A Review on Emerging Therapeutic Interventions for Corona Virus

Running Title: Therapeutic Interventions for COVID-19

Abstract: The Coronavirus (SARS-CoV-2) is one of the deadliest viruses of current era and is causative agent of coronavirus disease-2019 (COVID-19). This disease poses a tremendous threat to mankind due to its unexplored pathologies. The world health organization (WHO) has declared COVID-19 as a pandemic. This outbreak has challenged the public health concerns at large, killing the most vulnerable person, causing generalized panic and become a top debate among scientists, clinicians, physicians, pathologists, economists, athletes and politicians. Anti-viral vaccines and target drugs to treat this virus are unavailable due to its diverse genetic instability. Currently, its prevention, control and treatment are questionable as no proven remedies have been effective for its cure so far. From a research standpoint, various drugs are being developed at an extremely quick pace, new targets are being identified every day, and also numerous drugs are also undergoing clinical trials. Researchers are very curious about how to provide the best protection to the public before a vaccine can be made available to common community. To stop this disease, effective remedies (i.e., drugs, vaccines, personal protection elements, etc.) are urgently required. Red bells are ringing but there is no way out. Current review focuses on the ongoing regimes and therapeutic interventions for better combat with COVID-19.
Keywords: coronavirus, genetic instability, interventions, pandemic, therapeutic, vaccine

Introduction

The global challenge of COVID-19 started in late December, particular with rapid increase of critically ill patients having symptoms of pneumonia (Cascella, Rajnik, Cuomo, Dulebohn, & Di Napoli, 2020). Our global health system unfortunately has often seen an array of novel emerging diseases such as Ebola, Dengue, SARS and MERS (Favalli et al., 2020). The list of emerging pathogens updated again with the addition of novel coronavirus (2019-nCoV) (Hui et al., 2020). This virus strain was reported to infect humans for the first time (El Zowalaty & Järhult, 2020) . In early reports the mortality rate was appears to be around 2% but with the passage of time virus became more contagious, more pathogenic and deadly (Figure 1). Due to globalization the virus spread across international borders and WHO declared a pandemic (Khan & Naushad, 2020). In corona virus illness the efficacy of the treatment totally relies on the critical condition of patient health status and disease stage (Cascella et al., 2020).

Brief Overview of Corona Virus

SARS-CoV-2 Pathology

Coronaviridae family, having a total of 39 species, (Gorbalenya et al., 2020). Few of these species are zoonotic in nature (Schoeman & Fielding, 2019). Origin and spread of the virus,

remain as a mystery to world audience, currently, it is believed that SARS-CoV-2 has been introduced to human by an unidentified animal and further spread from human-to-human (Xu et al., 2020). Human coronaviruses are causative of upper respiratory tract illnesses ranging from mild to moderate including common cold (Woelfel et al., 2020). Human might catch infection with one or more of these viruses at some point in their lifetime (Killerby et al., 2018). Two major causes of severe pneumonia are SARS-CoV and MERS-CoV (Zhu et al., 2020). A comparative analysis of the symptoms among COVID-19, SARS, MERS and common flu has been described in (Figure 1). The WHO, on February 11, 2020, officially named the viral disease COVID-19 (Shen et al., 2020). The research group of the International Committee on Taxonomy of Viruses named the new pathogen as SARS-CoV-2 (Gorbalenya et al., 2020). In arrays of serious outbreaks SARS-CoV first emerged in 2002. During its course of infection, 8000 infections and 774 deaths were recorded across 35 countries (Peiris, Guan, & Yuen, 2004). Followed by the outbreak of MERS-CoV, responsible for infection of 2500 people and 858 dead in golf countries (Zaki, Van Boheemen, Bestebroer, Osterhaus, & Fouchier, 2012). Similar to this pattern, the SARS-CoV-2 appeared in December 2019 from the animal kingdom and spread to human populations. Currently 34,170,356 people are infected and reported deaths are 1,018,899 worldwide. Incubation period of SARS-CoV-2 is around 2 weeks. During this time the virus replicates in the upper and lower respiratory tract, forming lesions (Chan et al., 2020). The general symptoms observed in the infected individuals are fever, cough, dyspnoea and lesion in the lungs (Wu et al., 2020). In the advanced stage, the symptoms of this virus show pneumonia which progresses to severe pneumonia and acute respiratory distress syndrome (ARDS) which results in to the need for life-support to sustain the patient's life (Heymann & Shindo, 2020). The HCoVs generally are very long (30,000 bp) positive-sense single-stranded RNA viruses. Two groups of protein characterize HCoVs; the structural proteins, and non-structural proteins such as RNA dependent RNA polymerase (RdRp) (nsp12) (Figure 2) (Elfiky, 2020).

