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Immunotherapeutic Strategies for COVID-19

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Mini Review

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Abstract

The severe acute respiratory syndrome coronavirus 2 associated coronavirus disease 2019 (COVID-19) illness is a syndrome of viral replication in concert with a host inflammatory response. The cytokine storm and viral evasion of cellular immune responses may play an equally important role in the pathogenesis, clinical manifestation, and outcomes of COVID-19. Systemic proinflammatory cytokines and biomarkers are elevated as the disease progresses towards its advanced stages, and correlate with worse chances of survival. Immune modulators have the potential to inhibit cytokines and treat the cytokine storm. Current mini review discuss several immune modulators such as specific immune modulators (anti-cytokines such as IL-1and IL-6 receptor antagonists, JAK inhibitors, anti-TNF-α, GM-CSF, and convalescent plasma and non-specific immune modulators, human immunoglobulin, corticosteroids, hydroxychloroquine and chloroquine.

Keywords: COVID-19; Immunotherapy; Iraq

Abbreviations: WHO: World Health Organization; SARS: Severe Acute Respiratory Syndrome; MERS: Middle East Respiratory Syndrome; MERS-Cov: Middle East Respiratory Syndrome Related Corona Virus; SARS-Cov: Sever Acute Respiratory Syndrome Related Corona Virus; ARDS: Acute Respiratory Distress Syndrome; GM-CSF: Granulocyte Macrophage Colony Stimulating Factor; STAT: Signal Transducer and Activator of Transcription; BALF: Bronchoalveolar Lavage Fluid; MSCs: Mesenchymal Stem Cells; IVIG: Intravenous Immunoglobulin.

Introduction

Coronaviruses make up a large family of viruses that can infect birds and mammals, including humans, according to world health organization (WHO). These viruses have been responsible for several out-breaks around the world, including the severe acute respiratory syndrome (SARS) pandemic of 2002-2003 and the Middle East respiratory syndrome (MERS) outbreak in South Korea in 2015. Most recently, a novel coronavirus (SARS-CoV-2; COVID-19) triggered an outbreak in China in December 2019, sparking international concern. While some corona viruses have caused devastating epidemics, others cause mild to moderate respiratory infections, like the common cold [1].

The first recorded case of COVID-19 (also colloquially known as "coronavirus") was recorded in Iraq on 24-February, in the city of Najaf. Since then, additional cases have been confirmed, with the majority of affected persons in federal Iraq and approximately one-quarter of confirmed cases in the Kurdistan Region of Iraq. Eight fatalities due to COVID-19 have been confirmed [2].

Coronaviruses belong to the subfamily Coronavirinae in the family Coronaviridae. Different types of human coronaviruses vary in how severe the resulting disease becomes, and how far they can spread. Doctors currently recognize seven types of coronavirus that can infect humans [3,4]. The first group belongs to genus alpha corona virus which includes alpha corona virus 1, human corona virus 229E and human corona virus NL63. The second group belongs to genus Beta corona virus which include Beta corona virus 1 (human corona virus OC43), human corona

virus HKU1, Middle East respiratory syndrome related corona virus (MERS-CoV), Sever acute respiratory syndrome related corona virus (SARS-CoV), Sever acute respiratory syndrome related corona virus (SARS-CoV2).

Human Coronaviruses Infection

Six species of human coronaviruses are known, with one species subdivided into two different strains, making seven strains of human coronaviruses altogether. (HCoV 229E, HCoV NL63; HCoV OC43; HCoV HKU1) human coronaviruses produce symptoms that are generally mild and continually circulate in the human population and produce mild symptoms of the common cold in adults and children worldwide. These coronaviruses cause about 15% of common colds, while 40 to 50% of colds are caused by rhinoviruses [5] they have a seasonal incidence occurring in the winter months in temperate climates [6].

