A Review on Emerging Therapeutic Interventions for Corona Virus

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Review Article

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ABSTRACT

The Coronavirus (SARS-CoV-2) is one of the deadliest viruses of current era and is identified as the causative agent of novel coronavirus disease-2019 (COVID-19). This disease stances a severe risk to mankind due to its unexplored pathologies. It was declared as a COVID-19 pandemic by the world health organization. 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 assessment, many number of drugs or medicines are being manufactured and tested at fast pace, goals and objectives are being celebrated on daily basis, and also many drugs are be subjected to clinical tests. Scientists are interested about how to provide the better care to everyone before a vaccine can be made available to common community. To stop COVID-19, effective solutions (i.e., personal protection elements, vaccines, drugs, etc.) are needed urgently. 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.

1. INTRODUCTION

The global challenge of COVID-19 started in late December, particular with rapid increase of critically ill patients having symptoms of pneumonia [1]. Our global health system unfortunately has often seen an array of novel emerging diseases such as Ebola, Dengue, SARS and MERS [2]. The list of emerging pathogens updated again with the addition of novel coronavirus (2019-nCoV) [3]. This virus strain was reported to infect humans for the first time [4]. 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. Due to globalization the virus spread across international borders and WHO declared a pandemic [5]. In corona virus illness the efficacy of the treatment totally relies on the critical condition of patient health status and disease stage [1].

2. BRIEF OVERVIEW OF CORONA VIRUS

2.1 SARS-CoV-2 Pathology

Coronaviridae family, having a total of thirty nine species, [6]. Few of these species are zoonotic in nature [7]. Origin and transmission patterns of the virus, still remain as unidentified to world audience, recently, it is believed that SARS-CoV-2 has been transmitted to human being from mysterious animal and further transmitted from one individual to another [8]. Coronaviruses affecting human being are causative of upper respiratory tract diseases limiting from minor to moderate symptoms together with common cold [9]. Human might be infected with more than one species of this coronaviridae family at any stage during their life span [10]. Two main etiological agents of severe pneumonia are MERS-CoV and SARS-CoV [11]. There are sight variations among the signs and symptoms of MERS, SARS, COVID-19 and common. The World Health Organization publically named this viral disease COVID-19 on 11, February 2020 [12]. This new virus was termed as SARS-CoV-2 by the research group of the International Committee on Taxonomy of Viruses [6]. In arrays of serious outbreaks SARS-CoV first appeared in 2002. 8000 infections and 774 deaths were recorded across 35 countries during its course of infection [13]. Followed by the outbreak of MERS-CoV, responsible for infection of 2500 people and 858 dead in golf states [14]. Similarly, the newly emerged SARS-CoV-2 transmitted from animals to human beings in December 2019. Currently 34,170,356 people are infected and reported deaths are 1,018,899 worldwide. Incubation period of SARS-CoV-2 is about 14 days. It replicates in the lower and upper part of respiratory tract as a result produced lesions in the affected areas [15]. Most common clinical signs and symptoms found are cough, low to high grade fever, dyspnea and lesions in lungs [16]. There may be development of pneumonia in the later stages that leads to (ARDS) acute respiratory distress syndrome and severe pneumonia which follows into life-support to save the life of infected individual [17]. Generally, the HCoVs are long single-stranded positive-sense RNA viruses (30,000 bp). HCoVs characterize by

two groups of proteins; non-structural proteins and the structural proteins as RNA dependent RNA polymerase (RdRp) (nsp12) [18].

2.2 Therapeutic Interventions for Corona Virus

2.2.1 Modulation of immune system

Neither anti-viral therapeutic agents nor any effective vaccines have been approved for the treatment of any human CoV disease or COVID-19 till date. Coronaviruses like MERS and SARS are specifically capable of dampening immune responses and evading immune detection. It is not still understandable as to how COVID-19 affects the immune response [19]. During this viral disease, some host associated factors evoke the immune responses of the host against the viruses. Particularly, T cells (CD8+ & CD4+) play a critical antiviral response to raise the risk of expanding inflammation or autoimmunity and combat the pathogens [20].

