Pharmacological strategies for the treatment of COVID-19- A Review

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Abstract

The COVID-19 which causes respiratory system failure by novel coronavirus was first discovered in Wuhan city of China. The actual cases of deaths were as the results of development of pneumonia in later stages of the infection and resulted in severe acute respiratory syndrome. As of the 21 June, 2020, total of 8,921,618 cases were found worldwide of COVID-19, out of which 466,850 deaths were reported and 4,743,041 patients were recovered from the disease. The epidemic was spread all over the world through international travel. Even in India, 411,727 active cases of COVID-19 were reported out of which 13,277 deaths were reported till 19 June, 2020 and 228,181 patients were found to be recovered from this disease. Many prophylactic vaccines are under investigation and no vaccine till now has been reported to successfully eradicate this virus. As per the World Health Organization (WHO), a number of drugs has been reported for clinical trials for its treatment like hydroxychloroquine, chloroquine phosphate which are used to treat malaria disease. Remdesivir, Lopinavir-Ritonavir combination are also used for the treatment of COVID-19, these drugs are mainly used to treat HIV infection. Remdesivir, Lopinavir-Ritonavir combination sometimes used in combination with interferon to further reduce the impact of coronavirus. The convalescent plasma therapy which includes the use antibody from the body of a person who is recovered from novel coronavirus infection, is also promising alternative for these drugs. Many hospitals are claiming about their patient's recovery by using convalescent plasma therapy. All these events of the use of drugs and convalescent plasma therapy has been elaborated in this article. Until a definite therapy is developed for its treatment, the trials of these medications and other related to these are of promising role for the survival of human race.

Keywords: Coronavirus, COVID-19, SARS, SARS-CoV-2, pharmacotherapies

Introduction

The earliest case of coronavirus was found in Wuhan city of China which was known for origination hub of this virus in December 2019[1]. By January, 2020, a group of scientists from China had isolated this novel coronavirus from the patients suffering from acute respiratory diseases including pneumonia[2]. A Public Health Emergency of International Concern was declared on 30 January, 2020 by Chinese scientists[3]. The World Health Organization (WHO) in February, 2020, named it as SARS-CoV-2 as which is responsible for the coronavirus disease named as COVID-19. A number of 114 countries has been affected by this virus by March 11, 2020, then WHO declared COVID-19 as deadly disease[3]. The outbreak was initially started from a Huanan sea-food market in Wuhan city of China and it was believed that its initial transmission was zoonotic i.e. transfer from animal to animal but somehow it came into contact with humans with some kind of mutation and its mode of transmission occurred in humans. This virus then mutated and occurrence of transmission started from human to human[4]. From phylogenetic study, it was found that the original reservoir of this virus was bats and from bats it was transferred to pangolins which are considered as intermediate hosts and from them it is transferred to humans. But intermediate host was not yet cleared as suggested by many studies till date[5,6].

1. Epidemiology

As of the 21 June, 2020, total of 8,921,618 cases were found worldwide of COVID-19, out of which 466,850 deaths were reported and 4,743,041 patients were recovered from the disease. The epidemic was spread all over the world through international travel. Even in India, 411,727 active cases of COVID-19 were reported out of which 13,277 deaths were reported till 19 June, 2020 and 228,181 patients were found to be recovered from this disease[6]. India's testing rate is much low as compared to other countries and that may be the reason for less number of cases reported in the country[7]. The infection rate jumped by 21% in India from May 30 to June 11 and the recovery rate rises to 55.49% by June 21, 2020[8,9].

2. Clinical features

There are particularly two types of patients infected with COVID-19. These are symptomatic and non-symptomatic, well-marked symptoms cannot be seen in latter case. Some patients suffered from this disease shows symptoms like loss of smell, nasal congestion, fever, headache, shortness of breath, pain in muscles, chills, nausea or vomiting and diarrhoea. In case of asymptomatic patients, signs and symptoms are not seen but still virus is getting spread in the body and is transmitting to others. In severe cases, other symptoms like difficulty waking, confusion, bluish face or lips, persistent chest pain, coughing up blood, decrease in white blood cells, high fever and kidney failure has been reported. The figure 1 illustrate the signs and symptoms of COVID-19 in schematic view for better understanding.

