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COVID-19 Treatment Options and Their Mechanism of Action up to Now: An Overview of Clinical Trials

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ABSTRACT

Novel coronavirus causes the outbreak of COVID-19. There is still no verified treatment regimen against this novel virus; however, different drugs and compounds have been tested against it. Ample proposals have led to a good understanding of pathogenesis and drug efficacy against the novel virus disease. Excess systemic inflammation, which is described as cytokine storm, in the severe cases of COVID-19 can pass through the blood-brain barrier, enter the brain tissue, and activate the microglial cells and oligodenritcytes. Activation of the microglia cells and oligodenritcytes can increase generation of reactive oxygen species in the brain. Excess generation of reactive oxygen species can in turn increase neuro-inflammation in some cases of patients with COVID-19. Treatment of COVID-19 is far from clear. Today, some antiviral drugs such as remdisivir, favipiravir, ribavirin, kaletra, and arbidol are being tested against the disease. Besides these drugs, corticosteroids, anti-malaria drugs (such as chloroquine family), anticoagulants (such as heparin or enoxaparin) are repurposed. In this paper, first we explained the pathogenesis of COVID-19 particles, particularly in the brain. Second, we reviewed recent treatment options up to now, including interferon therapy, convalescent plasma exchange, plasmapheresis, immunoglobin therapy, and use of specified monoclonal anti-bodies in COVID-19 patients.

Keywords: COVID-19, Plasma Therapy, Immunoglobin Therapy, Interferon, Nucleoside Analogs

Introduction

Coronaviruses are known as a common cause of respiratory infectious disease in mammals and birds. They can cause gastrointestinal disorders, and also hepatic and neurologic problems. Coronavirus particles are transmitted to the respiratory system via aerosols and oral-fecal routes. This family of viruses was discovered in the 1960s. They are distinguished by their large positive single-strand non-segmented RNA, which are the largest among all RNA viruses [1]. In late December 2019, patients with pneumonia of unknown cause were reported in Wuhan, Hubei Province, China. These patients, directly or indirectly, were related to seafood and wet animal wholesale market. After using unbiased sequencing in samples from patients with pneumonia, human airway epithelial cells showed isolation of a novel coronavirus. It is called 2019-nCoV or SARS-Cov-2 and the disease is called COVID-19 [2]. It has been reported that alpha and beta coronaviruses are two species of coronavirus, which mainly infect mammals, whereas delta and gamma species are mostly distributed among birds. Four human species, including HCoV-229E, HCoV-NL63 of alpha viruses and HCoV-HKU1, HCoV-OC43 of beta viruses cause common cold in humans. There are three more species that cause zoonotic disease, SARS-CoV, MERS-CoV, and novel SARS-CoV2. These species are distinguished by protein sequencing; however, they have similar structure [3]. Both SARS-CoV and MERS-CoV previously caused pandemic diseases across the world in 2003 and 2012, respectively. It has been reported that the highest mortality rate belongs to MERS-CoV (35.67%) followed by SARS-CoV (9.6%) [4, 5], which means COVID-19 has the least mortality. Today, despite the classical symptoms of COVID-19 particles, COVID-19 patients may present with several neurological symptoms

(T). Indeed, central and peripheral nervous system disorders can develop in patients with COVID-19. These disorders are influenced by patient age, sex and pre-existing comorbidities. It has been reported that the existence of the IgG antibodies against COVID-19 spike protein and also inflammatory markers in the cerebrospinal fluid of patients with encephalopathy (R). In the present study, we first reviewed the pathogenesis and virology of COVID-19 particles. Next, we focused on some pharmacological agents for treatment of COVID-19.

Pathogenesis

COVID-19 particles can induce multi-organ dysfunction, including lungs, the liver, kidney, blood cells, and heart disorders. The most common signs of COVID-19 are non-productive cough, dyspnea and fever. It is well accepted that cytokine storm, which is excess production of pro-inflammatory cytokine, has a critical role in multi-organ dysfunction [6]. In the majority of patients with COVID-19, lung fibrosis leads to low O2 saturation of blood, which is a good marker for the recognition of severity of the disease. Furthermore, cytokine storm is involved in the pathological arterial and venous thromboses in patients with COVID-19. Excess generation of inflammatory cytokines can induce vascular thrombosis via (1) induction of tissue factor (TF) in mononuclear cells; (2) initiating acute endothelial cell activation; (3) activation of acute phase response and high generation of fibrinogen by hepatocytes; and (4) increased activation of platelet and aggregation [7]. Additionally, hyper-coagulable state in patients with COVID-19 increases the risk of stroke in infected persons. Although the mechanisms of hemorrhagic strokes in the patients with COVID-19 are far from clear, it is likely that the binding of the COVID-19 particles to ACE2 receptors damages intracranial arteries directly, leading to arterial and venous wall rupture [8]. ACE2 receptors are expressed in endothelial and arterial smooth muscle cells in the brain. Moreover, cytokine storm can induce hemorrhagic strokes in patients with COVID-19. Excess production of inflammatory cytokine can damage blood-brain barrier, leading to acute necrotizing encephalopathy in COVID-19 patients [8]. Taken together, hyper-coagulable state and neurovascular involvement worsen the clinical outcome of patients with COVID-19 infection. Today, it is well accepted that COVID-19 particles can cross the blood-brain barrier and directly exert neuroinvasive properties. Four pathways are suggested for the transmission of COVID-19 particles to the brain, including (1) olfactory epithelium, (2) cellular invasion, (3) microvascular endothelial cells of blood-brain barrier structure, and (4) trans-synaptic transmission via peripheral nerves [9]. Several neurological signs have been reported in patients with COVID-19 infection, including headache, loss of the ability to speak (aphasia), lethargy, confusion, dizziness, impaired consciousness, ataxia, epilepsy, and disorientation signs [9]. The central nervous system and blood-brain barrier are closely associated with the elevated circulating levels of inflammatory cytokines. It is suggested that inflammatory cytokines can increase the generation of reactive oxygen species via activation of astrocytes and glial cells. Additionally, COVID-19 leads to several cases with the demyelinating Guillain-Barré syndrome [10]. It is well accepted that oligodendrocytes can be infected, leading to prolonged neuro-inflammation. Therefore, both reactive oxygen species and peripheral cytokine storm activate microglia cells and oligodendrocytes. Excess activation of microglia cells and oligodendrocytes lead to increased generation of cytokine markers in the brain, resulting in encephalopathy in some cases of COVID-19 [10].