In addition to that, CD8+ T cells kill the cells infected with virus and are cytotoxic. More than 80% of total inflammatory cells are CD8+ T cells in the lung's interstitial tissue in SARS-CoV cases, also show a dynamic response in reducing coronaviruses in diseased cells and prompting immune damage. However, CD4 + T cells improve the production of specific antibodies by stimulating T cell-dependent B cells [21]. Moreover, T helper cells produce pro-inflammatory cytokines through NF-kB signaling [22]. Cytokines (IL-17) convert neutrophils & monocytes to the infected spot executing swelling and stimulates other downstream cataracts of chemokines and cytokines, containing TNF-β, MCP-1, IL-1, IL-6, IL-8 and IL-21 [23]. Different research studies revealed that, a unique BH3-like region to be found in the C-terminal cytosolic field of SARS-CoV protein facilitated by Bcl-xL induced T cell apoptosis [24]. It was also revealed that response of T cell to basic proteins comprising the N, M and S is persistent, long-term and offers indication for preparing novel vaccines and drugs for SARS-CoV-2 comprised of basic viral fundamental proteins that can produce active, long lasting and dominant memory cell reactions in contradiction of virus. On the other hand, earlier researches have described a critical role of both CD4+ and CD8+ T cells in COVID-19 clearance, [25] observed that CD4+ T helper cells are compulsory for production of SARS-CoV-2 specific neutralizing antibodies. Furthermore, the

ACE2 protein attached to a human IgG Fc (ACE2-Fc) domain of SARS-CoV-2 patients can have the advantages of a conventional counteracting antibody that might be effective for the therapy of disease. Conclusively, it will be essential for the medical trials to define any side effect or reactions of ACE2-Fc therapy [26]. Uncertainty, if the function of ACE2-Fc is inhibited, then ACE2-Fc may have had a vital part in the therapy of SARS-CoV-2. Recent immunological research trials have revealed the significance of immune responses against the SARS-CoV-2, so that these immune cells can be prompted efficiently to attack on causative agents with better accuracy. In addition to the immune system, researchers have also established a possible effect of the SARS-CoV-2 in the central nervous system [27].

Recent approach to coronavirus disease management concentrates on supportive therapy. Fast public health involvements with anti-viral, antibodies or novel vaccine approaches are extremely important to contain the virus and disease transmission. COVID-19 epidemics can be limited by passive antibody therapy. Immunoglobulins or convalescent plasma have been injected as a last possibility to boost the survival ratio of patients with SARS whose situation sustained to decline in spite of treatment with pulsed methylprednisolone [28]. Moreover, many studies revealed a limited hospital stay and lesser mortality in patients cured with convalescent plasma. The administration of convalescent plasma collected from individuals who had cured from Ebola virus disease was suggested by World Health Organization as an experiential treatment throughout outbreaks in 2014 [29].

In 2015 for the treatment of Middle East respiratory syndrome coronavirus, standard operating procedures for use of convalescent plasma were established [30]. According to World Health Organization, management of SARS-CoV-2 has primarily focused on prevention of infection, case monitoring & detection and supportive therapy. On the other hand, lack of evidence, no specific anti-COVID-19 treatment is suggested. Most importantly, the recent directions give emphasis to systematic corticosteroids would not be administered regularly for the treatment of COVID-19 [29]. Research studies show that convalescent plasma obtained from patients who have cured from viral diseases may be used as a treatment without the incidence of severe contrary effects.