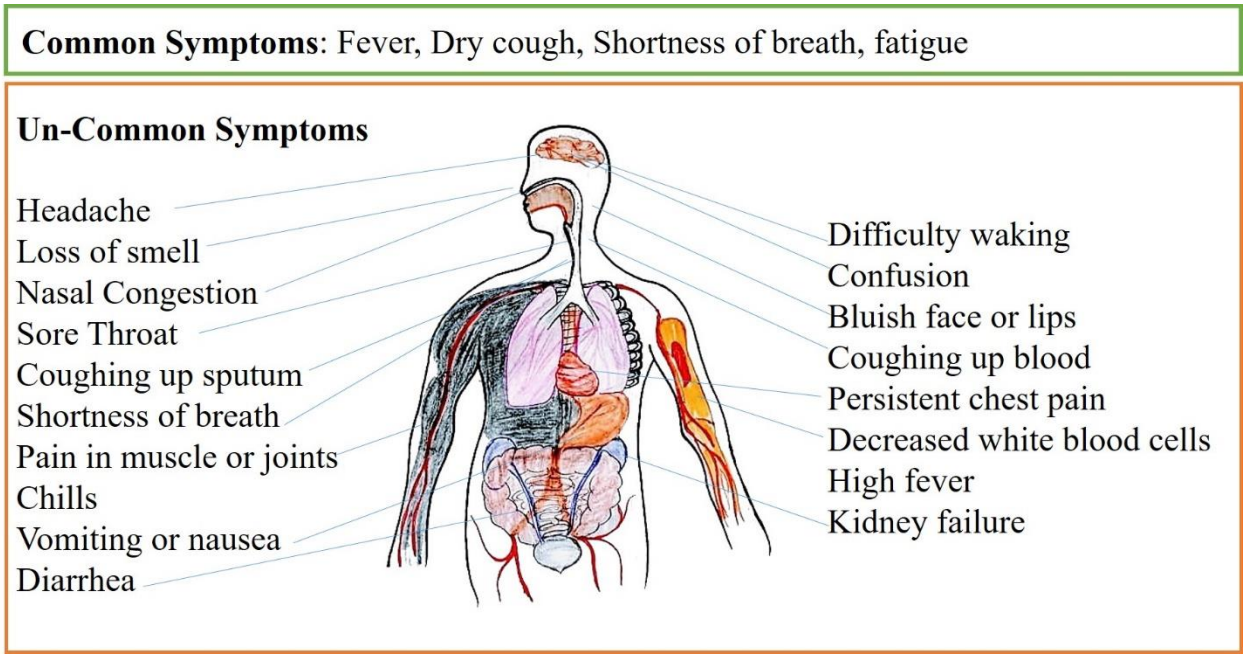

Figure 1: Commonly observed signs and symptoms of COVID-19 disease.

In spite of above mentioned signs, some patients develop pneumonia in later stages that become the actual reason for the death of the individuals.

3. Management guidelines

At present, many government and private agencies are coming forward in the management of Coivd-19 with their control measures and supportive care. The Ministry of Health and Family Welfare revised their guidelines for the clinicians taking care of hospitalized adult and pediatric patients of Coivd-19. They mainly focused on strengthening of clinical management of these

patients and provide up to date guidance. Best practices for COVID-19 includes IPC and optimized supportive care for severely ill patients are considered as essential[10]. The World Health Organization (WHO) also provided management guidelines for clinician, dealing with COVID-19 patients during all phases of their diseases (i.e. from screening till discharge). They recently updated their database to meet the needs of front line clinicians and promote a multi-disciplinary approach to care of patients infected with COVID-19, including those with mild, moderate, severe and critical disease[11]. The National Institute of Health also published some guidelines on prophylaxis use, testing and management of patients with COVID-19. They revised their guidelines for patients infected with mild to moderate disease, to deal with patients showing signs of hypercoagulable state and be at increased risk of thrombosis of blood vessels. They also keep their concern on pediatric management and therapeutic options for COVID-19[12].

