and

other supplements can help to boost up the immune system. Vitamin C, vitamin D, melatonin, selenium, cysteine and zinc can be used to help our immunity to fight against corona virus.

Vitamin C or ascorbic acid is a water-soluble vitamin that is present in substantial amounts in a variety of fruits and vegetables. It stimulates formation of interferon, supports lymphocyte proliferation, boosts neutrophil phagocytic activity, enhances innate immunity.

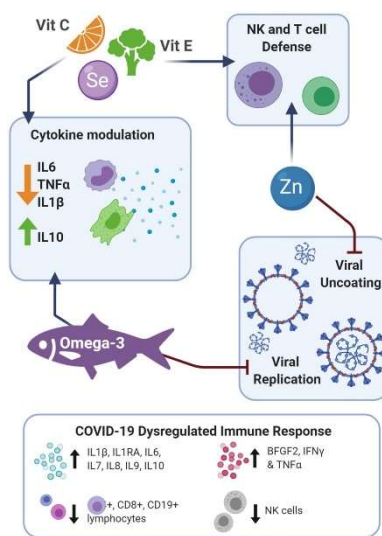


Figure: Vitamins and minerals boosts up immunity by regulating cytokine and other inflammation mediators [83].

Vitamin D, a group of lipid-soluble micronutrients, is obtained either by conversion of 7 dehydro-cholesterol in our skin through exposure to UV radiation or from some food sources. Its primary immunomodulatory function is to down regulating pro inflammatory cytokine, suppressing TH1 response and accelerating the activity of T regulatory cell.

Melatonin, is a hormone which is derived from tryptophan has both antioxidant and anti- inflammatory activities. Selenium is a trace element which shows an efficient anti-inflammatory, anti-oxidant and anti- clotting activity. N-acetyl cysteine plays role in increasing number of immune cell and zinc an important co-factor of different enzymes required for immune function, plays its role in regulation and formation of inflammatory response, lymphocyte and lymphocyte development [49].

Do not do this

a. Drinking or injecting bleach

Bleach is an effective disinfectant, it can kill different kinds of microbes such as virus, bacteria, fungus, protozoa and algae. Corona virus can be killed with it, so cleaning with bleach is one of the way to stop the dissemination of virus. But it should not be used for drinking as a remedy for CoVid-19, because bleach is poisonous. It is such corrosive that it may damage metal and may burn sensitive tissues of the body. Sometimes consequences maybe fatal. It has been warned by FDA not to drink Master Mineral Solution which is a industrial bleach [50][51].

b. UV radiation

UV radiation is a well known disinfectant for air, water and regular surfaces. It can kill viruses if proper dose and exposure is ensured. But it can cause irritation of skin, damage of the eyes and even can cause cancer [51][52][53]

c. Colloidal Silver

Colloidal silver is a small silver particle which is often mislead as dietary additive for fighting against CoVid-19. But there is no such evidence, rather it may harm the body by causing argyria (discoloration of the skin), diminishing absorption capacity of some drugs. FDA warned about its ineffectiveness and taken action against those companies which made misleading affirmation about colloidal silver products [55][56]

IV. CONCLUSION

As SARS-CoV-2 is changing its genetic material too fast, scientists are still unable to invent any effective and approved treatment method. Till date, About 1 Million people died because of corona virus. So, we are badly in need of an emergency treatment method which can cure and reduce the number of death from CoVid-19.

Remdesivir, favipiravir, Mk-4482, Recombinant human ACE-2, ivermectin, Disulfiram, convalescent plasma, monoclonal antibody, interferon, Dexamethanose and other corticosteroid, cytokine inhibitor, stem cell, blood filtration, prone positioning, anticoagulants, vitamins and minerals are the treatment methods that the doctors are using mostly to treat the corona infected patients. But till now no such fully approved treatment method has been found for fighting against CoVid-19. To evaluate the efficacy of the above mentioned drugs, different trials are going on which are in different phases (mostly in 2 or 3). Some of these drugs are approved for emergency use by FDA. The purpose of writing the article is to summarize all the important drugs, its mode of action, recent trials and its result (in case of completed trial). The world is keeping hope in these drugs to fight the corona virus and erase this pandemic situation very soon.

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