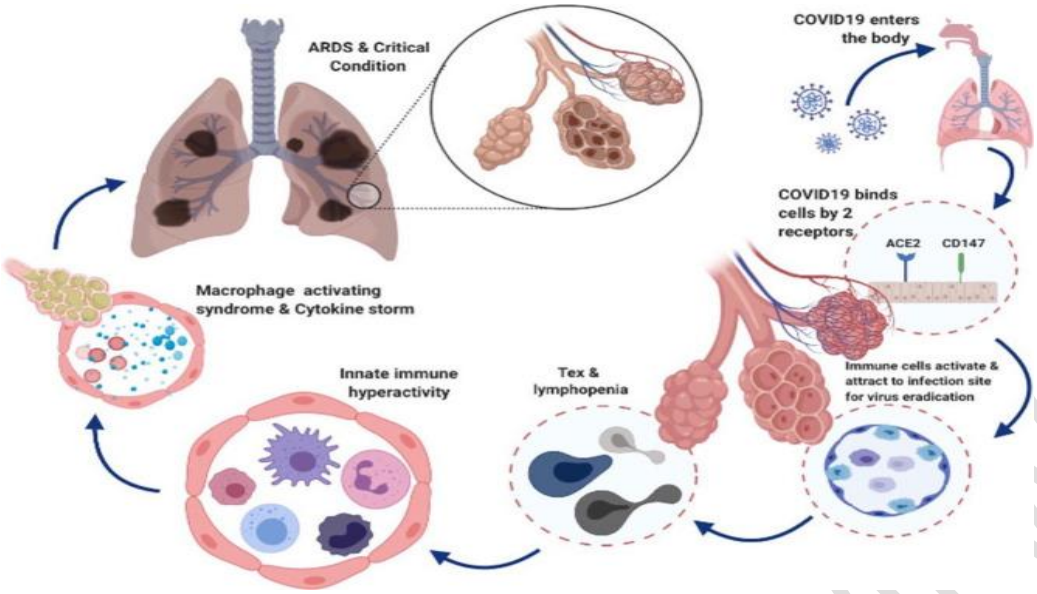

Fig. 1 Illustration indicating the pathogenesis and role of immune system in combating with viral load