4. Potential Pharmacotherapies

Most of the drugs that are manufactured for management of COVID-19 work against viral structure, genome and way of its replication. For RNA synthesis, the SARS-CoV-2 have RNA polymerase enzyme and most of the drugs are available that target against its enzyme. Nucleoside analogues that target HIV and some respiratory viruses are used to block RNA synthesis by blocking the action of RNA polymerase enzyme. Furthermore, some drugs act as protease inhibitors that prevents the formation of viral protein and thus assembly of the virus structure. Other drugs target the protein that help in attachment of the virus to host cell structure and one such protein is angiotensin converting enzyme-2 (ACE-2)[13]. Some of the most available drugs that are available for prevention and treatment of COVID-19 includes Remdesivir, Chloroquine, Hydroxychloroquine, LPV/r, Ribavirin, Nitazoxanide and Nelfinavir[13]. In addition to these, immuno-modulation therapies are also proposed against SARS-CoV-2. These drugs includes interferon α/β and baricitinib[13]. Besides this, some other drugs clinical trials and mode of action are also found promising that includes anti-proinflammatory cytokine drugs like Anakinra and Tocilizumab[14]. Passive immunity delivered by introduction of pre-formed antibodies from the body of the patients who recovered from COVID-19 also show promising feature. This therapy is known as convalescent plasma therapy[15].