Virology

Coronaviruses are named because of their crown-shaped particles. Its large RNA is the sign of its complicated replication process with lots of unknown proteins involved. Coronaviruses are enveloped, positive-sense, single-strand, non-segmented RNA viruses. They are mainly composed of four structural proteins and a genome. The main proteins are spike (S), envelope (E), membrane (M), and nucleocapsid (N). This structure is also used in laboratory diagnostic tests [11]. The envelope of coronaviruses is made of three proteins: S, M, and E. The S glycoprotein has an important role in the adhesion, cell entry, and viral camouflage. It is in the center of attention of scientists for repurposing past drugs or designing new agents to reduce virulence abilities. The S protein consists of two parts, including S1 and S2. The receptor-binding domain is located on the top of S1 part. The M glycoprotein is the biggest protein of the virus. It gives shape to the particle [11, 12]. The E protein is a thin layer over the virus. The function of E protein is far from clear. The N protein is different from those ofthe subfamilies of coronavirus. It is bonded to RNA. Additionally, it conducts dimerization of the virus [10, 11]. COVID-19 particles use the ACE2 receptor for cell entry [11]. Recent studies have shown that the novel coronavirus uses serine protease TMPRSS2 receptor for S priming additionally. Furthermore, CD147 receptor is still under evaluation [13]. Knowledge of the receptor and pathophysiology of the virus suggests repurposing of past drugs and better methods to stop the outbreak. In the present study, we will review some recommended agents for the treatment of COVID-19.

Nucleoside analogs

Nucleoside analogs (NA) are a wide spectrum of primarily anti-viral drugs, which are used for the management of many viral diseases in humans including human immunodeficiency virus, cytomegalovirus, heaptitis B virus, and herpes simplex virus. They usually interfere with virus replication via inhibiting virus polymerases such as RNA or DNA despondent RNA polymerase. As these drugs affect viral polymerases and not human polymerases they are generally safe and well-tolerated. Recently, some NAs are suggested for repurposing treatment of COVID-19, including ribavirin, favipiravir, remdisivir, and galidesivir [14]. Favipiravir is an approved drug against influenza in Japan. It inhibits virus replication via acting as a purine analog in RNA despondent RNA polymerase of viruses. When it enters the infected cells, it changes to favipiravir-RTP via being

phosphoribosylated and recognized as a purine nucleotide leading to disturbance of replication [15]. Ribavirin is a guanosine analog. Three mechanisms of action are mentioned for this drug: (1) inhibition of inosine and monophosphate dehydrogenase, (2) immunomodulatory effects, and (3) incorporation as a mutagenic nucleoside by the viral RNA polymerase [16]. It is approved as an option for the management of hepatitis C virus and some other RNA virus disease [17]. It has been reported that ribavirin can effectively treat COVID-19 [18]. However, Yuan and colleagues have shown no effectivity difference between interferon-α + lopinavir/ritonavir + ribavirin and interferon-α + lopinavir/ritonavir regimens in the outcome of patients with COVID-19 [19]. Remdesivir (GS-5734) is a broad-spectrum antiviral agent subtype of nucleotide analog prodrugs. Remdesivir is activated intracellularly, demonstrated as remdesivir-TP. Remdesivir-TP is an adenosine analog competing with adenosine incurporation. It is an inhibitor of RdRp of the Ebola virus and its efficacy on the RSV RdRp is under evaluation [20]. Despite its similar role against MERS-CoV and SARS-CoV, its mechanism of action is different between Ebola and coronaviruses' result of the diversity of the proteins [21, 22, 23]. Sabue Mulangu, and colleagues conducted a clinical trial that showed the drug has no effect on the treatment of the Ebola disease [24, 25]. Galidesivir is another nucleotide analog, which was designed to treat Ebola, a filovirus family member. It competes with adenosine incorporation in virus replication via inhibition of RNA polymerase. RNA strain replication terminates following galidesivir's action. Its efficacy against Ebola and some other filovirus disease is evaluated using in vitro and rodent studies [26, 27]. It is reported that tick-borne encephalitis virus is sensitive to galidesivir, in this case, clinical trial phase I results in an acceptable outcome [28]. Although molecular docking studies prove the interaction of this agent with COVID-19 RdRp, there is no clinical trial confirming the repurposed drug.