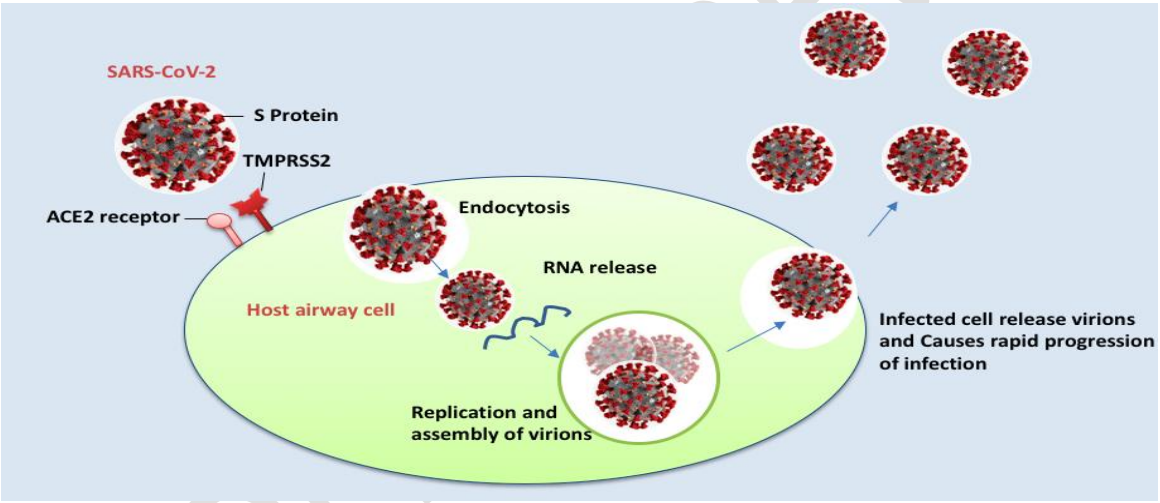

Fig. 2 SARS-CoV 2 virus infection in host cell; TMPRSS2 activates S protein of virus and cleaves ACE2 membrane receptors of host airway cell, virus enter host cell through endocytosis, releases RNA and utilize host cell machinery for replication and assembly of more viruses

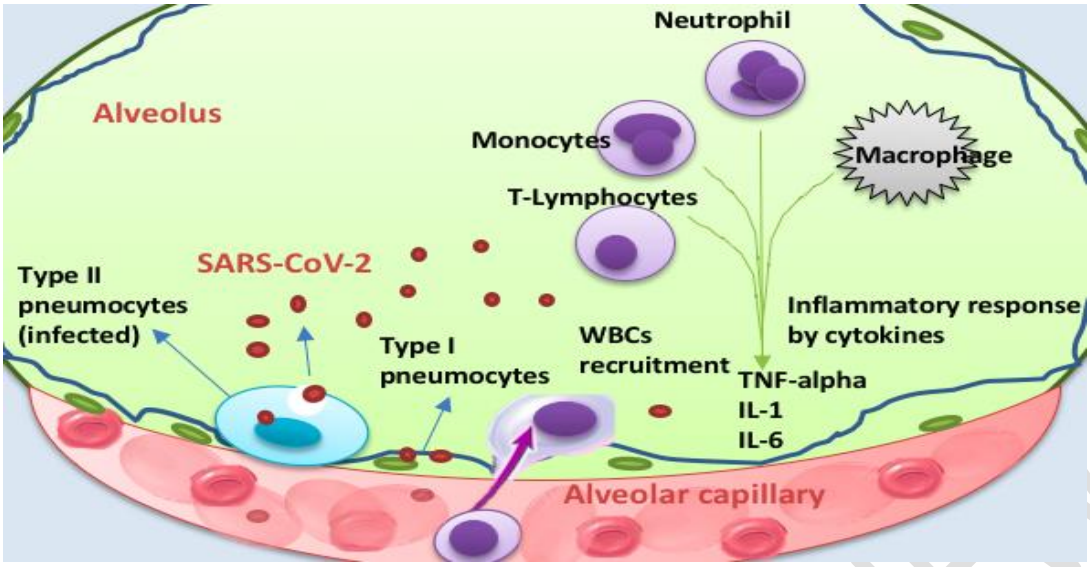

Fig. 3 Early stage SARS-CoV 2 virus infection; capillary endothelium and alveolar pneumocytes (type I and II) are infected with SARS-CoV 2 virus and inflammatory response initiates via cytokine release by recruitment of monocytes, neutrophil and T-lymphocytes