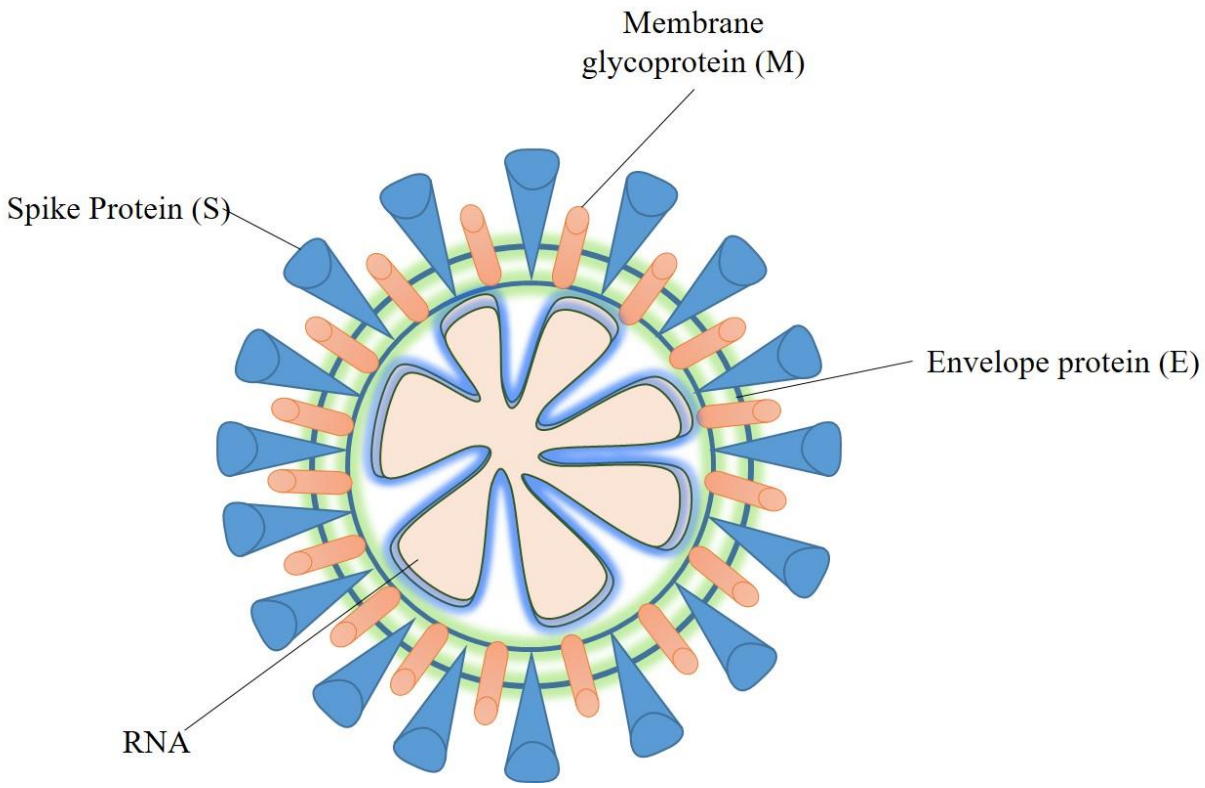

Figure 2: Structure of Novel coronavirus

As shown in the figure 2, the structure of SARS-CoV-2 includes envelope consisting of spike glycoprotein (S) envelope protein (E) and membrane protein (M) which are essential for entry of virus into the cell. This is a RNA virus and thus RNA genome is present in the core.

5. Pathophysiology and Potential therapeutic targets

Like other RNA viruses, the novel coronavirus contains a RNA containing core and various glycoproteins that are making the envelope. As shown in figure 3, virus cycle consisting of attachment, integration, replication, assembly and release, is followed by coronavirus as well. For antiviral drugs and vaccines, the most prominent targets are the steps of replication, transcription and translation[2]. The neutralizing antibodies are directed against glycoprotein S which involved in attachment of virus to the host cells. The entry of the virus can also be blocked by attachment of monoclonal antibodies and other ligands to specific virus receptors. For the membrane fusion and virus entry, receptor-induced confirmation changes occur in S protein that can be inhibited by peptides and thus ultimately prevent viral entry in the host cell.

Apart from pathophysiology of virus, the initial cause of mortality in susceptible patients is either due to cytokine storm or due to secondary bacterial infection. Antibiotics are employed for the treatment of bacterial infections. Recent research studies shows that cytokine storm which is an uncontrolled over production of some inflammatory markers, which in turn cause systemic inflammatory response, is majorly responsible for occurrence of Acute Respiratory Distress Syndrome (ARDS)[16]. The coronavirus bind to Toll like receptor (TLR) which in turns induce the production of pro-inflammatory cytokine interleukin 1 (IL-1). The IL-1 is the mediator of fever and fibrosis, which causes further problems in the patient's body. The drugs that can target IL-1 and IL-1 receptors can also be used to treat coivd-19[3].