Umifenovir

Umifenovir, which is also called arbidol, is a broad-spectrum antiviral agent approved for treating influenza in Russia and China. It affects different steps of the virus life cycle. Arbidol eliminates virus activities of both enveloped and non-enveloped ones [29]. Its efficacy is tested by in vivo studies against orthomyxoviridae, paramyxoviridae, and some other viruses specially SARS-CoV coronavirus. Arbidol has been successfully tested against IBV as a coronavirus. The EC50/CC50 ratio equals 8.5 [30]. It has been reported that four patients were treated with a regimen (lopinavir/ritonavir, and Shufeng Jiedu Capsule: SFJDC, a traditional Chinese medicine) containing arbidol in Shanghai Public Health Clinical Center [31]. Recently, a clinical study by Chen and colleagues showed no significant difference time to improve the clinical recovery rate by 7 days between arbidol and favipiravir regimen. However, reduction of symptoms duration was effectively low in the favipiravir group versus Arbidol [32]. Another clinical trial by Deng and colleagues compared lopinavir/ritonavir regimen with and without arbidol in two groups composed of 16 and 17 patients, respectively. It is revealed that 75% of patients were treated after 7 days with multi-drugtherapy compared to 35% of the mono-therapy group. Also, chest CT scan significantly improved in the multi-drugtherapy group [33]. Additionally, in another study, 50 patients were divided into two groups. Mono-therapy of arbidol and lopinavir/ritonavir results were observed during the study. It was identified that 7 days after the admission, the virus was undetectable in 50% of the patients that had taken arbidol and 23.5% in lopinavir/ritonavir group. Within 14 days, all patients of the arbidol group were treated versus 44.1% of the other group. Arbidol treated the patients in significant shorter time than lopinavir/ritonavir [34].

Anti-malaria Drugs

Chloroquine, hydroxychloroquine, quinine, and mefloquine are anti-malaria drugs that are being repurposed against COVID-19 pandemic disease. These drugs can manage COVID-19 via inhibition of virus replication. Chloroquine derived from aminoquinoline in the 1940s, is as an alternative to quinine for malaria prevention and therapy. Chloroquine is similar to quinine but more potent against different species of plasmodium [35]. It suppresses virus replication by two means, first increasing intracellular pH (as virus replication needs acidic environment), and second altering the glycosylation of the cellular receptors of coronaviruses [36]. Chloroquine and its derivative hydroxychloroquine, which is less toxic than chloroquine itself, have been successfully repurposed for other infectious (such as HIV, Q fever, Whipple's disease, and fungal infections). Additionally, it is identified that chloroquine is useful in the treatment of auto-immune diseases, including systemic lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis,and Sjögren's syndrome. Hence, chloroquine has anti-inflammatory effects [37]. However, safety interest of drug-using should be evaluated by the authorized physician. Interaction of lopinavir/ritonavir with chloroquine leads to prolonged Q-T interval [38]. Individuals with G6PD deficiency should use this drug with close attention to complications [39]. The FDA has approved chloroquine phosphate and chloroquine hydrochloride under the names of aralen and aralen hydrochloride, respectively. The FDA issued an Emergency Use Authorization (EUA) for using hydroxychloroquine sulfate and chloroquine phosphate for certain hospitalized patients with COVID-19 on March 28, 2020. Recently, the FDA has announced a warning of hydroxychloroquine usage due to its cardiac complications. In- vitro studies in China, have suggested that chloroquine in combination with remdisivir can treat COVID-19 outcomes [23]. Another study assessed combination of chloroquine and azithromycin, an antibiotic with anti-viral features, in the management of COVID-19 patients. In an open-label non-randomized clinical trial patients were divided into two groups in the preliminary study: first taking hydroxychloroquine in comparison with the second control group. It is reported that 14 of 20 patients on day 6 post inclusion test were negative versus 2 of 16 in the control group. In another complementary the outcomes of

COVID-19 patients were evaluated in three groups, including the control group, hydroxychloroquin group, and hydroxychloroquin/azithromycin group. Post inclusion test was 12.5% negative patients inthe control group, 57.1% negative patients in Hydroxychloroquin treatment only group, and 100% treated patients in Hydroxychloroquin/azithromycin combined treatment group [40]. Another clinical study showed a mere drawback in treating with hydroxychloroquin. Among 30 PCR positive patients, 13 of 15 were negative after 7 days of taking hydroxychloroquin versus 14 of 15 taking standard care. However, the result was insignificant [41, 42].

Corticosteroids

Corticosteroids are a large number of steroid hormones produced from adrenal cortex. Regulation of immune response (inflammation), stress response, and electrolytes are massively controlled by corticosteroid secretion [43]. Corticosteroid analogs are widely used due to their immune compromising effect in medicine. This feature is mostly used to control unwanted immune system responses such as auto-immune disease or to reduce adverse effects of inflammatory responses such as hypersensitive reactions [44]. Zha and colleagues haved tested corticosteroids on 31 patients with COVID-19 in two hospitals. All patients took lopinavir/ritonavir and interferon-alpha by inhalation. They took methylprednisolone as a corticosteroid. All patients had mild condition of COVID-19 without acute respiratory distress syndrome. No corticosteroid- related effect was found between the two groups (with methylprednisolone group and without methylprednisolone group) in virus clearance time, hospital length of stay, or duration of symptoms [45]. A meta-analysis by Yang and colleagues in China has included 5270 cases from 15 articles containing SRARS-CoV, MERS-CoV, and COVID-19. Overall, analysis of mortality rate showed higher mortality rate in the patients receiving corticosteroids. However, subgroup analysis did not show the influence of the drug in SARS-CoV and MERS-CoV. Length of hospital stay was also longer in the corticosteroid group. Additionally, bacterial infection and hypokalemia were also more common in the corticosteroid group. This study suggests that patients who are severely ill may be eligible for corticosteroid receiving [46]. In another clinical trial, low dose of methylprednisolone was used orally and intravenously for mild and severe cases of COVID-19, respectively. No difference was identified in time of COVID-19 RNA clearance between the groups [47]. Additionally, WHO announced, "Do not routinely give systemic corticesteroids for the treatment of viral pneumonia outside of clinical trials,"[48] since, most of the patients admitted to ICU suffer from cytokine storm. Therefore, suppressing the immune system in critically ill patients may lead to decreasing the symptoms [49]. A retrospective study evaluated the low and medium doses of methylprednisolone on COVID-19 patients. There was no significant correlation between the time of e improvement of lung imaging and length of illness with methylprednisolone [50]. A case series of a familial cluster patient using glucocorticoids showed higher incubation period. Additionally, atypical and superinfection possibility will probably increase [51].