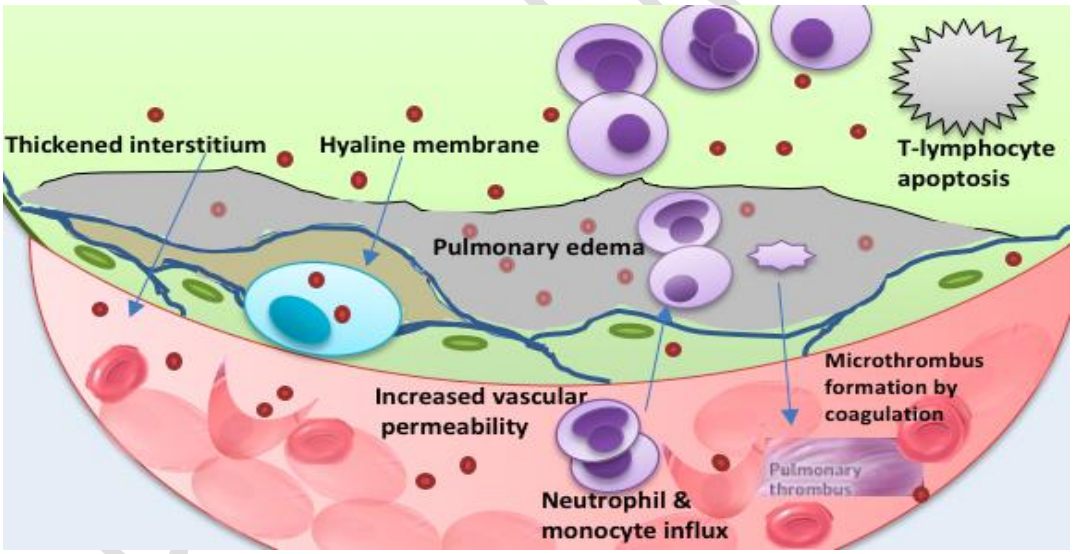

Fig. 4 Increased vascular permeability and alveolar interstitial thickening due to continues inflammatory response

Therapeutic Interventions for Corona Virus

Modulation of Immune system

Neither an effective vaccines nor anti-viral therapeutic agents have been approved to treat COVID-19 or any other human CoV infection till date. Coronaviruses such as SARS and MERS are particularly adept at evading immune detection and dampening immune responses. It's not yet clear as to how SARS-CoV-2 affects the immune system (Nikolich-Zugich et al., 2020). During viral infection, host factors elicits immune response against the viruses. T cells (Figure 3), particularly CD4+ and CD8+ play a significant antiviral role to combat the pathogens and elevate the risk of developing autoimmunity/inflammation (Cecere et al., 2012).

The CD4 + T cells advance the production of viral-specific antibodies by activating T cell-dependent B cells. However, CD8+ T cells are cytotoxic and kill virus infected cells. The CD8+ T cells account for about 80% of total inflammatory cells (Figure 4) in the pulmonary interstitium in SARS-CoV infected patients and play a critical role in clearing coronaviruses in infected cells and inducing immune injury (Maloir, Ghysen, von Frenckell, Louis, & Guiot, 2018). In addition, T helper cells make proinflammatory cytokines via NF-kB signaling (Manni et al., 2014). The cytokines, such as IL-17 recruit monocytes and neutrophils to the infection site showing inflammation and activates other downstream cascades of cytokines and chemokines, including IL-1, IL-6, IL-8, IL-21, TNF-β, and MCP-1 (Bunte & Beikler, 2019). It was observed that, T cell apoptosis was induced by a novel BH3-like region located in the C-terminal cytosolic domain of SARS-CoV protein mediated by Bcl-xL (Yang et al., 2005). From the experimental evidences it was shown that T cell response to S protein and other structural proteins (including the M and N proteins) is long-lasting, persistent and provides evidence for designing new drugs and vaccines for SARS-CoV-2 composed of viral structural proteins, which can induce dominant, effective, and long-term memory cell responses against the virus. However, earlier studies have also reported a crucial role of both CD8+ and CD4+ T cells in SARS-CoV-2 clearance, (Zhou & Zhao, 2020) observed that development of SARS-CoV-2 specific neutralizing antibodies requires CD4+ T helper cells. Moreover, the ACE2 protein fused to a human immunoglobulin G Fc domain (ACE2-Fc) of SARS-CoV-2 patients may have the benefits of a traditional neutralizing antibody which could be used as a treatment for the infection. Ultimately, there will be a need for clinical trials to delineate any specific side effects of ACE2-Fc treatment (Kruse, 2020). Therefore ACE2-Fc might play an important role in the treatment of SARS-CoV-2, if the function of ACE2-Fc is inhibited. These immunological studies show how crucial it is to understand the basics of the immune responses in these viruses, so these

immune cells can be induced to further attack the virus with increased specificity. Besides the immune system, scientists have also found a possible involvement of the COVID-19 in the nervous system (Vellingiri et al., 2020).

