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STRATEGIC THERAPY IN THE MANAGEMENT OF SARS-CoV-2 (COVID-19)

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ABSTRACT

The novel COVID-19 is the disease caused by corona virus that led to the global pandemic. The virus is primarily characterised by a Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which is a lung disease and the impact is on heart as well. The entry of influenza and corona virus are through two proteins they are ACE2 (Angiotensin converting enzyme 2) and TMPRSS2 (Trans-membrane protease serine 2) prominently. The primary objective is to restrict the entry of these viruses into the cells (or) to inhibit the viral replication after entering into the cells. ACE2 protein can be blocked by ACE inhibitors. This blockade can be beneficent in case of hypertensive patients as ACE inhibitors aid in lowering blood pressure and also to restrict viral entry. SARS-CoV-2 and other corona viruses use TMPRSS2 for 'S' protein activation and the protease is expressed in SARS-CoV-2 target cells throughout the human respiratory tract. Nafamostat mesylate is a serine protease inhibitor with antiviral activity may inhibit the activity of TMPRSS2 a host cells serine protease that mediate viral entry for corona virus, thereby inhibiting viral entry and replication. The global pandemic is associated with several symptoms such as fever, cold, dry cough, sore throat, wheezing and blood clot. Aspirin has triple effects of anti-viral activity, anti-coagulant, anti-inflammatory. The early use of aspirin in COVID-19 patients is expected to shorten the duration of hospitalization and reduces the incidence of cardiovascular complications. This review gives knowledge of using Nafamostat mesylate and Aspirin drugs against SARS-CoV-2.

INTRODUCTION

The Novel Coronavirus-induced pneumonia, which was named as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO).The International Committee on Taxonomy of Viruses named the coronavirus as the 'Severe Acute Respiratory Syndrome coronavirus 2'(SARS-CoV-2).The coronavirus have caused three epidemic diseases they are COVID-19, 'Severe Acute Respiratory Syndrome coronavirus' (SARS-CoV) and 'Middle East Respiratory Syndrome Coronavirus' (MERS-CoV) are well known respiratory syndromes characterised by severe respiratory consequences which results in shortness of breath. The COVID-19 was first Reported in late 2019 in Wuhan, China and has spread extensively in China, India and worldwide [1].COVID-19 is communicable disease from one person to other person through airborne droplets that are sneezed or coughed out by COVID-19 infected patient. This virus is usually transmitted by an individual with symptoms of the infection, but it is known to transmit from people before they exhibit symptoms and even from by people who are infected but never develop symptoms. Antiviral are the class of drugs that generally inhibit the process of viral replication. There also exist other classes of drugs which possess antiviral activity. Presently, clinical trials are

carried out on many pre-existing drugs, antibody therapy and other vaccines to ensure therapeutic activity against COVID-19[2]. The primary objective is to restrict the entry of these viruses into the cells through TMPRSS2 and ACE2 receptors by blocking these receptors using suitable class of drug. In COVID-19, the impact is mainly on lungs and heart so the secondary objective is by prior administration of drugs which protect these organs before the virus attacks them which may lead to various complications if untreated. In current review, we summarize the effects on cardiovascular system and respiratory tract due to COVID-19 infection. The study also reveals various strategies for COVID-19 therapy, development of vaccine and recommendation for COVID-19.

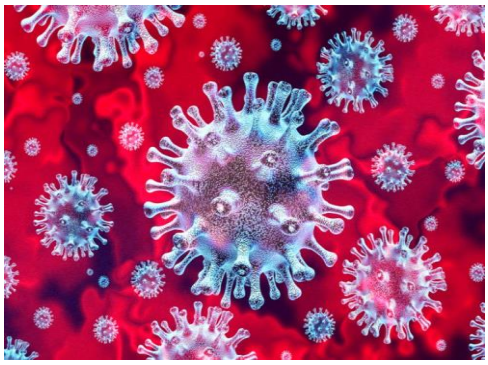

Figure No. 1: Structure of SARS-CoV-2

Pathophysiology of SARS-CoV-2:

Coronavirus mainlytarget the human respiratory system and also affects cardiovascular system. Patients infected with COVID-19 showed higher leucocyte values, abnormal respiratory system and increased levels of plasma pro-inflammatory cytokines [3]. The virus SARS-CoV-2 contains four structural proteins namely spike(S), envelope (E), membrane(M) and nucleocapsid(N) protein of which S protein mediates the viral entry into host cells[4]. The RNA of Coronavirus such as SARS-CoV-2 is surrounded by a lipid bilayer and mainly envelope proteins. SARS-CoV-2 enters human cell after the spike(S) protein present on the envelope binds to cell membrane ACE2(Angiotensin converting enzyme 2) receptor. After gaining entry through ACE2 receptors, SARS-CoV-2 down regulates the expression of the receptor such that enzyme is unable to exert organ protective effects [5].

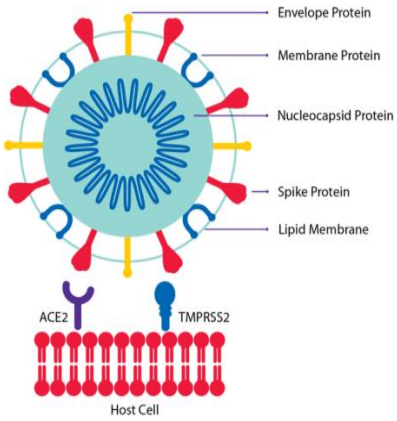

Figure No. 2: Anatomy of SARS-CoV-2

ACE inhibitors(ACEI) and Angiotensin receptor blockers(ARB) upregulate the number of ACE2 receptors on the surface of myocardial, gastrointestinal and alveolar cells which result in raised concern of ACEI and ARB induced increase in COVID-19 acquisition into alveolar and myocardial cells[6].The S protein is divided into S1 and S2 by human cell derived protease (proteolytic enzyme). S1 has the affinity to bind to receptor ACE2 and S2 binds to TMPRSS2, a human cell surface serine protease which results in membrane fusion [7]. SARS-CoV-2 infection depends on the host cell factors ACE2 and TMPRSS2 which are blocked by clinically proven protease inhibitors [8].