MERS-CoV; SARS-CoV; SARS-CoV2 human coronaviruses produce severe symptoms. SARS-CoV virus was identified as the causative agent of the global pandemic SARS, which led to substantial morbidity and mortality. An outbreak of MERS-CoV emerged in 2012 [7]. Camels were identified as an intermediate host for MERS-CoV [8]. Patients with SARS or MERS present with a variety of clinical features, ranging from asymptomatic or mild respiratory illness to fulminant severe acute respiratory distress syndrome (ARDS) with extra-pulmonary complications [9].

SARS-CoV-2 belongs to the genus of Beta corona virus, and on the basis of evolutionary analysis, is most similar to the SARS-like coronavirus from the Chinese horseshoe bat, with a nucleic acid homology of 84% [10]. SARS-CoV-2 has 78% similarity with SARS-CoV and 50% with MERS-CoV, at the nucleic acid level [10]. Several reports suggested that snakes, mink, and pangolins could be intermediate hosts, based on codon preference and viral infection patterns [11]. At the onset of the COVID-19 pandemic, the main symptoms were fever (98%), cough (76%), and myalgia (44%) [12]. About half of the patients developed breathing difficulty in one week and ARDS, acute cardiac injury, secondary infections. The diagnosis of the disease mainly de-pends on SARS-CoV-2 RNA detection in nasopharyngeal swab by real-time polymerase chain reaction, epidemiological history, clinical manifestations, and lung imaging.

Immunotherapy Strategies for COVID-19

Cytokines-Modulating Drugs

IL-6 is a key inflammatory cytokine that has a critical part in inflammatory cytokine storm and is elevated in patients with COVID-19 [13,14]. Tocilizumab, a recombinant humanized monoclonal antibody against the IL-6 receptor, used for treatment of autoimmune diseases, such as rheumatoid arthritis [15]. In patients with COVID-19, IL-6-producing monocytes were significantly increased in lung tissue under the direct effect of granulocyte macrophage colony stimulating factor (GM-CSF) and IFNγ producing Th1 [16].

Tocilizumab used for treatment of cytokine storm in patients with comorbidities. Tocilizumab binds to both the membrane and soluble forms of IL-6 receptor, thereby suppressing the JAK-signal transducer and activator of transcription (STAT) signaling pathway and production of downstream inflammatory molecules [17]. Experimental studies reported that IL-6 is required for the viral clearance from lung and control of pulmonary inflammation. For this reason it should be used with extreme care and caution due to blocking IL-6 could interfere with viral clearance or exacerbate lung inflammation [18].

Blockade of the IL-1 pathway is used for the treatment of some hyperinflammation conditions. The IL-1 receptor antagonist (anakinra) is works by inhibiting the proinflammatory cytokines IL-1α and IL-1β and approved for rheumatoid arthritis. Treatment of severe sepsis with anakinra was associated with a significantly lower mortality in patients who were septic with hyperinflammation, without increased adverse events [19]. As IL-1 was reported to be increased in some patients with COVID-19, blockade of IL-1 via using of anakinra seems a reasonable approach for the treatment of hyperinflammation in COVID-19 patients [20]. Emapalumab an anti-interferon (IFN)-γ antibody, was used for treatment of hyper inflammatory syndrome caused by the cytokine storm in patients with COVID-19 [21].

Granulocyte–Macrophage Colony Stimulating Factor

GM-CSF is a pleiotropic growth factor and proinflammatory cytokine that is released from alveolar epithelial cells and has been shown to drive pulmonary host defense function against pathogens, including the influenza virus. GM-CSF stimulates epithelial repair, including epithelial proliferation and barrier restoration, through direct interaction with the alveolar epithelial cells, thereby providing a lung-protective effect [22]. In patients with ARDS, elevated GM-CSF levels in the bronchoalveolar lavage fluid (BALF) are associated with antiapoptotic effects and improved epithelial barrier integrity and survival. Studies have shown that GM-CSF can have a dual role as a proinflammatory and regula-tory cytokine, depending on the dose and presence of other relevant cytokines [23].