The current approach to coronavirus disease management focuses on supportive care. Rapid public health interventions with antibodies, anti-virals or novel vaccine strategies are highly essential to contain the virus and disease transmission. Passive antibody therapy can be considered as a way to limit COVID-19 epidemics. Convalescent plasma or immunoglobulins have been used as a last resort to improve the survival rate of patients with SARS whose condition continued to deteriorate despite treatment with pulsed methylprednisolone (Chen, Xiong, Bao, & Shi, 2020). Moreover, several studies showed a shorter hospital stay and lower mortality in patients treated with convalescent plasma than those who were not treated with convalescent plasma. In 2014, the use of convalescent plasma collected from patients who had recovered from Ebola virus disease was recommended by WHO as an empirical treatment during outbreaks (L. Chen et al., 2020).

Protocol for the use of convalescent plasma in the treatment of Middle East respiratory syndrome coronavirus was established in 2015 (Zumla, Hui, & Perlman, 2015). According to WHO, management of COVID-19 has mainly focused on infection prevention, case detection and monitoring, and supportive care. However, no specific anti-SARS-CoV-2 treatment is recommended because of the absence of evidence. Most importantly, the current guidelines emphasise that systematic corticosteroids should not be given routinely for the treatment of COVID-19, which was also the recommendation in *The Lancet* (L. Chen et al., 2020). Evidence shows that convalescent plasma from patients who have recovered from viral infections can be used as a treatment without the occurrence of severe adverse events. Therefore, it might be worthwhile to test the safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients. Huang et al. reported the clinical features and cytokine profile of critically ill patients with COVID-19 in Wuhan, China (Li et al., 2020), and suggested that a cytokine storm (i.e. higher concentrations of granulocyte-colony stimulating factor, interferon gamma-induced protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α and tumour necrosis factor α) could be associated with the severity of disease (Zhao, 2020). Another study from China reported that increased expression of interleukin (IL)-2R and IL-6 in serum appears to predict the severity and prognosis of patients with COVID-19. Additionally, pathological examination of a biopsy sample from a patient who died from COVID-19 revealed interstitial mononuclear

inflammatory infiltrates in both lungs, dominated by lymphocytes (Zhao, 2020). Furthermore, peripheral blood flow cytometric analysis showed that over activation of T cells accounted, in part, for the severe immune injury in this patient (Krebs et al., 2013). Thus, cytokine storms should not be neglected in the treatment of COVID-19. Immunomodulatory therapy to down-regulate the cytokine storm may provide insights into the treatment of COVID-19 (Zhao, 2020). Corticosteroids are among the most commonly used drugs for immunomodulatory therapy of infectious diseases. However, the use of corticosteroids in the treatment of COVID-19 can cause host immune suppression and delay viral clearance. Recently, chloroquine and its derivative hydroxychloroquine have been used in the treatment of COVID-19 (Liu et al., 2020). In February 2020, results from more than 100 Chinese patients with COVID-19 showed that chloroquine phosphate had good efficacy against the virus. In addition to their antimalarial and antiviral effects, their anti-inflammatory properties have been demonstrated in the treatment of autoimmune diseases such as rheumatoid arthritis and lupus erythematosus. Chloroquine and hydroxychloroquine can inhibit major histocompatibility complex class II expression, antigen presentation and immune activation (reducing CD154 expression by T cells) via Toll-like receptor signalling and cGAS stimulation of interferon genes (Rainsford, Parke, Clifford-Rashotte, & Kean, 2015). Thus, chloroquine and hydroxychloroquine can reduce the production of various pro-inflammatory cytokines, such as IL-1, IL-6, interferon-α and tumor necrosis factor, which are involved in the cytokine storm.