Therefore, it could be valuable to test the efficacy and safety of convalescent plasma transfusion in SARS-CoV-2-infected patients. Li et al., [31] described the medical characteristics & cytokine structural profile of serious patients in Wuhan, China with COVID-19 and recommended that a cytokine storm (i.e. interferon gamma-induced protein 10, higher concentrations of granulocyte-colony exciting factor, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α and tumor necrosis factor α) might be related with the severity of disease [32]. Another research report from China described that improved expression of interleukin (IL-6 & IL-2R) in serum acts to anticipate the severity and prognosis of patients with SARS-CoV-2. Furthermore, histopathological analysis of a biopsy section obtained from an expired person infected with COVID-19 showed that interstitial mononuclear inflammatory infiltrates dominated by lymphocytes, in right and left lungs [32]. Additionally, et al., [33] reported that marginal blood flow cytometric analysis revealed that the over activation of T cells accounted for the serious immune damage in the diseased person. Therefore, the cytokine storms would never be ignored in the treatment of novel COVID-19. Immunomodulatory therapy to down-regulate the cytokine storm can facilitate the insights in COVID-19 treatment [32]. In immunomodulatory therapy of infectious diseases, corticosteroids are among the most normally used medicines. However, in the treatment of COVID-19 the use of corticosteroids can cause host immune suppression and postponed viral clearance. Recently Liu et al., [34] reported that chloroquine and its derivative like hydroxychloroquine have been found effective in the cure of SARS-CoV-2. In China in February, 2020, outcomes from more than hundred COVID-19 infected patients revealed that chloroquine phosphate had better effectiveness against the virus. Additionally, their anti-inflammatory properties, antiviral and antimalarial effects have already been confirmed in the therapy of autoimmune diseases like lupus erythematosus and rheumatoid arthritis. Hydroxychloroquine and chloroquine can prevent the main histocompatibility complex class II expression, immune stimulation (reducing CD154 expression by T cells) and antigen appearance through cGAS activation of interferon genes and Toll-like receptor signaling [35]. Thus, hydroxychloroquine and chloroquine can decrease the growth of numerous pro-inflammatory cytokines, such as interferon-α, IL-6, IL-1 and tumor necrosis factor associated in the cytokine storm.

The virus completes its cycle in the five stages as; attachment, penetration, biosynthesis, maturation and release. The COVID-19 virus binds with its spine proteins (S protein) to the angiotensin exchanging enzyme-2 receptor (ACE2), [29] whose expression levels are higher in lungs, heart, ileum, kidneys and bladder could explain the involvement of multiorgan failure in COVID-19 patients [29]. Within lungs, ACE2 receptors are greatly expressed on apical aspect of lung epithelium in alveolar space [36]. 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 vial agent into the host cell [37]. The SARS-CoV-2 preferably attacks the alveolar cells type II compared to type I cells [38].

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 [39]. 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 [31]. 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 [40]. 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 that leads to severe respiratory distress syndrome & multiorgan dysfunction [41]. These events cause diffuse alveolar injury with fibrin rich hyaline membranes and a few multi-nucleated giant cells. In terminal stages of COVID-19 patients, consumption of clotting factors and stimulation of coagulation occur with resultant diffused intravascular coagulation [42]. Swollen lung parenchyma and pulmonary endothelial cells may cause the thrombi