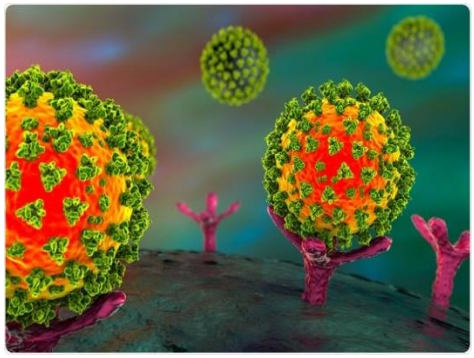

Figure No. 3: Binding of SARS-CoV-2 to receptors

According to new research, the serine protease inhibitor namely Nafamostat can prevent the fusion of the envelope protein of the virus with membranes of host cell surface, considered as the first step in infection with the causative virus SARS-CoV-2[9].

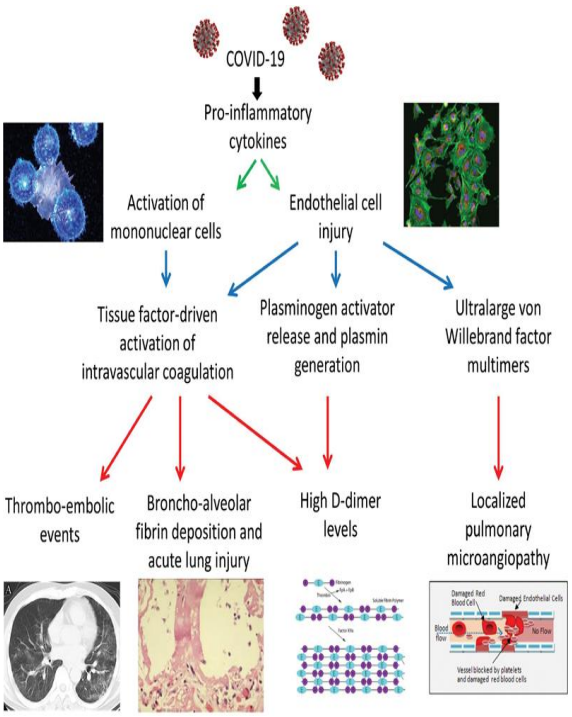

Figure No. 4: Pathophysiology of SARS-CoV-2

COVID-19 and Cardiovascular Disease:

The virus is primarily characterised by SARS-CoV-2 which is a lung disease and the impact is on heart as well. COVID-19 may have severe effects on the cardiovascular system. Patients with persisting cardiovascular disease may be more susceptible to COVID-19 infection, and also subjected to increased mortality rate, especially when patients observed with elevated troponin T levels, where mortality is expected three folds higher when compared to normal patients [10]. Although respiratory tract is the primary target for SARS-CoV-2, there also occurs few cardiovascular complications are as follows:

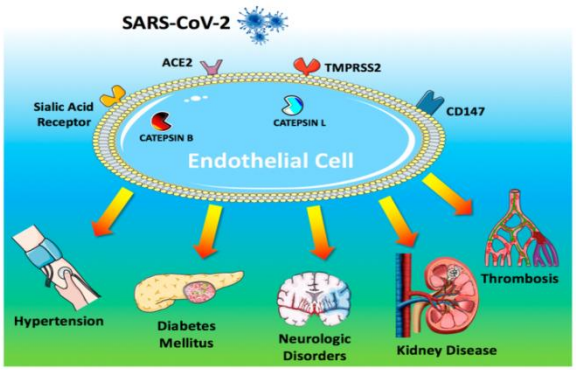

Figure No. 5: Endothelial cell damage causes severe disorders

Systemic inflammation -

The Coronavirus are characterized by cytokine storm and acute inflammatory response, which can cause damage to multiple organs resulting in multiorgan failure. The studies have shown high levels of pro-inflammatory cytokines in patients with severe COVID-19[11].

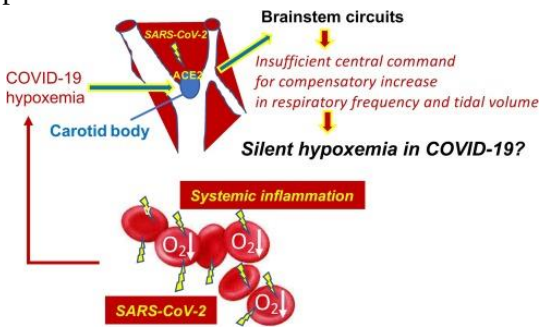

Figure No. 6: Systemic inflammation caused by SARS-CoV-2

Acute Myocardial injury –

The involvement of cardiomyocytes the cells which make the cardiac muscle and the effect of systemic inflammation appear to be most common mechanisms responsible for direct myocardial injury. In patients with pre-existing cardiovascular disease develop an acute myocardial injury which is associated with significant worsen symptoms [12]. It is repeatedly an increase in troponin-I level and also can occur due to myocardial ischemia, including myocarditis with severe respiratory infection and hypoxia in the setting of severe infection and acute respiratory distress syndrome (ARDS) due to COVID-19, a number of patients will likely to develop such injury. In the recent studies, the troponin levels are found to be high in patient with severe COVID-19[13].