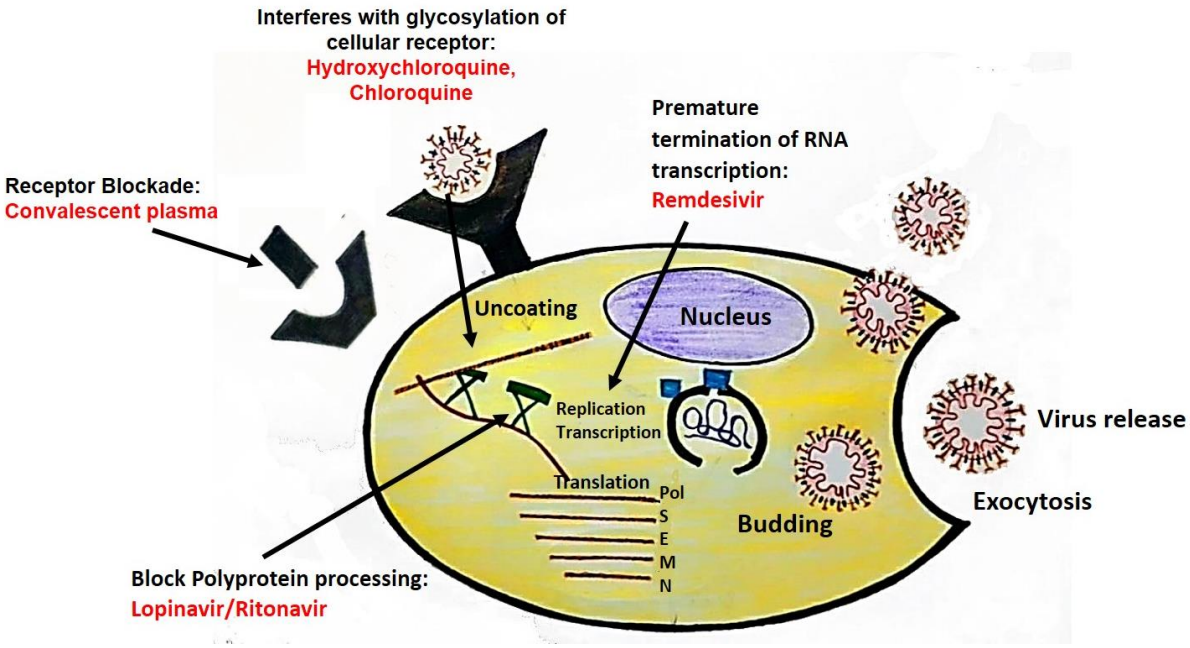

Figure 3: Experimental therapeutic strategies showing action of drugs on various sites during virus life cycle.

Antiviral Therapeutics

1. Remdesivir

No specific medicine has been proved till date for the effective treatment of COVID-19. Remdesivir, a nucleoside analogue drug, have an inhibitory effect on human and animal coronaviruses including SARS-CoV-2 in vitro and inhibit Middle East respiratory Syndrome (MERS) and SARS-Cov-2 in animal models. Remdesivir normally have a broad antiviral

spectrum including paramyxoviruses, filoviruses, pneumoviruses and coronaviruses [17,18]. In the epithelial cells of nasal cavity and bronchia, Remdesivir inhibit replication of SARS-CoV-2. For the treatment of disease produced by Ebola virus, intravenous injection of Remdesivir was given[19]. Remdesivir act by inhibition of RNA polymerase enzyme[20]. The dosage of this drug at the rate of 200mg intravenously followed by 100 mg intravenously for 5 to 10 days in adult is prescribed in ongoing clinical trials. Some of the adverse effects were also reported in some patients that includes nausea, vomiting and gastroparesis. The elevated amino-transferase activity was also observed in these patients in the initial days of Remdesivir injection[22].

2. Chloroquine and hydroxychloroquine

Chloroquine analogues and their derivatives have been used for the treatment of malaria. The same medicine can also be used for the treatment of COVID-19[23]. Aside from these two properties, chloroquine and hydroxychloroquine can also be used in autoimmune disorders like systemic lupus erythematosus and rheumatoid arthritis. The multimodal properties of chloroquine derivatives and minimum toxicity have led the scientists to explore its beneficial use to target the antiviral tendencies including anti-HIV-1 activity[24]. Chloroquine and their analogues are weak bases which in their non-protonated form get accumulated and concentrated in acidic environment of some cellular organelle like endosomes and lysosomes. When they reach inside these organelles, they become protonated and increase pH of the localized environment and therefore, decrease cellular activity by depleting the action of cellular enzymes, endosome trafficking and protein synthesis[25]. This pH alteration prevent early inhibition of viral replication by interfering endosome mediated viral entry or late transport of the virus envelope. It also appear to cause inhibition of ACE2 receptor expression by interfering with its terminal glycosylation that prevent SARS-CoV-2 receptor binding and thus it's further expression[25]. The hydroxy derivative of chloroquine, the Hydroxychloroquine have three fold higher cytotoxic potential as compared with chloroquine. The plasma concentration of 6.90µM have shown potent antiviral effect on pre and post entry states and this concentration can be safely achieved in humans[26]. For the treatment of COVID-19, the experts recommend, a chloroquine tablet at a dose of 500 mg daily through oral route for the duration of 10 days[27]. The chloroquine and Hydroxychloroquine is generally well tolerated in patients. In some cases, common adverse effects related to gastrointestinal intolerances occur like nausea, vomiting, and abdominal

cramping and in some cases a metallic taste. To mitigate these effects the doses of these drugs are often recommended with food. Thus this mechanism of antiviral and anti-inflammatory effect of chloroquine make it a suitable compound against COVID-19 infection.