Lopinavir/Ritonavir

Lopinavir/Ritonavir, which is also named Kaletra, is approved by FDA for the treatment of HIV infection. It had an important role during the SARS pandemic in 2003 [52]. It acts against virus via main M protein. The M protein is an important proteinase in the virus replication process. It is also known as 3C like protein. This mechanism of Kaletra against COVID-19 is proven by several documents [53, 54]. An open-label, randomized, controlled trial in China evaluated the effectivity of lopinavir/ritonavir against standard care on severe COVID-19 patients. The researchers observed no difference in the clinical improvement. Mortality rate within 28 days of randomization was numerically lower in lopinavir/ritonavir group. Also, patients treated with lopinavir/ritonavir regimen had shorter stay length in the ICU [55]. Chen and colleagues evaluated the efficacy of lopinavir and ritonavir in the four patients with severe COVID-19 infection and also five moderately- ill patients. The five moderately -infected patients were treated with interferon alfa-2b, lopinavir and ritonavir tablets,and moxifloxacin hydrochloride. The severe cases of COVID-19 group took methylprednisolone, and high-flow nasal oxygen therapy [56]. None of the patients died. A retrospective study showed the superiority of arbidol mono-therapy over lopinavir/ritonavir therapy [34]. During the study, 47 patients with COVID-19 were divided into two groups: the control and trial groups. The patients in the trial group took lopinavir/ritonavir besides their adjuvant treatments. Adjuvant drugs consisted of interferon aerosol inhalation, arbidol, methoxyphenamine, eucalyptol limonene, pinene enteric, and moxifloxacin. Oxygen therapy was carried out whenever needed. The researchers reported that blood tests such as lymphocytes, WBC, PLT, and CPR were generally closer to normal in the trial group. in the trial group almost 8 days after admission PCR test turned negative versus 12 days in the control group which was significantly shorter [57, 58, 59].

Interferon

Interferons (INFs) are immunomodulatory proteins, a subtype of cytokines. They are signaling proteins divided into three major groups of alpha, beta, and gamma. Interferons are mostly induced by viral pathogens. Two mechanisms are involved: they can upregulate immunological cell genes such as MHC and also downregulate viral gene expression. This is ignited by secreting interferon by infected cell and its attachment to specific interferon receivers on the cell surface [60]. The INF attachment to its receptor (IFNAR) leads to the phosphorylation of several transcriptional factors that activate interferon-stimulated genes. Consequently, activation of such genes will interfere with viral replication. The efficacy of IFNs against coronaviruses is under evaluation in several studies [61]. A retrospective cohort study showed that 14 of 20 confirmed cases with MERS survived after 14 days of treatment with IFN in

comparison with 7 survived individuals of 24 in the control group. The trial group had taken oral ribavirin and pegylated IFN-alfa-2a added to supportive care. The Control group had just taken supportive cares [62]. Another open-label study assessed outcomes of patients with COVID-19 between corticosteroid mono-therapy and corticosteroid besides IFN-alfacon-1 group. Fewer patients needed intensive care units and fewer died in the group with IFN therapy. Other factors such as oxygen saturation and keratin kinase were improved following IFN therapy [63].

Immunoglobulins

Immunoglobulins (Ig) are glycoproteins, produced by plasma cells. These proteins have an important role in the adaptive humoral immunity. There are several Immunoglobulin subtypes, including IgM, IgG, IgD, IgA, and IgE. Intravenous immune globulin (IVIg), refers to highly-purified antibodies that are isolated from donated blood and administered in a large dose through the vein. It consists mostly of IgG and IgA, and cytokines and soluble receptors [64]. There are two methods for IVIg therapy. The first method is low-dose therapy as a replacement dose for antibody deficiency. The second method is high-dose therapy, which is used as immunomodulatory and anti-inflammatory. IVIg therapy was initially used for immune thrombocytopenic purpura (ITP) in children [65]. In a retrospective study, the effectivity of IVIg therapy on severely- ill patients with COVID-19 was evaluated. Reduced ventilator need and length of stay in the hospital and ICU, and mortality rate after IVIg therapy were reported. Xie and colleague reported that IVIg therapy in combination with usual antiviral drugs can decrease mortality rate of the sever cases of COVID-19 [66, 67]. A case report of a patient refusing to use ventilator while facing respiratory failure and shock accompanied by persistent diarrhea, showed clinical and radiological indices improvement immediately after plasma exchange (PE) followed by IVIg [68].