Recent studies on COVID-19 patients show that increased

levels of GM-CSF contribute to the im-munopathology of ARDS. Given their effects in driving immune functions, GMCSFs may confer benefit to COVID-19 patients by providing the stimulus to restore pulmonary hemostasis and repair. Sargramostim (Leukine®), the only FDA-approved GM-CSF, is a yeast-derived recombinant humanized GM-CSF (rhuGMCSF) that is currently being investigated as an adjuvant therapy for the management of COVID-19 associated with acute hypoxic respiratory failure and ARDS.

Targeted Synthetic Immunosuppressants

Baricitinib is a small molecule compound that selectively inhibits the kinase activity of Janus kinase 1and 2 (JAK1 and JAK2). Baricitinib can be used in combination with one or more TNF inhibitors and is approved for the treatment of rheumatoid arthritis 48 [24]. Baricitinib might effectively reduce the ability of SARS-CoV-2 virus to infect lung cells. SARS-CoV-2 binds to the ACE2 receptor on host cells and enters lung cells through receptor-mediated endocytosis. High concentrations of ACE2 expression on pulmonary AT2 alveolar epithelial cells makes these cells particularly susceptible to SARS-CoV-2 infection [25]. In addition, baricitinib can also bind to cyclin G-related kinases, which also regulate receptor-mediated endocytosis [26]. Baricitinib might be preferred over other JAK-STAT signaling inhibitors, given its once-daily dosing and acceptable adverse effect profile. Additionally, its low plasma protein binding properties and minimal interaction with CYP enzymes and drug transporters allows for well-tolerated concomitant use of baricitinib with the direct-acting antivirals (e.g. remdesivir) and other drugs [27]. However, the use of baricitinib is associated with increased thromboembolic events, which is concerning given that COVID19 patients are at risk of developing these events [28]. The immunosuppressive function of baricitinib might also be of benefit to the hyperactive immune status in severe cases of COVID-19 where immune-mediated lung injury and ARDS might occur.

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine initially used as antimalarial drugs and have been widely used in treatment of systemic lupus erythematosus and other immunological diseases [29]. The mechanism of action of hydroxychloroquine is diverse and includes anti-inflammatory action, immune regulation, anti-infection, anti-tumour, metabolic regulation, and antithrom-bosis. Chloroquine has been shown to have anticoronavirus effects in vitro. Based on this, and the immunoregulatory actions of these drugs, chloroquine and hydroxychloroquine were proposed in the treatment of COVID-19. These drugs increase the endosomal pH required for SARS-CoV-2 endocytosis and cell fusion. Chloroquine interferes with the glycosylation of ACE2, which is required for virus attachment to host cells [30].

Chloroquine was first reported in 2020 to be a potent inhibitor of COVID-19 using an in vitro SARS-CoV-2- infected Vero-E6 cell culture model [31]. Hydroxychloroquine is a derivative of chloroquine that has similar pharmacokinetics and mechanism of action as chloroquine, but substantially fewer side-effects [32]. Compared with other immunosuppressant drugs such as methotrexate, the use of hydroxychloroquine and chloroquine is associated with a reduced risk of infection, even with chronic use. Therefore, hydroxychloroquine is more commonly used in patients with rheumatic diseases and other conditions. Although it takes 1–3 months for hydroxychloroquine and chloroquine to fully take effect in patients with rheumatic disease, the drugs' anti-viral effect is relatively rapid.

Hydroxychloroquine treatment as short as 3 days was shown to accelerate virus clearance treatment in patients with COVID-19 and azithromycin reinforced the anti-viral effect [33]. Notably, treatment in patients with COVID-19 might cause cardio toxicity, especially when used at a high dose. Therefore, results from ongoing trials are required to assess the efficacy and safety of hydroxychloroquine in COVID-19 [34].