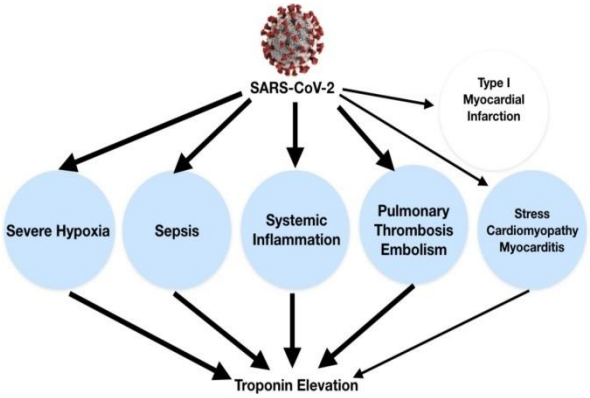

Figure No. 7: increased levels of Troponin in myocardial infarction

Cardiac arrhythmia and Cardiac arrest -

Cardiac arrhythmia is the common cardiovascular event observed in COVID-19 infection. The Cardiac arrhythmia is characterised by disturbance in heart rate, rhythm, generation or conduction of impulse. High prevalence of arrhythmia found in part attributed to hypoxia, inflammatory or neuro-hormonal stress in setting of viral infection in patients with COVID-19. Arrhythmia found in COVID-19 patients is usually atrial fibrillation which is characterized by rapid, continuous and irregular beat. In some cases ventricular fibrillation type of arrhythmia is observed. Patients with COVID-19 also found with rapid life threatening heart rhythm starting in the bottom chambers of heart, it can be triggered by a heart attack [14].Cardiac arrest is the sudden loss of blood flow to heart which results in loss of heart function. In COVID-19 most initial reports were based on the respiratory effects caused by the virus, recently serious cardiovascular complications are found repeatedly in hospitalized patients. In case of patients with COVID-19 with pre-existing cardiovascular complications may develop a cardiac arrest or congestive heart failure [15]. This increased worsening of cardiovascular events is likely to be due to a combination of several viral attacks and its increased demands on the heart, only heightened by oxygen levels due to pneumonia and increased blood clot formation.

Cardiogenic shock and electrolyte imbalance

The clinical representation of COVID-19 had led to ARDS which manifests as ground glass opacities on chest imaging and hypoxemia. Similar features are also seen in case of de-novo or coexisting cardiogenic pulmonary edema. As such, it is important to consider cardiogenic or mixed shock primary pulmonary causes of respiratory manifestations in COVID-19[16].The electrolyte imbalance in any severe systemic illness and precipitate arrhythmias especially in patients with an cardiovascular disorder. There exist particular concern about hypokalaemia is when blood potassium is low in COVID-19, due to interaction of SARS-CoV-2 with RAAS (Renin-angiotensin-aldosterone-system). The hypokalaemia condition results in tachyarrhythmia.

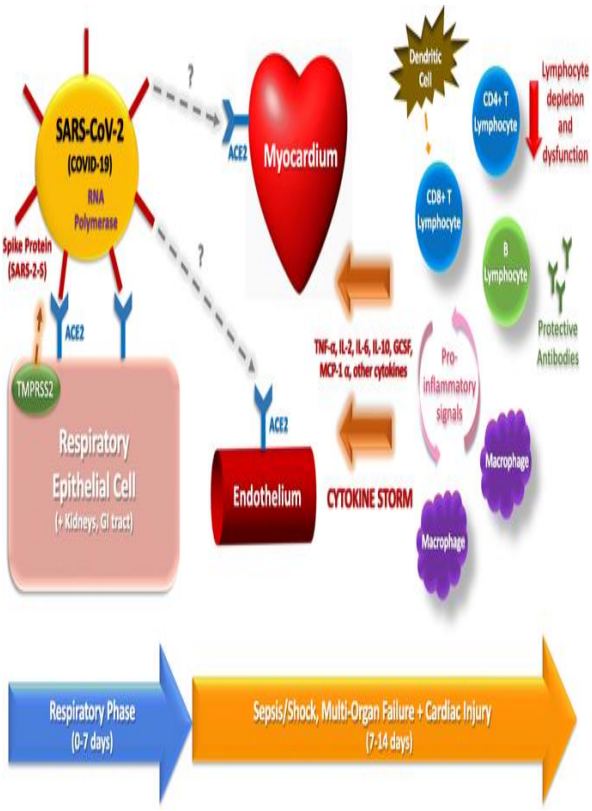

Figure No. 8: Cardiogenic shock caused by SARS-CoV-2

Atherosclerosis and coronary thrombosis -

Atherosclerosis is the accumulation of fat, cholesterol and other substances on the artery walls which can restrict the blood flow. It is characterised by plaque formation. Systemic inflammation as well as raised shear stress due to increased coronary blood flow can precipitate plaque rupture resulting in cardiovascular complications. In the recent studies, it is found that Prothrombin level relates to progression of atherosclerosis, with increased coagulability producing advanced atherosclerosis. Thrombin is a fundamental part of clotting factor [17]. The dense fibrin rich micro thrombin of the pulmonary capillaries reported in COVID-19 acute lung injury indicate high activity of thrombin, which is the primary enhancer of coagulation and fibrin formation. The increased levels of thrombin activity is reflected by the high levels of thrombin-anti-thrombin(TAT) complexes seen in most severe COVID-19 patients[18].