Convalescent plasma

Convalescent plasma (CP) therapy is a method of treatment in which plasma of treated patients is collected and given to severe or moderate cases of patient with COVID-19. Previously CP was used to treat many infectious diseases such as SARS, MERS, and Ebola [69-72]. To evaluate the effectivity of CP in COVID-19, neutralizing antibody titer (NAT) of the exchanging plasma should be measured; e.g. against influenza, a NAT level of ≥1:160 is recommended. Fever, chills, anaphylactic reactions, circulatory overload, and risk of transfusion-transmitted infections should be taken into consideration as complications [73]. FDA also has approved the CP therapy in the sever cases of COVID-19 [74]. In one study, 5 patients under mechanical ventilation, took methylprednisolone, and antiviral drugs. In 3 days following receiving CP, 4 patients did not show fever anymore. Also, blood oxygen saturation increased and viral load decreased by 14 days [75, 76]. Another study on 10 patients undergoing CP therapy in Mexico reported that over 8 days, PaO2 to FiO2 ratio increased, fever became better and ferritin level declined significantly [77, 78].

Monoclonal Antibodies

Monoclonal antibodies (mab) are immunoglobulins bound to the specific same epitopes. Almost all substances can be used as an epitope to produce monoclonal antibodies. Diverse mabs is suggested for treatment of patients with COVID-19. These mabs target various cells of humans besides acting against the virus itself. Tian and colleagues suggested that CR3022, as a potent mab, can bind to COVID-19 particles, leading to neutralizing the virus. Receptor binding of CR3022 is different from ACE2 receptor, although it could be developed as a candidate for treating COVID-19 [79]. Tocilizumab or atlizumab is a humanized monoclonal antibody against IL-6 receptor. It is one of the IgG1 subclass members. This drug is approved by EMA (Europe) and FDA under the name of actemra [80]. Tocilizumab can reduce cytokine storm via disrupting IL-6 inflammatory route [81, 82]. Evaluation of tocilizumab therapy on 15 COVID-19 patients was investigated by Luo and colleagues. Their results showed that the levels of CRP and IL-6 decreased markedly after the first dose of tocilizumab. the researchers found that a single dose of tocilizumab does not have enough efficiency, but repeated doses may improve the condition of patients. The combination therapy with methylprednisolone for better treatment of COVID-19 [83] is also recommended. Schleicher and colleagues treated one patient with COVID-19 accompanied by asthma by tocilizumab-/prednisone combination therapy [84]. Bevacizumab is another mab against vascular endothelial growth factor (VEGF), which is a vessel growth factor. VEGF is produced in response to hypoxia, inflammation, and infection. It is reported that targeting VEGF can decrease lung edema in COVID-19 patients [85, 86]. Since CD147 is mentioned as a receptor for COVID-19 particles entry, its specific mab could be effective against COVID-19 [87]. Meplazumab is tested by a pre-published study. This study shows the impact of mab on the time of discharge so that the virus PCR test becomes negative [88]. Anakinra is an immunosuppressive drug, a monoclonal antibody targeting interleukin 1a receptor. It is used for the treatment of systemic-onset juvenile idiopathic arthritis and adult-onset Still disease [89]. FDA approved it under the name of KINERET. Its inhibitory effects on the cytokine storm in macrophage activation syndrome is proven by Monteagudo and colleagues. Regarding the inhibitory effectsof onakinra on the cytokine storm, COVID-19 treatment with anakinra should be taken into consideration [90]. It has been reported that TNF-alpha is an important mediator in the initiation of cytokine storm [91]. Therefore, TNF blockers may be effective on outcomes of COVID-19. A case reported by Tursi and colleagues revealed that the administration of adalimumab improved severe outcomes of COVID-19. Therefore, immunosuppressants might be useful for treating COVID-19. However, it is likely that they are harmful during the disease because they can suppress the immune system against the virus [92].

Anti-coagulants

Heparin, an anticoagulant factor, is used for several conditions including deep vein thrombosis, pulmonary embolism, and anti-fibrillation [93-95]. Besides its anticoagulant feature, it is reported that it has anti-inflammatory properties [96]. Heparin can decrease COVID-19 outcomes via protecting endothelium, impacting microcircular dysfunction, and some antiviral effects [97]. A clinical trial showed that mortality rate in COVID-19 was decreased in heparin users [98]. Furthermore, it is revealed that severe cases of COVID-19 receiving mechanical ventilation improved with TF and PAI-1 therapy [99].

Conclusion

Although the high secretion of inflammatory markers, as a host anti-viral response, is required for the clearance of COVID-19 particles, excessive secretion of inflammatory markers can induce multi-organ failure and death. Today, several drugs are suggested for improving COVID-19 outcomes, but still, no drug is approved for the treatment of the disease. Today, some immunosuppressants and immune therapies in clinical trials seem to be effective against COVID-19 such as convalescent plasma exchange, interferon-alpha, monoclonal antibodies against inflammatory cytokines, and corticosteroid therapy. However, there are several limitation in the treatment of COVID-19 patients. One possible limitation of immunosuppressant therapy is its inhibitory effects on host anti-viral immune machine. Therefore, the appropriate timing of immune-suppressant infusion should be carefully considered. Unfortunately, the appropriate timing of immune-suppressant therapy is far from clear. One way to prevent the suppression of host anti-viral machine is to choose selective immunosuppressive drugs. The various ongoing clinical and experimental studies will hopefully provide the appropriate timing of immune-suppressant administration in COVID-19. However, more meta-analyses are needed to make a final decision. Many countries have published different guidance for their health care personnel, but there is not much common consent. In this emergency situation in which the disease is spreading all over the world all suggestions and ideas should be taken into close consideration.

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Conflict of Interest

Authors declared no conflict of interests.

