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COVID-19, Wide Spread and Treatment Need

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Abstract

Human coronavirus, hCoV-19, is highly pathogenic with severe pneumonia linked to rapid replication of the virus and worldwide spread. Originating in Wuhan China December 2019, the current COVID-19 epidemic has grown rapidly with individual-to-person infection expanding to become a pandemic-scale global health emergency. As a pandemic, COVID-19 has led many researchers from various areas of biomedicine to pursue approaches or therapies to handle the pandemic. COVID-2019 cure is in part based on the patient's own immune system. When the over-activated immune system kills the virus, a large number of inflammatory factors are produced which lead to severe cytokine storms. This appears that the key explanation for damage to these organs may be due to a cytokine storm caused by the virus. Current therapies available-including non-specific anti-viral, antibiotics to treat secondary bacterial infections and sepsis, and inflammatory corticosteroids-fail in serious disease where the hallmark is the COVID-19-induced cytokine storm in the lung. Until now, however, no specific treatment has been found for this disease. Thus, there is a significant unmet need for safe and efficient care.

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INTRODUCTION

Since patients were first identified in Wuhan, China in December 2019, the novel coronavirus disease 2019 (COVID-19) has developed into a global public health emergency [1]. Since then, the number of confirmed COVID-19 patients has increased sharply and is expanding not only in China but throughout the world, including Germany, South Korea, Vietnam, Singapore, Italy, and the USA [2]. COVID-2019 cure is in part based on the patient's own immune system. When the over-activated immune system kills the virus, a large number of inflammatory factors are produced which lead to severe cytokine storms [1, 3] This appears that the key explanation for damage to these organs may be due to a cytokine storm caused by the virus [3].

Many studies showed that the first step of HCoV-19 pathogenesis is that the recognition of the virus to angiotensin I by its spike protein converting enzyme 2 (ACE2) receptor [4, 5]. As with SARS-2003 [6,7], ACE2-positive cells are infected with HCoV-19. The battlefield for the novel coronavirus and immune cells may be all tissues and organs expressing ACE2. This explains why not only all compromised ICU patients suffer from acute respiratory distress syndrome but also complications from multiple organ failure syndrome such as acute myocardial injury, arrhythmia, acute kidney injury, shock and death [8].

In addition, a research team from Germany discovered that the TMPRSS2 cell serine protease for HCoV-19 Spike protein priming is also important for the entry and spread of host cells [9], as is the case with the other coronavirus (i.e. SARS-2003) [10, 11]. Inappropriately, the ACE2 receptor is widely distributed on the surface of human cells, especially the Type II alveolar cells (AT2) and capillary endothelium [12], and the TMPRSS2 highly expressed AT2 cells [11]. Nevertheless, ACE2 is reliably negative in the bone marrow, lymph nodes, thymus, and spleen, immune cells, such as T and B lymphocytes, and macrophages [11,12].

Current therapies available-including non-specific anti-viral, antibiotics to treat secondary bacterial infections and sepsis, and inflammatory corticosteroids-fail in serious disease where the hallmark is the COVID-19-induced cytokine storm in the lung, visible as inflammatory lesions with ground-glass opacity on CT scan [13,14]. Triggering of cytokines by viral infection (e.g.: IL-2, IL-6, IL-7, GSCF, IP10, MCP1, MIP1A and TNF) cause pulmonary edema, air circulation dysfunction, acute respiratory distress syndrome, acute heart injury, and sometimes secondary infection, leading to death [13]. There are currently no different medications or vaccines available to treat COVID-19-infected patients. Hence, there is a large unmet need for a safe and effective treatment for COVID-19 infected patients, especially the severe cases.