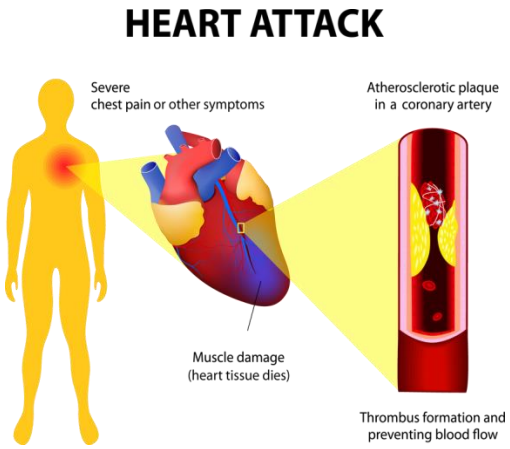

Figure No. 9: SARS-CoV-2 triggers thrombin inflammation

Hyperferritinemia -

It is characterised by elevated levels of ferritin which indicates the presence of virus or bacteria in the body. In recent studies, increased ferritin levels may indicate severe COVID-19. Ferritin is considered as major intracellular iron storage protein in all organisms. It binds free ions of the trace elements, neutralising its toxic properties and thus increase its solubility. The body is capable to expend iron as needed, for regulation of cellular oxygen metabolism mainly in the soluble form. Low ferritin levels result in low iron concentrations and iron deficiency anaemia. At low concentration they are found to be safe and help to protect it against viruses and bacteria [19].

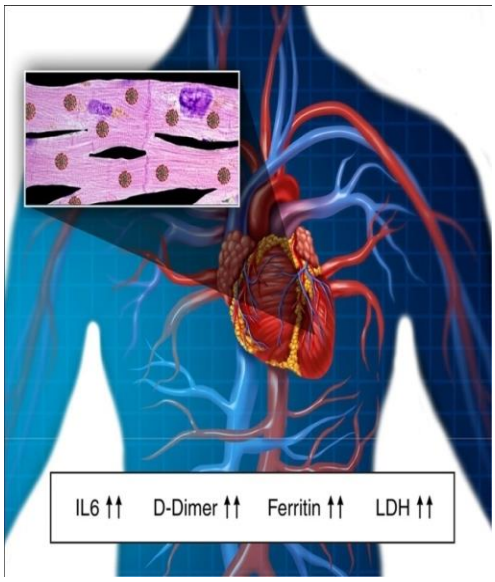

Figure No. 10: indication of SARS-CoV-2 with elevated Ferritin levels

Severe Acute Respiratory Syndrome Coronavirus-2 and Respiratory system:

Earlier Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) are well known respiratory syndromes characterised by severe respiratory consequences which results in shortness of breath. In recent days, another highly pathogenic coronavirus named SARS-CoV-2 also known as COVID-19 emerged in Wuhan, China in 2019. SARS-CoV-2 is a homological sequence of SARS-CoV, and results acute and high lethal pneumonia coronavirus disease 2019(COVID-19) the clinical symptoms are similar toMERS-CoV and SARS-CoV. The most familiar and characteristic symptoms of COVID-19 patient is respiratory distress, and most patients admitted to hospital could not breath spontaneously. In majority of cases that are 80% will exhibit symptoms when affected with corona infection, 14% will be pneumonia, 5% suffer from septic shock and organ failure mostly respiratory failure and 2% cases it will be fatal. The main symptoms of ARDS cause dry cough, high breathing rate, shortness of breath and increased heart rate. COVID-19 has direct impact on the lungs and damage alveoli (tiny air sacs)[20]. The function of alveoli is to transfer oxygen to blood vessels.

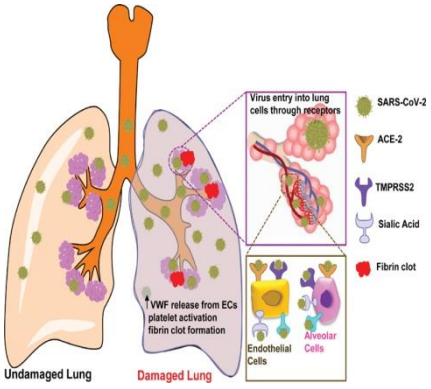

Figure No. 11: COVID-19 impact on respiratory system

These blood vessels or capillaries carry the oxygen to red blood cells (RBCs). Finally the RBCs deliver the oxygen to all the internal organs in the body. The virus works by damaging the wall and the lining of alveolus and capillaries. The debris from the damage, which is plasma protein accumulated on the alveolus wall and thickens the lining. As the

walls thicken, the transfer of oxygen to RBCs is impaired. The thicker the wall makes it difficult to transfer oxygen to RBCs, which results in difficulty in breathing as the body lacks oxygen. This deficiency of oxygen in the internal organs results in complications in the body and impairs the function of organs. As a result, the body fights to increase oxygen intake and the body first response is to destroy the virus and prevent its replication in the cell. If the individual immunity is weaker than the body is unable to inhibit the virus replication [21].

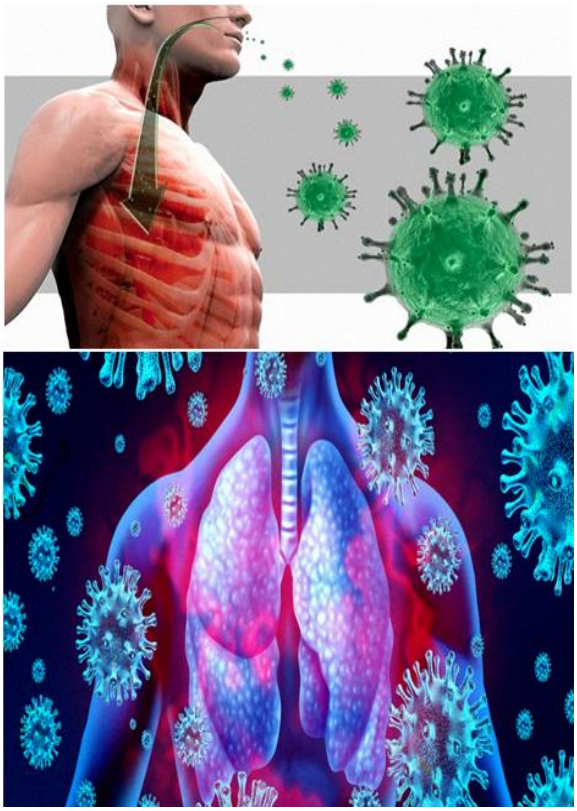

Figure No. 12: Corona virus damages alveoli and blood vessels

Treatment for COVID-19:

According to the research on molecular mechanics of coronavirus infection and the genomic organisation of SARS-CoV-2 there are several potential therapeutic agents to repurpose the existing antiviral agents or develop effective intravenous against this novel corona virus. Unlike SARS-CoV and MERS CoV, there is currently no clinically proven specific antiviral agent available for SARS-CoV-2 infection. An in vitro research has investigated seven potential anti-SARS-CoV-2 vaccines including Nafamostat, favipiravir, remdesivir, penciclovir, nitazoxanide, ribavarin and chloroquine have favourable selectivity index[22].

Serine protease inhibitors:

Nafamostat mesylate is a broad spectrum, synthetic serine protease inhibitor. The drug may effectively block the SARS-CoV-2 entry process into the cells and it is basically used to treat acute pancreatitis. The fusion of envelope of the virus with the host cell surface membrane, this action can be inhibited by serine protease inhibitor drug and considered as the first step in infection with the causative virus (SARS-CoV-2). Nafamostat may increase the mucus clearance in the airways by decreasing epithelial sodium channel activity and also be useful during virus induced wheezing in case of COVID-19. Nafamostat mesylate is a serine protease inhibitor with antiviral activity may inhibit the activity of TMPRSS2,a host cells serine protease that mediate viral entry for corona virus and influenza virus, thereby inhibiting viral entry and replication[9,23].

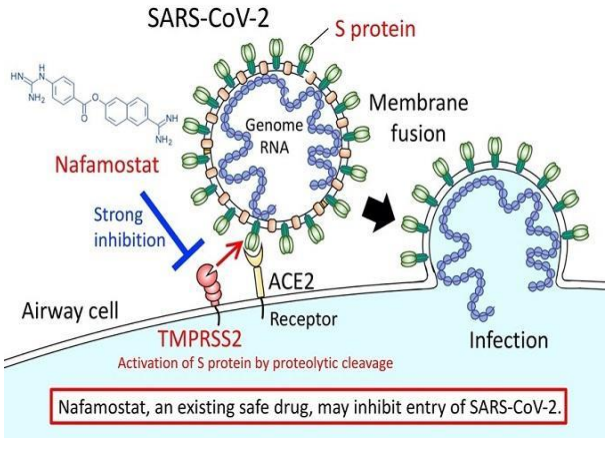

Figure No. 13: Nafamostat inhibit entry of Coronavirus

Renin-Angiotensin system blockade:

As the studies report that ACE2 mediates SARS-CoV-2 entry into the cell as a functional receptor along with TMPRSS2 of coronavirus. To block the binding the S protein with these receptors is also beneficial strategy against SARS-CoV-2 infection.ACE2 protein plays a favourable role in protecting tissues which can be blocked by ACE inhibitors. This blockade can be beneficent in case of hypertensive patients as ACE inhibitors aid in lowering blood pressure and also to restrict viral entry. It was suggested that any agent which increases expression of ACE2 could be potentially increase the susceptibility to severe COVID-19 by improving viral cellular entry. ACE2 also converts angiotensin 2 to angiotensin 1-7, which result in vasodilatation and may protect against lung injury by lowering angiotensin receptor binding [24, 30].

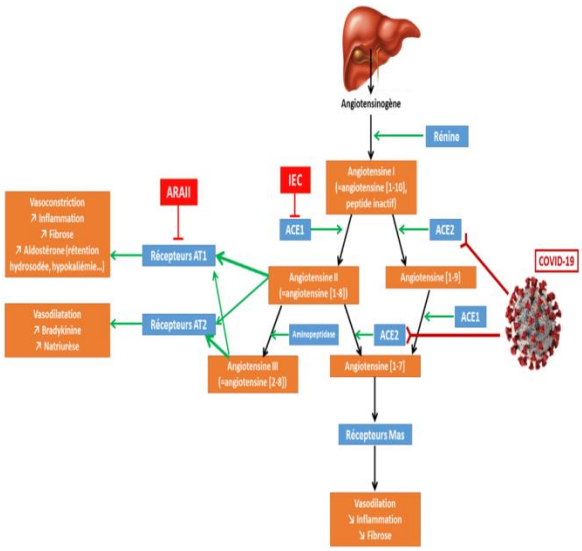

Figure No. 14: blockade of ACE2 by ACEI and ARB to inhibit entry of virus

Aspirin therapy in COVID-19:

Aspirin is a non-steroidal anti-inflammatory drug (NSAIDs) used to treat rheumatic fever.Aspirin are well known as Acetylsalicylic acid (ASA). Aspirin is a medication used to treat pain, fever, inflammation.Aspirin has been used for more than 115 years in medicine for various complications caused in the body. Aspirin possess wide therapeutic activity and also show antiviral effects in vitro by blocking the virus propagation via NF-kB inhibition when used at high concentrations and short term incubation steps. Aspirin also restrict viral replication by inhibiting prostaglandin E2 (PGE2) in macrophages and increase the response of type I interferon production [25]. Aspirin causes an inhibitory effect on platelet aggregation to block the formation of Thromboxane A2 in platelets. It has a positive influence on the prevention of blood clots and can be used in COVID-19 patients as coronary thrombosis is observed in few cases. Aspirin has several effects of inhibiting viral replication, anticoagulant, anti-platelet aggregation, anti-lung injury and anti-inflammatory activity. The early use of aspirin in COVID-19 patients, as it may reduce the incidence of COVID-19 induced coagulability and also its use may reduce the symptoms of COVID-19 patients such as fever, headache and high temperature. It is also used to treat or prevent cardiovascular disorders in COVID-19 patients such as heart attack, stroke, angina (chest pain) and blood related issues in people at high risk. Aspirin also reduce the hazards of certain types of cancer mainly colorectal cancer [26].