Glucocorticoids

Glucocorticoids and their synthetic analogues have been widely used in rheumatic disease to control auto-immune response [35]. Due to their rapid immunosuppressive effect, glucocorticoids are frequently used in hyperinflammatory syndromes, such as ARDS. In patients with ARDS, glucocorticoid treatment improves oxygen saturation, inflammatory markers, ICU length of stay, and ventilator-free days, although its effect on mortality was not consistent between trials. In coronavirus disease, inflammation induced lung injury and ARDS are associated with adverse outcomes. Histological investigations showed severe lung inflammation and diffuse alveolar damage in patients with coronavirus disease. Therefore, corticosteroids are commonly used in severe cases of coronavirus disease including SARS, MERS, and COVID-19 to control immune mediated damage of lung tissue. However, clinical evidence has not supported a beneficial effect of glucocorticoids in coronavirus illness [36].

Leflunomide

Leflunomide is a low-molecular weight, synthetic, oral anti-rheumatic drug. The mechanism of its action includes inhibition of pyrimidine synthesis, inhibition of protein tyrosine stimulation, inhibition of nuclear factor

kappa beta, and anti-tumour effects. Leflunomide has immunosuppressive function, used in organ transplantation and inhibits virus replication [37]. The active metabolite of leflunomide protects umbilical cord epithelial cells and fibroblasts from infection with human cytomegalovirus. There is currently a clinical trial aiming to evaluate the efficacy and safety of oral leflunomide tablets against pneumonia caused by SARS-CoV-2.

Thalidomide

Thalidomide has both antiinflammatory and anti-proliferative activity has been used in viral infections. Thalidomide has immunomodulatory and immune remodeling effects by inhibiting TNF, another critical cytokine in COVID-19-associated lung injury. Thalidomide can treat pulmo-nary interstitial fibrosis and combat cytokine storm and has potential therapeutic value of in viral infection [38]. Concentrations of IL-6, IL-10, and IFNγ all returned to normal range after 6 days of treatment of patient with severe COVID-19 with thalidomide, SARS-CoV-2 tests in swab specimens were negative after 1 week of treatment, and lung lesions disappeared 12 days after treatment [39].

Mesenchymal Stem Cells Therapy

Mesenchymal stem cells (MSCs) are of increased importance in inflammatory disease due to their anti-inflammatory properties. Animal experiments showed that MSC treatment was able to reduce influenza A H5N1-induced acute lung injury in vivo [40]. Stem cells are able to suppress the activities of viruses via Chaf1amediated and Sumo2-mediated epigenetic regulation [41]. Clinical trials have confirmed the safety of MSC therapy in patients with ARDS, and have shown beneficial effects [42]. However lack of clarity with regard to optimal dose and route of MSC delivery, difficulties in large-scale production and cryopreservation, and the potential for substantial variability, limited it's used in clinical setting.

Convalescent Plasma

Convalescent plasma from patients who have recovered from SARS-CoV-2 infection has also been pro-posed as a potential treatment for COVID-19. Convalescent plasma has been used in many severe infections such as SARS, MERS, and Ebola, as one of the few therapeutic strategies in the absence of vaccines or other specific treatments [43]. The efficacy of such therapy, especially in COVID-19, is being evaluated in ongoing trials.

Human Immunoglobulin

Intravenous immunoglobulin (IVIG) contains immunoglobulin G of all subclasses obtained from pooled human plasma [44]. IVIG has been used to provide immunity to viral infections [45], including SARS. The mechanisms of action of IVIG are complex, and several mechanisms might account for its therapeutic benefit [46]. IVIG can inhibit the activation and functions of various innate immune cells, and can neutralize activated complement components. It also impacts the adaptive immune system by modulating B-cell functions and plasma cells, regulating regulatory T cells and effector T cells such as T-helper (Th) 1 and Th17 subsets, and inhibiting inflammatory cytokines. It has also been proposed that IVIG can exert anti-inflammatory action by saturating Fcγ receptor binding, and binding to antiviral antibodies and proinflammatory cytokines. The use of commercially available non-SARS-CoV-2-specifc IVIG was not recommended for treatment of COVID-19 because the current IVIG preparations are not likely to contain SARS-CoV-2 antibodies [47].

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