I. Repurposed Drugs for COVID-19

I.1. Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine are used in the prevention and management of malaria and used as therapeutic agents for chronic inflammatory diseases including systemic lupus erythematosus(SLE) and rheumatoid arthritis (RA) [15,16]. Chloroquine has been tested against several different infections because viruses – including SARS-CoV-2 – can be prevented in the

laboratory from entering cells contained in a dish and thereby avoid infection. Chloroquine and hydroxyl chloroquine work by preventing the entry of viruses into cells by blocking host receptor glycosylation, proteolytic processing and endosomal acidification [17,18,19]. Moreover, their immunomodulatory activity could be referred to their ability to diminish cytokine releasing [20,21,22], and suppress autophagy and lysosomal activity in host cells [23,24,25]. Dosing of chloroquine to treat COVID-19 has consisted of 500mg orally once or twice daily [26]. However, the optimal dosing regimen for hydroxyl chloroquinein COVID-19 treatment is a loading dose of 400 mg twice daily for 1 day followed by 200mg twice daily [27]. In comparison, alternative guidelines for a total daily dose of 600 mg are made based on safety and clinical experience for Whipple disease [26]. Further studies are needed to delineate the optimal dose for COVID-19

I.2. Lopinavir/ritonavir

This is a drug combination utilized against viruses like HIV. It acts through blocking a key viral proteins called “proteases”. It is challenging to assess the impact of lopinavir/ritonavir on COVID-19 management as reports are case reports and small retrospective, non-randomized cohort studies [28]. The most commonly used and studied lopinavir/ritonavir dosing regimen for CVID-19 treatment is 400mg/100 mg twice daily for up to 14 days [29]. Adverse effects of lopinavir/ritonavir comprise gastrointestinal distress such as nausea and diarrhea (upto 28%) and hepatotoxicity (2%-10%) [30]. These contrary effects in patients with COVID-19, may be aggravated by combination therapy or viral infection because approximately 20% to30% of patients have raised levels of transaminases at presentation with COVID-19 [**31]**.

I.3. Ribavirin

Ribavirin, aguanine analogue, is an intravenous antiviral drug that suppress viral RNA-dependent RNA polymerase activity. It is considered as a good candidate for COVID19 treatment due to its potent activity towards other nCoVs [30]. Though, higher concentrations. (eg,1.2 g to2.4g orally every 8 hours) and combination therapy, needed to suppress SARSCoV viral replication in vitro limits its usage [32]. Additionally, hematologic toxicity, hemolytic anemia (dose dependent side effects), and its contraindication in pregnancy limits its usage [32,33]. thus, due to its substantial toxicity, its therapeutic value for COVID-19 is limited [30].

II. Investigational Drugs for COVID-19

II.1. Remdesivir

Remdesivir, defined as GS-5734, is a monophosphate pro-drug that converted to an active C-adenosin e nucleoside triphosphate analogue after metabolism [30]. It importance during the search for appeared antimicrobial with activity against RNA viruses, such as Corona viridae and Flaviviridae and due to its low EC_{50} and host polymerase selectivity against the Ebola virus [34]. Moreover, due to its broad spectrum and low EC_{50} and EC_{90} values against nCoVs, including SARS-CoV-2 it could considered as a potent therapeutic agent for COVID-19 [14]. In murine lung infection models with MERS-CoV, remdesivir disallowed lung hemorrhage and reduced viral lung titers more than comparator agents [35]. The safety and pharmacokinetics of remdesivir were evaluated in single-and multiple-dose phase1 clinical trials [30].

II.2. Favipiravir

Favipiravir, defined as T-705, is a pro-drug of a purine nucleotide, favipiravir ribo furanosyl-5′-triphosphate. Its therapeutic activity could refer to its ability to block viral replication and suppress RNA polymerase. It has abroad activity against RNA viruses including influenza and Ebola [36]. Dose regimens for Favipiravir differ based on the type of infection. Lower EC_{50} value was noticed for influenza treatment in relative to Ebolaa ndSARS-CoV-2. Management of COVID-19 may demand raising the dose at the higher end of the dosing rang [37]. The recommended treatment regimen included (2400 mg to3000 mg every 12hours × 2 doses) followed by a maintenance dose (1200 mg to1800 mg every 12 hours). A mild adverse impact was notified combined with overall well-tolerance [38]. Clinical studied are limited due to its availability in Japan as influenza drug and its limitation in the United States thus, supporting the use of favipiravir for COVID-19 was demonstrated in limited clinical experience [30].