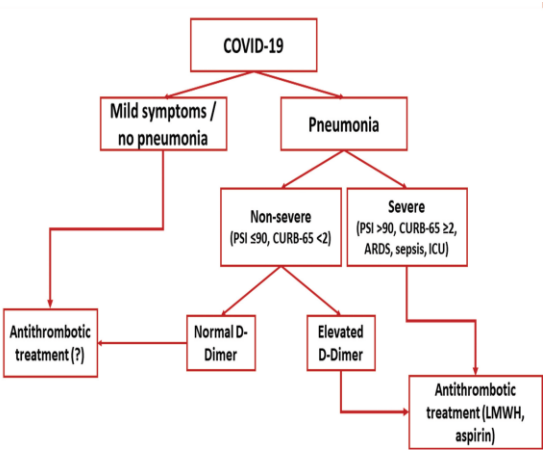

Figure No. 15: Aspirin used as antithrombotic drug in SARS-CoV-2 pneumonia

Convalescent plasma therapy:

Plasma therapy or Convalescent plasma therapy (CPT) can be possible treatment for patients with COVID-19. CPT is one such clinical trial where many scientist and researchers are exploring various ways in recent times. CPT is the plasma from recovered

patients, has been used for more than 100 years to treat variety of illness including SARS. Pathogens attack our body and the immune system release antibodies to fight against the infection. If the infected person has good immunity then the patient will be recovered by the antibodies itself.In case of low immunity patients, the immunity can be transferred from a healthy person to sick person with the help of blood plasma. Here Convalescent plasma is the liquid component of the blood from the recovered patients of COVID-19[27].

In CPT the blood of recovered person as it is rich in antibodies is used to treat other sick patients. The strategy behind this therapy is that the antibodies produced by the patients who had survived the virus will boost the immune system of those patients who are infected with COVID-19. In this plasma therapy, the serum is separated and screened for virus neutralising antibodies. The antibodies are then administered to a COVID-19 patient with severe symptoms. When the body comes in contact with external pathogens like virus or germs, it automatically starts a defence mechanism by releasing antibodies. In recent study, a trial was conducted in which 200ml dose of convalescent plasma was administered to 10 adult COVID-19 patients with severe symptoms. The result significantly showslittle improvement and in 7 patients virus found disappeared without any severe adverse effects. This technique was used in SARS, as COVID-19 is similar to it.This therapy proves to be effective and safe [28, 30].

Viral targeted drugs:

In recent studies, remdesivir and chloroquine have been proved to inhibit SARS-CoV-2 effectively in vitro. Hence, other nucleoside analogues, such as Favipiravir, ribavirin and galidesivir may be effective clinically.

Remdesivir:

Remdesivir is an antiviral class of medication, a synthetic drug molecule which is known to target the synthesis of RNA. In animal models, this drug has proved in vitro and in vivo activity against the viral pathogens that cause MERS and SARS. These viruses are also type of corona viruses structurally similar to SARS-CoV-2, the coronavirus that cause COVID-19.

Remdesivir, an adenosine analogue that can inhibit viral RNA synthesis, has been promising antiviral drug against a wide array of RNA viruses in cultured cells, mice and nonhuman models. The clinical trials on animal indicate the drug can effectively reduce the viral load in lung tissue of mice infected with MER-CoV and improve lung infection. Remdesivir potentially inhibit SARS-CoV-2 infection and low range of micro molar concentrationand has high selectivity index (half maximal effective concentration (EC50)), 0.77µM; half cytotoxic concentration (CC50) >100µM; SI >129.87. It is early to conclude the direct antiviral activity of remdesivir on the enhanced clearing of viral loads in the respiratory tract, but indeed suggest a promising effect of remdesivir [29].