References

1. Almeida JD, Tyrrell D. The morphology of three previously uncharacterized human respiratory viruses that grow in organ culture. J Gen Virol. 1967; 1(2):175-8. [DOI:10.1099/0022-1317-1-2-175] [PMID]
2. Zhu N, Zhang D, Wang W, et al. A Novel coronavirus from patients with pneumonia in china, 2019. N Engl J Med. 2020; 382(8):727-33. [DOI:10.1056/NEJMoa2001017] [PMID] [PMCID]
3. Fan Y, Zhao K, Shi ZL, Zhou P. Bat coronaviruses in China. Viruses. 2019; 11(3):210. [DOI:10.3390/v11030210] [PMID] [PMCID]
4. Emanuel EJ. The lessons of SARS. Ann Intern Med. 2003; 139(7):589-91. [DOI:10.7326/0003-4819-139-7-200310070-00011] [PMID]
5. Nassar MS, Bakhrebah MA, Meo SA, Alsuabeyl MS, Zaher WA. Middle East respiratory ryndrome coronavirus (MERS-CoV) infection: epidemiology, pathogenesis and clinical characteristics. Eur Rev Med Pharmacol Sci. 2018; 22(15):4956-61.
6. Henderson LA, Canna SW, Schulert GS, et al. On the alert for cytokine storm: immunopathology in COVID-19. Arthritis Rheum. 2020; 72(7): 1059-63. [DOI:10.1002/art.41285] [PMID] [PMCID]
7. Zakeri A, Jadhav AP, Sullenger BA, Nimjee SM. Ischemic stroke in COVID-19-positive patients: an overview of SARS-CoV-2 and thrombotic mechanisms for neurointerventionalist. J NeuroIntervent Surg. 2021; 13:202-06. [DOI:10.1136/neurintsurg-2020-016794] [PMID]
8. Spence JD, de Freitas GR, Pettigrew LC,et al. Mechanisms of stroke in COVID-19. Cerebrovasc Dis. 2020; 49:451-58. [DOI:10.1159/000509581] [PMID] [PMCID]
9. Sepehrinezhad A, Shahbazi A, Negahcorresponding SS. COVID-19 virus may have neuroinvasive potential and cause neurological complications: a perspective review. J Neurovirol. 2020; 16 :1-6. [DOI:10.1007/s13365-020-00851-2] [PMID] [PMCID]
10. Tremblay ME, Madore C, Bordeleau M, Tian L, Verkhratsky A. Neuropathobiology of COVID-19: The Role for Glia. Front Cell Neurosci. 2020; 14: 592214. [DOI:10.3389/fncel.2020.592214] [PMID] [PMCID]

11. Masters PS. The molecular biology of coronaviruses. Adv Virus Res. 2006; 66:193-292. [DOI:10.1016/S0065-3527(06)66005-3]
12. Prajapat M, Sarma P, Shekhar N, et al. Drug targets for corona virus: A systematic review. Indian J Pharmacol. 2020; 52(1):56-65. [DOI:10.4103/ijp.IJP_115_20] [PMID] [PMCID]
13. Wang K, Chen W, Zhou YS, et al. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. BioRxiv. 2020 (In Press). [DOI:10.1101/2020.03.14.988345]
14. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. 2019; PMID: 31643176.
15. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci. 2017; 93(7):449-63. [DOI:10.2183/pjab.93.027] [PMID] [PMCID]
16. Crotty S, Cameron C, Andino R. Ribavirin's antiviral mechanism of action: lethal mutagenesis? J Mol Med. 2002; 80(2):86-95. [DOI:10.1007/s00109-001-0308-0] [PMID]
17. Yee HS, Currie SL, Tortorice K, et al. Retreatment of hepatitis C with consensus interferon and ribavirin after nonresponse or relapse to pegylated interferon and ribavirin: a national VA clinical practice study. Dig Dis Sci. 2011; 56(8):2439-48. [DOI:10.1007/s10620-011-1746-3] [PMID]
18. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sci. 2020; 248:117477. [DOI:10.1016/j.lfs.2020.117477] [PMID] [PMCID]
19. Yuan J, Zou R, Zeng L, et al. The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected discharged patients. Inflamm Res. 2020 (In Press). [DOI:10.21203/rs.3.rs-16554/v1]
20. Tchesnokov EP, Feng JY, Porter DP, Götte M. Mechanism of inhibition of ebola virus RNA-dependent RNA polymerase by remdesivir. Viruses. 2019;11(4): 326. [DOI:10.3390/v11040326] [PMID] [PMCID]
21. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem. 2020; 295, 4773-4779. [DOI:10.1074/jbc.AC120.013056] [PMID] [PMCID]
22. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017; 9(396):eaal3653. [DOI:10.1126/scitranslmed.aal3653] [PMID] [PMCID]
23. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020; 30(3):269-71. [DOI:10.1038/s41422-020-0282-0] [PMID] [PMCID]
24. Mulangu S, Dodd LE, Davey RT, et al. A randomized, controlled trial of ebola virus disease therapeutics. N Engl J Med. 2019; 381(24):2293-303. [DOI:10.1056/NEJMoa1910993] [PMID]
25. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020; 395(10236):1569-78. [DOI:10.1016/S0140-6736(20)31022-9]
26. Warren TK, Wells J, Panchal RG, et al. Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430. Nature. 2014; 508(7496):402-5. [DOI:10.1038/nature13027] [PMID] [PMCID]
27. Westover JB, Mathis A, Taylor R, et al. Galidesivir limits Rift Valley fever virus infection and disease in Syrian golden hamsters. Antiviral Res. 2018; 156:38-45. [DOI:10.1016/j.antiviral.2018.05.013] [PMID] [PMCID]
28. Eyer L, Nougairède A, Uhlířová M, et al. An E460D substitution in the NS5 protein of tick-borne encephalitis virus confers resistance to the inhibitor galidesivir (BCX4430) and also attenuates the virus for mice. J Virol. 2019; 93(16): e00367-19. [DOI:10.1128/JVI.00367-19] [PMID] [PMCID]
29. Blaising J, Polyak SJ, Pécheur EI. Arbidol as a broad-spectrum antiviral: an update. Antiviral Res. 2014; 107:84-94. [DOI:10.1016/j.antiviral.2014.04.006] [PMID] [PMCID]
30. Brooks MJ, Burtseva EI, Ellery PJ, et al. Antiviral activity of arbidol, a broad-spectrum drug for use against respiratory viruses, varies according to test conditions. J Med Virol. 2012; 84(1):170-81. [DOI:10.1002/jmv.22234] [PMID]
31. Wang Z, Chen X, Lu Y, Chen F, Zhang W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. Biosci Trends.