formation. Viral sepsis is considered as among the important complications that are associated with COVID-19 is caused by dysregulated reaction of host defense system and this sepsis could also play its part in multiorgan failure [37].
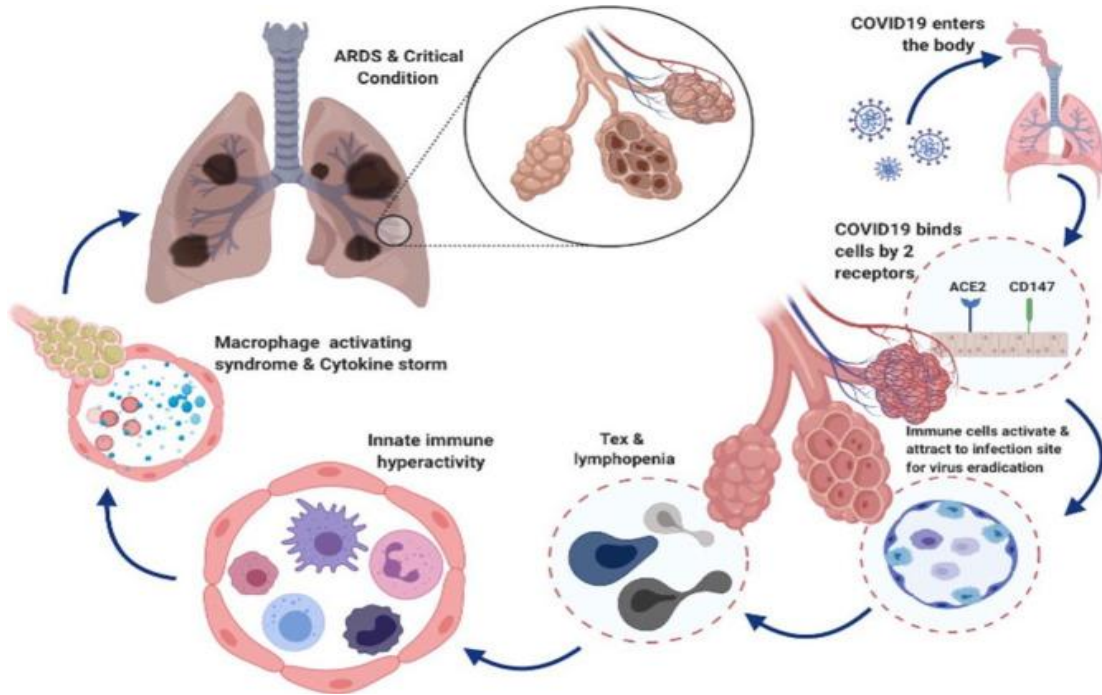

Fig. 1. Illustration indicating the pathogenesis and role of immune system in combating with viral load
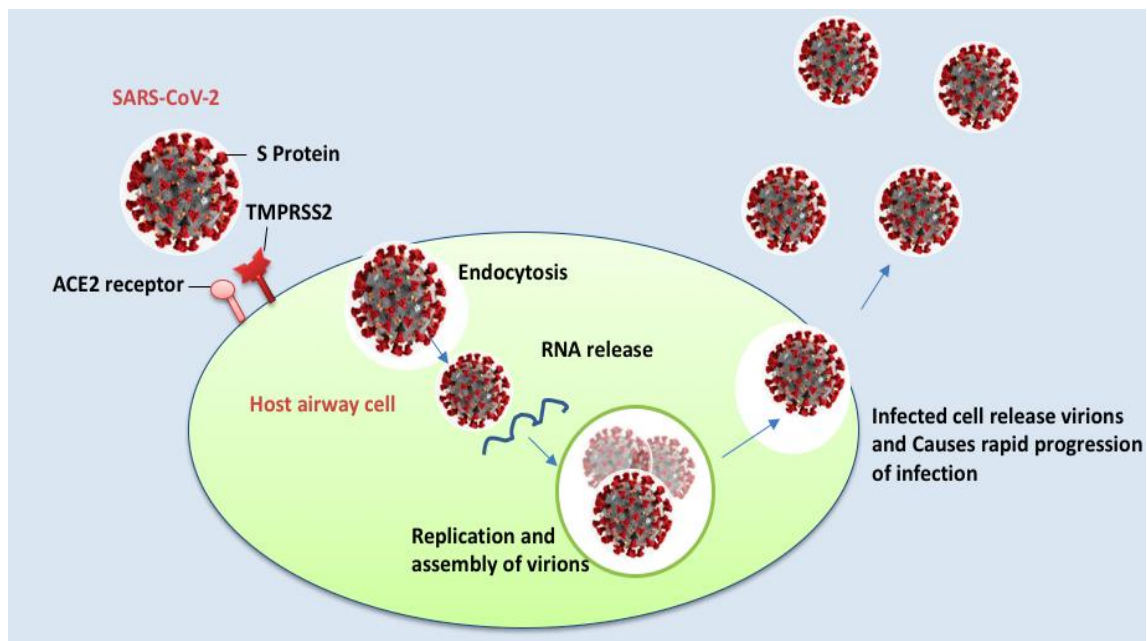