3. Lopinavir/Ritonavir

Lopinavir is an aspartic acid protease inhibitor which is developed for the treatment of HIV. The polyprotein of replicase protein of the virus is inhibited by this drug and therefore inhibiting proteolysis. The lopinavir and ritonavir combination is considered a potentially useful treatment for the COVID-19 in vitro[28]. For production of viral genome and its maturation, protease enzymes plays a crucial role. For limiting viral spread into the host, proteases first inhibit viral replication[29]. The lopinavir/ritonavir in combination with interferon-β1b had a better outcome in treated animals. The results are also promising with improved radiological, clinical and pathological findings and lower mean viral loads in necropsied lung and extra-pulmonary tissues[30]. The initial treatment with lopinavir/ritonavir resulted in significant reduction in overall death rate and incubation rate compared with match control (p,0.05)[31]. Lopinavir/ritonavir is available as a single tablet formation (Kaletra) in dosage strengths of 400/100 mg or 200/100 mg. But its dose of 400 mg/100mg by mouth is recommended for 14 days[32]. If the patient is suffering from a liver disease then adjustments are recommended in the dosage[33]. Gastrointestinal toxicities resulted in some patients due to lopinavir/ritonavir treatment. But these conditions are stabilized when these drugs are administered with food. Up to 24% of patients experience diarrhoea which usually improves in 2 weeks[33]. The delivery of these drugs via nasogastric tube is preferred in patients with limited oral access[33].

4. Convalescent plasma therapy

In this therapy, the readymade antibodies from the person recovered from COVID-19 are administered in patients and it offers a novel therapeutic approach. It restores the immune system of the patients during critical illness and neutralize the virus to suppress viremia[34]. Importance of this therapy was recognized from the treatment of H1N1 patients that derived a clinically significant mortality benefits and improved viral clearance from convalescent blood products[35]. The convalescent plasma therapy has been utilized in severe pandemic cases including the Spanish flu, SARS-CoV, West Nile virus, and Ebola virus[36,37,38,39,40]. This therapy administered

in early stages (before day 16) of the disease provide much benefits because viremia from SARS shown to be at peak in the first week of treatment followed by primary immune response by days 10-16[41]. No signs of adverse effects has been associated with this therapy for the treatment of SARS-CoV[42]. However, the targeted anti-SARS-CoV-2 antibodies against coronavirus are in developmental stages and further investigation need to be done for its clinical efficacy and safety treatment of COVID-19[43].

Drugs available in the market to combat COVID-19

Recently many pharmaceutical and biotechnology companies launched their products for the treatment of COVID-19. One such drug is produced by Glenmark and named as Favipiravir under the brand name Fabiflu for the treatment of COVID-19. The Glenmark gets regulatory approval for the utilization of this drug to treat mild to moderate COVD-19. In cells the drug is converted into an active phosphoribosylated form (favipiravir-RTP), which is then identified by RNA polymerase as a substrate, in turn blocking RNA polymerase activity. Clinical improvements was observed in the age group of 20 to >90 years[44]. Pharma Major Cipla Limited antiviral drug which is generic version of antiviral drug remdesivir is the latest to join Glenmark's Fabiflu and Hetero's Covifor to treat covid-19 patients in the country[45].

Conclusion

The enormous global health crisis has been presented by COVID-19 pandemic. All the pharmaceutical and biotechnology companies are working on the improvement of vaccines and drug development for effective treatment of COVID-19. The medical companies are using the drugs made by these pharmaceutical companies for clinical trials to find out the mechanisms to combat this virus. Most of the effective therapeutic agents has been discussed in this review for the treatment of COVID-19. Some drugs are shown to poses promising features for the effective treatment and prevention of this disease while others show some kind of mild to moderate side effects. The side effects further depends on many parameters including person's age, nutritional state and immunity. Therefore more research need to be done in future that provide us more resources for effective treatment of the disease.

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