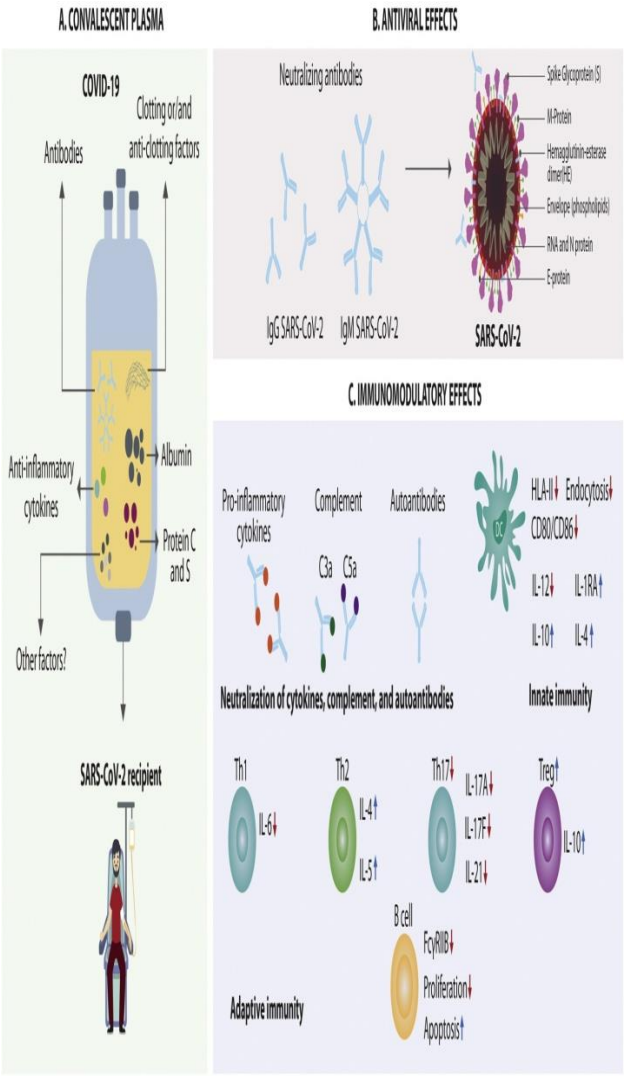

Figure No. 16: Convalescent plasma therapy increase immune response against COVID-19

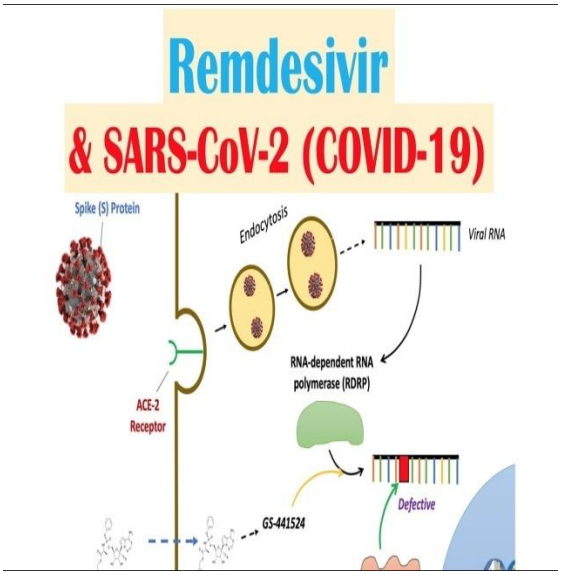

Figure No. 17: Remdesivirinhibits RNA synthesis

Favipiravir:

Favipiravir has been used in the treatment of various infectious diseases caused by RNA viruses such as influenza, Ebola and nor virus. In recent studies, clinical trials on humans have modified favipiravir is an experimental agent against enveloped, positive sense, single strand RNA virus SARS-CoV-2. In addition, this trials showed favipiravir has exerted efficacy in Vero E6 cells infected with SARS-CoV-2 with half maximal effective concentration (EC50) of 61.88µM and half cytotoxic concentration (CC50) at over 400µM, resulting the high concentration is required for safe and effective treatment. A randomized control trial has shown that favipiravir is used in COVID-19 patients have superior recovery rate (71.43%)[30].

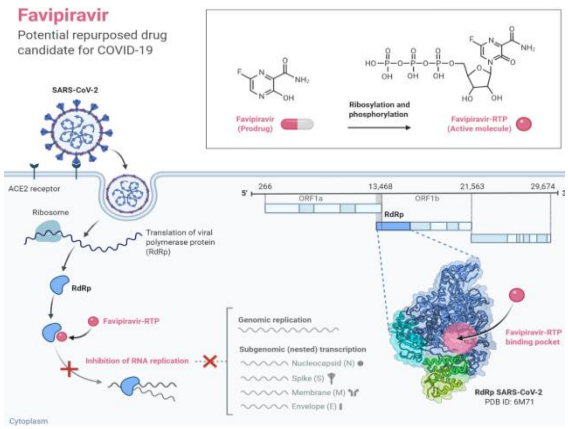

Figure No. 18: Favipiravir inhibits RNA replication in COVID-19

Hydroxy chloroquine and Chloroquine:

These are the anti-malarial drugs used to treat or prevent disease caused by parasites that enter the body through the bite of mosquito. The above drugs proved to show clinical use with similar chemical structures of lupus, erythematous, malaria and rheumatoid arthritis. Chloroquine can inhibit the entry of SARS-CoV-2 and prevent virus-cell fusion by interfering with glycosylation of ACE2 receptor and the binding with spike protein, suggesting that chloroquine treatment might be more effective in early stage of COVID-19 infection. When compared to chloroquine drugs, the drug Hydroxy chloroquine has a hydroxyl group which makes it less toxic while maintaining similar activity. There are more clinical trials progressed to evaluate the safety and efficacy of Hydroxy chloroquine as a prophylactic and treatment for COVID-19. The USFDA has issued emergency authorisation for the use of Hydroxychloroquine and chloroquine for the treatment of COVID-19 infection [31].

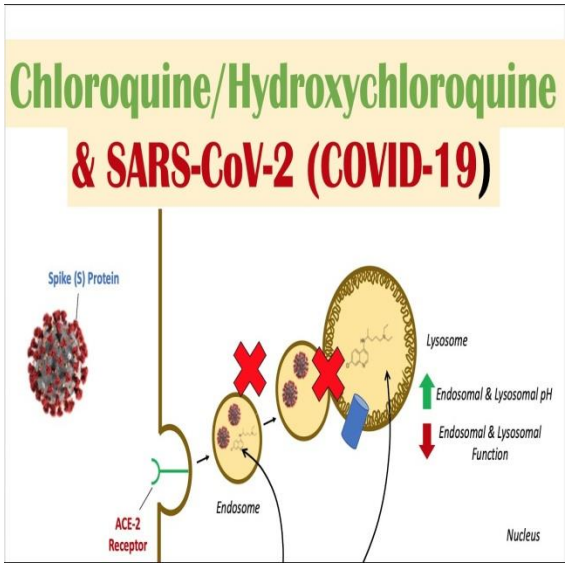

Figure No. 19: Chloroquine inhibits viral cell fusion in SARS-CoV-2 infection

Vaccines:

In present scenario, there may be many promising targets for SARS-CoV-2, but more clinical and laboratory evidence has to be explored against the COVID-19 infection. The WHO is working with many researchers and scientists to launch more than 80 clinical trials on potential treatments for SARS-CoV-2. Some

new pharmaceutical drugs, including HIV drugs and stem cells, were tested in those clinical trials. There are various vaccination strategies against SARA-CoV and MERS-CoVtesting in animals, including a live-attenuated virus, inactivated virus, viral vectors, subunit vaccines, recombinant DNA and protein vaccines. The trials are in progress, but it requires months to years to perform tests and to develop the vaccine for SARS-CoV-2.

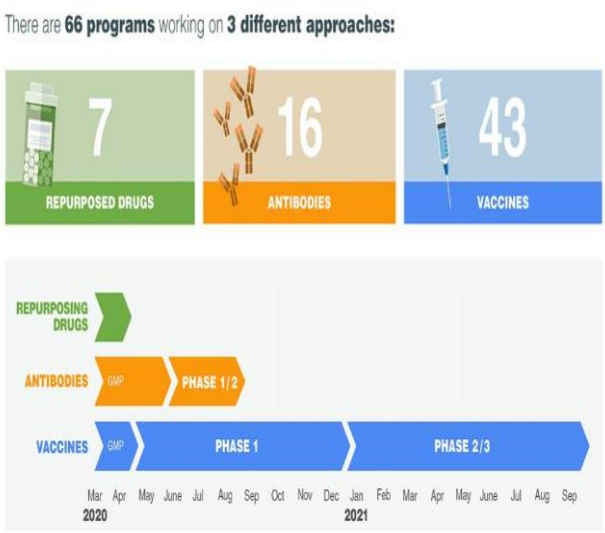

Figure No. 20: Projected strategic therapies for COVID-19

SYMPTOMS:

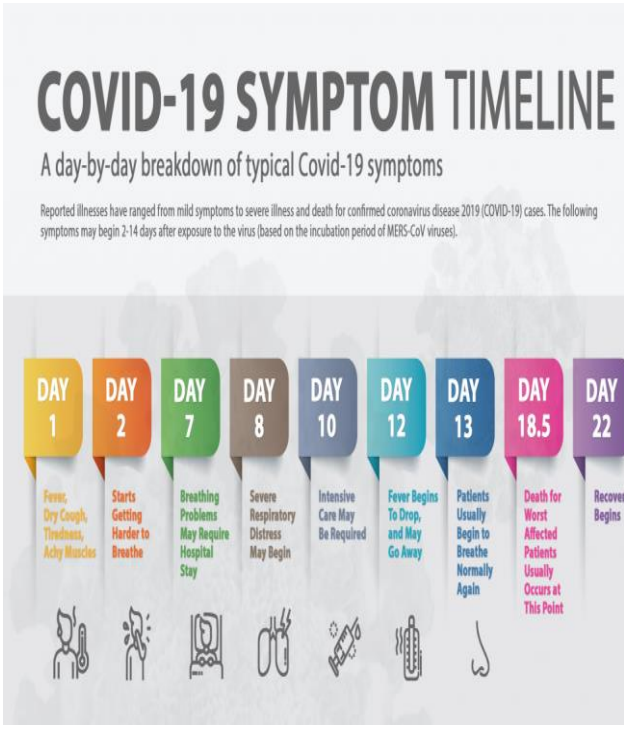

Figure No. 21: Typical Symptoms of COVID-19

Drug discovery and difficulties:

An antiviral drug must be able to target the specific part of viruses life cycle that is necessary for it to replication. In addition, an antiviral drug should possess the potential to kill the virus without affecting the human cell it occupies. The viruses are highly adaptive because they reproduce so rapidly, they have plenty of opportunity to mutate with each generation, potentially developing resistance to whichever drugs or vaccines we develop. It is necessary to consider all these factors during drug discovery and develop an accurate therapy for COVID-19 infection [22].

CONCLUSION:

The occurrence and development of SARS-CoV-2 depend on the interaction between virus and our immune system. According to the reports, the ratio of recovered patients is increased; some of drugs show immune response for various SARS-CoV-2 caused complications. It was noted that pneumonia caused SARS-CoV-2 can be prevented or treated with promising antiviral therapies, starting with pre-existing drugs, antibody therapy and other vaccines with minimal side effects. The early drug treatment of COVID-19 may prevent severe symptom development, lung injury and heart related illness making a difference in saving lives of infected patients. The impact is on lungs and heart and it is necessary to ensure that the organs function is not impaired by using various strategies for COVID-19 therapy for fast recovery and minimise the duration of hospitalization. Many clinicians are using Aspirin and the proven safety of Nafamostat mesylate and its increased antiviral activity, and as a serine protease inhibitor of TMPRSS2 protein to restrict the entry of SARS-CoV-2 into the cells. These drugs should be evaluated in clinical trials as therapy for COVID-19. The blockade of ACE2 also restricts the viral entry by using ACEI and ARB can be used in case of hypertensive patients. The fixed dose combinations of the various strategies of COVID-19 therapy could be the most awaiting vaccine for the treatment of COVID-19 infection. Following these guidelines could increase the ratio of recoveries and will encourage the scientific community

and researchers to focus their energies and resources, on the ultimate goal in completion of clinical trials against novel SARS-CoV-2 infection successfully. It is necessary to develop new, safe, accurate dosage, fast and simple vaccine against COVID-19 infection.

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