The virus completes its cycle in following 5 steps: attachment, penetration, biosynthesis, maturation and release. The SARS-CoV-2 virus binds with its spike proteins (S protein) to the angiotensin converting enzyme-2 receptor (ACE2), (X. Chen et al., 2020) whose expression levels are higher in lungs, heart, ileum, kidneys and bladder could explain the involvement of multiorgan failure in COVID-19 patients (X. Chen et al., 2020). Within lungs, ACE2 receptors are highly expressed on apical aspect of lung epithelial cells in alveolar space (Ziegler et al., 2020). This initial binding of the virus with the ACE2 receptors initiate the cleavage of the S proteins by host proteases such as furin or TMPRSS2 which presumably result in the exposure of the fusion sequence of viral protein with cell membranes of host cell, a mechanism necessary for entry of the virus into the host cell (Yuki, Fujiogi, & Koutsogiannaki, 2020). The SARS-CoV-2 preferably attacks the alveolar cells type II compared to type I cells (Lopes et al., 2020).

The alveolar units situated under the pleura are the ones that are affected first. The virus then multiplies inside type II cells and multiple copies of the virus are then released, resulting in the apoptosis and death of these type II cells with the new viruses attacking nearby type II cells and this process goes on (Danser, Epstein, & Batlle, 2020). The SARS-CoV-2 also infects alveolar endothelial cells and hence compromises epithelial-endothelial barrier resulting in endothelialitis and infiltration of mononuclear cells edema of the alveolar space (Li et al., 2020). Moreover, type II alveolar cells are also the precursors of type I cells, hence after their destruction, the regeneration mechanism of alveolar units is severely impaired (Wiersinga, Rhodes, Cheng, Peacock, & Prescott, 2020). Much of the damaged inflicted by SARS-CoV-2 is presumably due to a robust immune reaction called cytokine storm with IL-6 as a major protagonist. This IL-6 is also a major culprit implicated in production of acute phase proteins, thermoregulation fever and multiple organ dysfunction.

Moreover, inhibition of ACE2 receptor by the virus further promotes lung injury as occupied ACE2 receptors fail to breakdown angiotensin II which leads to acute respiratory distress syndrome and multiorgan dysfunction (Gupta, 2020). These events result in diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells. In terminal stages of COVID-19 patients, activation of coagulation and consumption of clotting factors occur with resultant diffused intravascular coagulation (Andreakos & Tsiodras, 2020). Inflamed lung tissues and pulmonary endothelial cells may result in thrombi formation. Viral sepsis that is one of the complications associated with COVID-19 is caused by dysregulated reaction of host defense system and this sepsis could also play its part in multiorgan failure (Yuki et al., 2020).

Specific strategies to combat

The choice of whether to admit a patient in the hospital or not depends on the extent of progression of virus in the respiratory tract (Thomas-Rüddel et al., 2020). The patients in which the SARS-CoV-2 has just spread to the upper and conducting part of respiratory airways exhibit mild symptoms, such as fever, cough and do not need immediate hospitalization. Instead they need to be isolated at home to contain and mitigate the spread of the disease and such house-quarantined patients should receive much of their treatment at home including spirometry or breathing exercises, rest, and adequate fluid intake and antipyretics. It is only in severe case in which the virus has acquired access to gas exchange area of the respiratory airways and other parts of the body where the situation gets