2020; 14(1):64-8. [DOI:10.5582/bst.2020.01030] [PMID]

32. Chen C, Huang J, Cheng Z, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. medRxiv. 2020 (In Press). [DOI:10.1101/2020.03.17.20037432]
33. Deng L, Li C, Zeng Q, et al. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. J Infect. 2020; 81(1). [DOI:10.1016/j.jinf.2020.03.002] [PMID] [PMCID]
34. Zhu Z, Lu Z, Xu T, et al. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. J Infect. 2020. [DOI:10.1016/j.jinf.2020.03.060] [PMID] [PMCID]
35. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. 2019; PMID: 31643176.
36. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases. Lancet Infect Dis. 2003; 3(11):722-7. [DOI:10.1016/S1473-3099(03)00806-5]
37. Plantone D, Koudriavtseva T. Current and future use of chloroquine and hydroxychloroquine in infectious, immune, neoplastic, and neurological diseases: a mini-review. Clin Drug Investig. 2018; 38(8):653-71. [DOI:10.1007/s40261-018-0656-y] [PMID]
38. Sahraei Z, Shabani M, Shokouhi S, Saffaei A. Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine. Int J Antimicrob Agents. 2020:105945. [DOI:10.1016/j.ijantimicag.2020.105945] [PMID] [PMCID]
39. Jie Z, He H, Xi H, Zhi Z. Multicenter collaboration group of department of science and technology of Guangdong province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. 2020; 43(3):185-188.
40. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020; 2020:105949. [DOI:10.1016/j.ijantimicag.2020.105949] [PMID] [PMCID]
41. Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ (Med Sci). 2020; 49(2):215-19.
42. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ. 2020; 369:1849. [DOI:10.1136/bmj.m1849] [PMID] [PMCID]
43. Nussey SWS. Endocrinology: An Integrated Approach. Oxford: BIOS Scientific Publishers; 2001. [DOI:10.4324/9780203450437]
44. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. All Asth Clin Immun. 2013; 9:30. [DOI:10.1186/1710-1492-9-30] [PMID] [PMCID]
45. Zha L, Li S, Pan L, et al. Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19). Med J Aust. 2020; 212 (9): 416-20. [DOI:10.5694/mja2.50577] [PMID] [PMCID]
46. Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. J Infect. 2020; 81(1): e13-e20. [DOI:10.1016/j.jinf.2020.03.062] [PMID] [PMCID]
47. Fang X, Mei Q, Yang T, et al. Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-1. J Infect. 2020; 81(1): 147-78. https://doi.org/10.1016/j.jinf.2020.03.013 [DOI:10.1016/j.jinf.2020.03.039]
48. WHO. Clinical management of severe acute respiratory infection when COVID-19 is suspected. 2020.
49. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The perspectives of clinical immunologists from China. Clin Immunol. 2020; 214:108393. [DOI:10.1016/j.clim.2020.108393] [PMID] [PMCID]
50. Ni Qin DC, Li Yongtao, et al. Retrospective analysis of low-dose glucocorticoids on virus clearance in patients with new coronavirus pneumonia. Chinese J Clin Infect Dis. 2020.
51. Han Y, Jiang M, Xia D, et al. COVID-19 in a patient with long-term use of glucocorticoids: A study of a familial cluster. Clin Immunol. 2020; 214:108413. [DOI:10.1016/j.clim.2020.108413] [PMID] [PMCID]

52. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004; 59(3):252-6. [DOI:10.1136/thorax.2003.012658] [PMID] [PMCID]

53. Liu X, Wang XJ. Potential inhibitors against 2019-nCoV coronavirus M protease from clinically approved medicines. J Genet Genomics. 2020; 47(2):119-21. https://doi.org/10.1016/j.jgg.2020.02.001 [DOI:10.1016/j.jgg.2016.12.004] [PMID] [PMCID]

54. Yao TT, Qian JD, Zhu W-Y, Wang Y, Wang G-Q. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. J Med Virol. 2020; 92(6):556-63. [DOI:10.1002/jmv.25729] [PMID] [PMCID]

55. Cao B, Wang Y, Wen D, et al. A Trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020; 382:1787-99. [DOI:10.1056/NEJMoa2001282] [PMID] [PMCID]

56. Chen Q, Quan B, Li X, et al. A report of clinical diagnosis and treatment of nine cases of coronavirus disease 2019. J Med Virol. 2020; 92(6): 683-7. [DOI:10.1002/jmv.25755] [PMID] [PMCID]

57. Ye XT, Luo YL, Xia SC, et al. Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019. Eur Rev Med Pharmacol Sci. 2020; 24(6):3390-6.