III. Adjunctive Therapies for COVID-19

III.1. Corticosteroids

However, corticosteroids have potential effect in reducing host inflammatory responses in the lungs, adverse effects, including the delay of viral clearance and the elevated risk of secondary infection could be an obstructer. Illuminating results for utilizing corticosteroids were obtained in several viral pneumonias while its utilization for COVID-19 needs more studies [39]. Corticosteroids have been shown to be more likely to cause bacterial infections than viral infections [40]. This could have referred to the development of several adverse effects in patients with SARS and MERS (e.g.: delayed viral clearance from the respiratory tract and blood, hyperglycemia, psychosis, and avascular necrosis) [30, 41].

III.2. Anti-cytokine or Immunomodulatory Agents

Targeting COVID-19 induced-cytokine storm that leads to immune response amplification, elevated cytokine production consequently, organ damage in the lungs and other organs by monoclonal antibodies could be a potential therapeutic strategy [42]. Targeting IL-6 which was defined as a key driver of this dysregulated inflammation by monoclonal antibodies could theoretically inhibit this process and improve clinical outcomes [43,44]. Tocilizumab, a monoclonal antibody IL-6 receptor antagonist, is FDA approved to treat RA and cytokine release syndrome following chimeric antigen receptor T-cell therapy. Profitable early results were obtained for its utilization in severe COVID-19 cases receiving one dose - (400 mg), associated with significant improvement in respiratory function, rapid effervescence, and successful discharge [45]. Several studies are carried on using IL-6 receptor antagonist (Sarilumab) (NCT04315298) [46], bevacizumab (anti–vascular endothelial growth factor medication; NCT04275414), fingolimod (immunomodulator approved for multiple sclerosis; NCT04280588), and eculizumab (antibody inhibiting terminal complement; NCT04288713) [30].

III.3. Immunoglobulin Therapy

The use of convalescent plasma or hyper-immune immunoglobulins from recovered COVID-19 patients as adjunctive therapy could have referred to the ability of their antibodies to mediate virus removal and immune clearance of

infected cells. Anecdotal reports or protocols for convalescent plasma have been reported as salvage therapy in SARS and MERS [41]. Theoretically, this therapeutic strategy could be potential in the first week of infection before activation of immune response. Certainly, a report case about treatment with convalescent plasma against COVID-19 in China was recently carried on [47]. Moreover, a case series of 3 patients with COVID-19 in Wuhan, China, treated with intravenous immunoglobulin at a dose of 0.3 to 0.5 g/kg/d for 5 days was recently published [48].

IV. MSCs Therapy for COVID-19

MSCs utilization in cell-based therapy showed effective and save outcomes especially in the immune-mediated inflammatory diseases, such as graft versus-host disease (GVHD) [49,50,51], and systemic lupus erythematosus (SLE) [52]. This effective results mediated by immunomodulatory effects and differentiation abilities of MSCs (WHO, 2020). MSCs can mediate the release of several cytokines by paracrine secretion or through direct crosstalk with immune cells, leading to immunomodulation [53]. pathogen-associated molecules such as LPS or double-stranded RNA from virus (e.g. HCoV-19) stimulated TLR receptor in MSCs leading to its activation and triggering of MSCs immunomodulatory effects [54].

A study was performed on seven patients with COVID-19 infected pneumonia in Beijing YouAn Hospital, Capital Medical University, China, and approved by the ethics committee of the hospital (LL2020-013-K). The immunomodulating function of MSCs contributed to the main efficacy outcome and the transplantation of MSCs showed impressive positive results. efficacy outcome includes reduction in plasma C-reaction protein indicating t the quick elevation of inflammation status, increase of the oxygen saturation indicating the pulmonary alveoli regained the air-change function, improvement of lymphopenia, fever and shortness of breath disappeared and Chest CT imaging showed that the ground-glass opacity and pneumonia infiltration were largely reduced after MSC transplantation [55].

Finally, development of a vaccine providing protective immunity would be needed to prevent future outbreaks of this virus. Before widespread vaccine deployment, though, a minimum of 12 to 18 months will be needed.

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