complicated with acute respiratory distress syndrome, sepsis and septic shock, multiorgan failure, including cardiac and renal failure (Zaim, Chong, Sankaranarayanan, & Harky, 2020), that the patient should be admitted to the hospital and be treated according to the complications involved. The severity of the disease is assessed by the development to of ARDS which is a syndrome characterized by sudden onset of hypoxemic respiratory failure along with bilateral infiltrates (Coperchini, Chiovato, Croce, Magri, & Rotondi, 2020). The COVID-19 patients who suffer from other comorbid conditions such as diabetes and cardiac diseases also require immediate medical intervention as the chances of complication are elevated in these patients (Guan et al., 2020). The most common condition for requiring extensive care has been respiratory support. Therefore, those patients who develop respiratory distress, hypoxia or shock should immediately be given supplemental oxygen therapy and their SpO2 should be tried to maintain at >94% (Alhazzani et al., 2020). If the patients continue to develop hypoxemia even after oxygen therapy should be opted to treat with mechanical ventilation with prone ventilation of 12-16 hours is recommended (Bhatraju et al., 2020). Similarly, those individuals who suffer from co-infections should be empirically treated with antimicrobial within an hour of their assessment.

Availability of Targeted Drugs

Ivermectin is a potential drug of choice against parasites and it is also proposed for treatment against COVID-19 (Caly, Druce, Catton, Jans, & Wagstaff, 2020). The concentration at 5 mmol/L causes the disappearance of RNA of virus and it is 50 times over higher after 700 lg/kg attained (Muñoz et al., 2018). Ivermectin showed a great anti-viral activity (broad spectrum) in vitro and it inhibits SARS-CoV-2 with addition Vero-hSLAM cells. Its affects showed activity 2 hours after post infection and reduced the viral RNA ~5000-fold in 48 hours.

A nucleoside analogues drug, Remdesivir has antiviral activety and used for treatment of infections caused by Nipah and Ebola virus (Lo et al., 2019). Remdesivir has greater effects on SARS-CoV-2 as it is an RNA virus and has great potential candidate drug for treatment of COVID-19 (Cao, Deng, & Dai, 2020). The mechanism of action Remdesivir which targets the divergent RNA-dependent RNA polymerase (RdRp) of the host viral replication and its nucleoside analogues shows the antiviral results as in HIV, hepatitis C and B. it is used with ribavirin and mutation was increased by 9.7-fold reduce infection at 99.3% (Crotty, Cameron, & Andino, 2001). Azidothymidine loses its 3′-hydroxyl group which is

necessary for synthesis of additional DNA. Remdesivir blocks the transcription process at 3′-hydroxyl and produced phosphodiester bond with nucleotide. Patient infected with COVID-19 received Remdesivir 200 mg I/V in 1 day up to 10 days. So, 61 patients recovered successfully as they belong from different countries as Europe, United States, Canada and Japan.

Favipiravir inhibited the RNA-dependent RNA polymerase (RdRp) (Dong, 2020) and block the replication of alpha-, flavi-, bunya-, filo-, noro-, arena-, and other RNA viruses (Delang, Abdelnabi, & Neyts, 2018). Many clinical trials are undergoing for the use of treatment of COVID-19. 120 patients of COVID-19 treated with Favipiravir and compared Arbidol. Recovery rate is day 7 and recovery rate was 0.0954; 95%. Serum uric acid was raised by using of Favipiravir and it helps to relief from cough and pyrexia and adverse effects can be manageable.

MK-4482 is an emerging drug which has antiviral potential, so it can be used for treatment of COVID-19 (Vasudevan et al., 2020). A new route has been developed for MK-4482 from cytidine which is desirable for many reasons. It emits *O*-acylation which is undesirable and less chemical esterification plan. Further trails are necessary to check its efficacy for the treatment of COVID-19. MK-4482 shows more better results than that of remdesivir for the treatment of COVID-19 patients and its trials have been completed in mice (Cross, 2020).

Conclusion

The COVID-19 pandemic is an ongoing issue that affects the lives of most people around the world. Most countries are now semi-closed, strict travel regulations have been enacted, international relations have been affected, and humans are experiencing an unprecedented regime, which has changed ordinary life. Immune system plays an important role in fighting COVID-19, paradoxically it could also be harmful. Now a day's target drugs are available and due to limitation of choice being catagories as best treatment for corona virus. It is necessary to find efficient drugs and vaccines to return to the normal situation and reduce the mortality rate.

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