Fig. 2. SARS-CoV 2 virus infection in host cell; TMPRSS2 activates S protein of virus and cleaves ACE2 membrane receptors of host airway cell, virus enter host cell through endocytosis, releases RNA and utilize host cell machinery for replication and assembly of more viruses
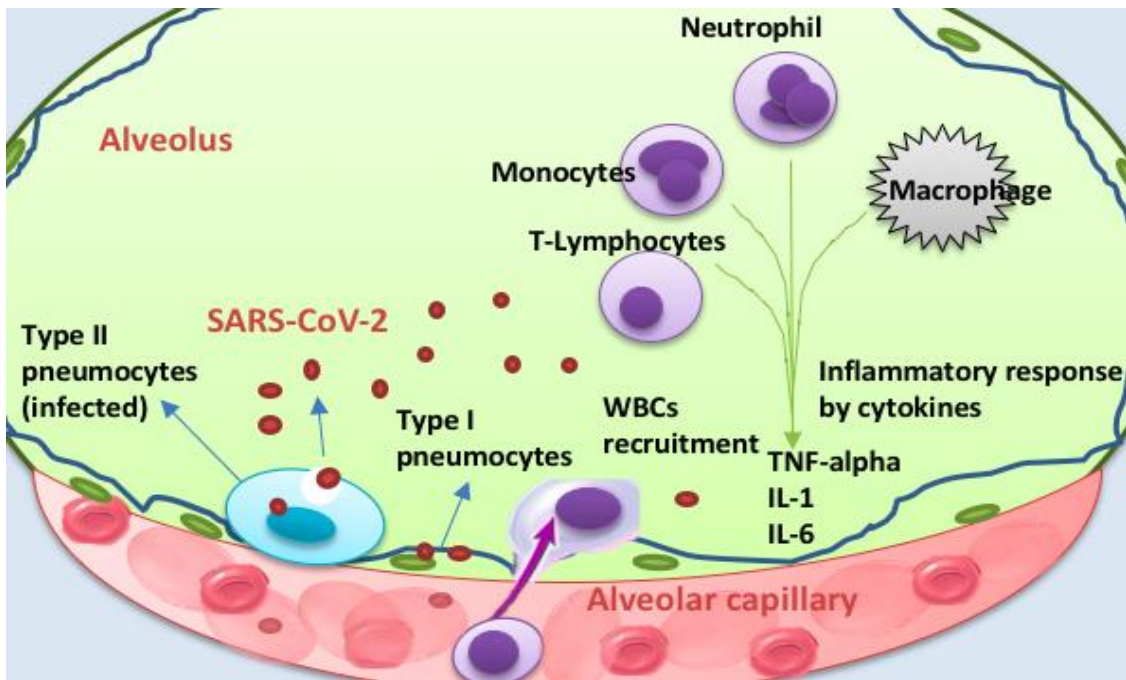
Fig. 3. Early stage SARS-CoV 2 virus infection; capillary endothelium and alveolar pneumocytes (type I and II) are infected with SARS-CoV 2 virus and inflammatory response initiates via cytokine release by recruitment of monocytes, neutrophil and T-lymphocytes
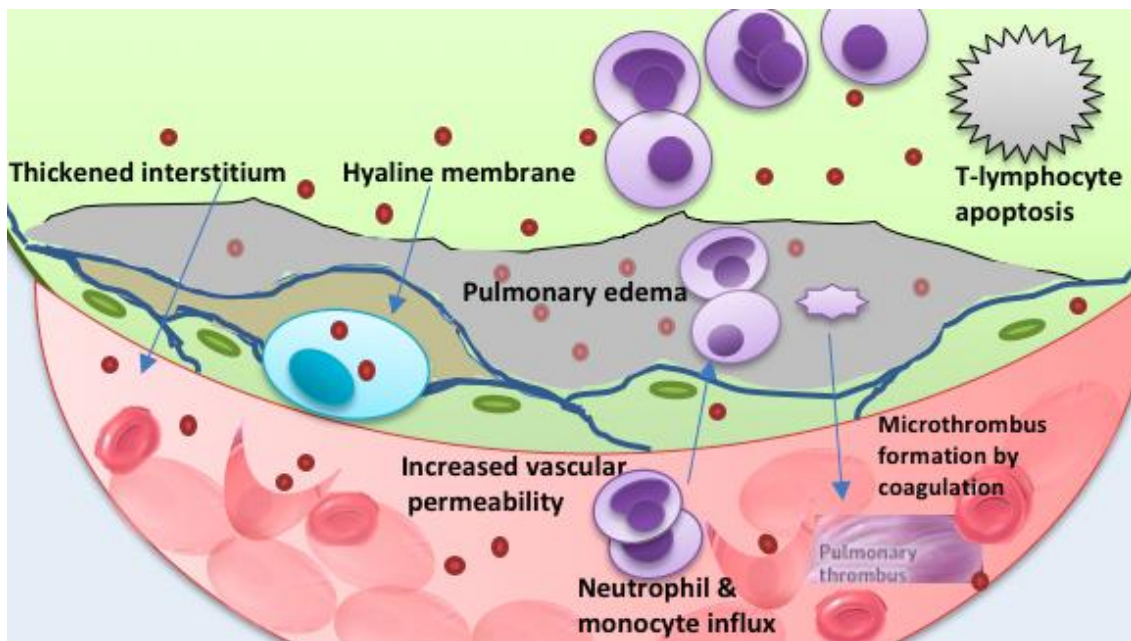

Fig. 4. Increased vascular permeability and alveolar interstitial thickening due to continues inflammatory response

2.2.2 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 [43].

The patients in which the COVID-19 has just spread to 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 reduce and mitigate the transmission of infection 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 sepsis, severe respiratory distress syndrome, multiorgan failure and septic shock including cardiac and renal failure [44], 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 described by sudden commencement of hypoxemic respiratory failure along with bilateral infiltrates [45]. 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 [46]. 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% [47]. 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 [48]. Similarly, those individuals who suffer from co-infections should be empirically treated with antimicrobial within an hour of their assessment.

2.3 Availability of Targeted Drugs

Ivermectin is a potential drug of choice against parasites and it is also proposed for treatment against SARS-CoV-2 [49]. 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 [50]. Ivermectin showed a great anti-viral activity (broad spectrum) in vitro and it prevents COVID-19 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 [51]. Remdesivir has greater effects on SARS-CoV-2 as it is an RNA virus and has great potential candidate drug for the therapy of COVID-19 [52]. The mode of action of Remdesivir which targets the divergent RNA-dependent RNA polymerase (RdRp) of 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% [53]. 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 [54]. 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 [55]. 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 effectiveness for the treatment of COVID-19. MK-4482 shows more better results than that of remdesivir for the treatment of patients infected with COVID-19 and its trials have been conducted in mice [56].

3. CONCLUSION

The COVID-19 pandemic is an ongoing problem that disturbs the normal living of most of the people all over the world. Many countries of the world are now closed or semi-closed, strict transportation and travel regulations have been passed, international dealings have been suffered seriously and humans are exposed to an exceptional regime, which has changed the normal phenomenon of life. Immune system plays a significant role in combating COVID-19, unexpectedly it could also be dangerous. Now a day's target drugs are available and due to

limitation of choice being catagories as best treatment for corona virus. It is compulsory to find effective drugs and vaccines to return towards the normal situation and reduce the mortality rate.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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