58. Ning L, Liu L, Li W, et al. Novel Coronavirus (SARS-CoV-2) Infection in A Renal Transplant Recipient: Case Report. Am J Transplant. 2020; 20(7):1864-68. [DOI:10.1111/ajt.15897] [PMID] [PMCID]

59. Bartiromo M, Borchi B, Botta A, et al. Threatening drug-drug interaction in a kidney transplant patient with Coronavirus Disease 2019 (COVID-19). Transpl Infect Dis. 2020; 22(4):e13286. [DOI:10.1111/tid.13286] [PMID] [PMCID]

60. De Andrea M, Ravera R, Gioia D, Gariglio M, Landolfo S. The interferon system: an overview. Eur J Paediatr Neurol. 2002; 6 Suppl A:A41-6. [DOI:10.1053/ejpn.2002.0573] [PMID]

61. Sallard E, Lescure FX, Yazdanpanah Y, Mentre F, Peiffer-Smadja N. Type 1 interferons as a potential treatment against COVID-19. Antiviral Res. 2020; 178:104791. [DOI:10.1016/j.antiviral.2020.104791] [PMID] [PMCID]

62. Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. Lancet Infect Dis. 2014; 14(11):1090-5. [DOI:10.1016/S1473-3099(14)70920-X]

63. Loutfy MR, Blatt LM, Siminovitch KA, et al. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. JAMA. 2003; 290(24):3222-8. [DOI:10.1001/jama.290.24.3222] [PMID]

64. Arumugham VB, Rayi A. Intravenous Immunoglobulin (IVIG). Treasure Island (FL): StatPearls Publishing; 2020.

65. Jolles S, Sewell WAC, Misbah SA. Clinical uses of intravenous immunoglobulin. Clin Exp Immunol. 2005; 142(1):1-11. [DOI:10.1111/j.1365-2249.2005.02834.x] [PMID] [PMCID]

66. Xie Y, Cao S, Li Q, et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. J Infect. 2020; 81(2): 318-56.. [DOI:10.1016/j.jinf.2020.03.044] [PMID] [PMCID]

67. Cao W, Liu X, Bai T, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. Open Forum Infect Dis. 2020; 7(3):102. [DOI:10.1093/ofid/ofaa102] [PMID] [PMCID]

68. Shi H, Zhou C, He P, et al. Successful treatment of plasma exchange followed by intravenous immunogloblin in a critically ill patient with 2019 novel coronavirus infection. Int J Antimicrob Agents. 2020:105974. [DOI:10.1016/j.ijantimicag.2020.105974] [PMID] [PMCID]

69. Lai ST. Treatment of severe acute respiratory syndrome. Eur J Clin Microbiol Infect Dis. 2005; 24(9):583-91. [DOI:10.1007/s10096-005-0004-z] [PMID] [PMCID]

70. Soo Y, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol Infect. 2004; 10(7):676-8. [DOI:10.1111/j.1469-0691.2004.00956.x] [PMID] [PMCID]

71. Marano G, Vaglio S, Pupella S, et al. Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus. 2016; 14(2):152-7.

72. Arabi YM, Hajeer AH, Luke T, et al. Feasibility of using convalescent plasma immunotherapy for

MERS-CoV infection, Saudi Arabia. Emerg Infect Dis. 2016; 22(9):1554-61. [DOI:10.3201/eid2209.151164] [PMID] [PMCID]

73. Zhao Q, He Y. Challenges of convalescent plasma therapy on COVID-19. J Clin Virol. 2020;127:104358. [DOI:10.1016/j.jcv.2020.104358] [PMID] [PMCID]

74. Tanne JH. Covid-19: FDA approves use of convalescent plasma to treat critically ill patients. BMJ. 2020; 368:1256. [DOI:10.1136/bmj.m1256] [PMID]

75. China puts 245 COVID-19 patients on convalescent plasma therapy. 2020; 16:55.

76. Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients with COVID-19 with Convalescent Plasma. JAMA. 2020; 323(16):1582-89. [DOI:10.1001/jama.2020.4783] [PMID] [PMCID]

77. Olivares-Gazca JC, Priesca-Marín JM, Ojeda-Laguna M, et al. Infusion of convalescent plasma is associated with clinical improvement in critically ill patients with COVID-19: A Pilot Study. Rev Invest Clin. 2020;7 2(3):159-64. [DOI:10.24875/RIC.20000237] [PMID]

78. Cunningham AC, Goh HP, Koh D. Treatment of COVID-19: Old tricks for new challenges. Critical Care. 2020; 24(1). [DOI:10.1186/s13054-020-2818-6] [PMID] [PMCID]

79. Tian X, Li C, Huang A, et al. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerg Microbes Infect. 2020; 9(1):382-5. [DOI:10.1080/22221751.2020.1729069] [PMID] [PMCID]

80. Venkiteshwaran A. Tocilizumab. mAbs. 2009; 1(5):432-8. [DOI:10.4161/mabs.1.5.9497] [PMID] [PMCID]

81. Fu B, Xu X, Wei H. Why tocilizumab could be an effective treatment for severe COVID-19? J Transl Med. 2020; 18(1):164. [DOI:10.1186/s12967-020-02339-3] [PMID] [PMCID]

82. Zhang C, Wu Z, Li JW, Zhao H, Wang G-Q. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents. 2020; 55(5):105954. [DOI:10.1016/j.ijantimicag.2020.105954] [PMID] [PMCID]

83. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. J Med Virol. 2020; 92(7): 814-18. [DOI:10.1002/jmv.25801] [PMID] [PMCID]

84. Schleicher GK, Lowman W, Richards GA. Case study: a patient with asthma, Covid-19 pneumonia and cytokine release syndrome treated with corticosteroids and tocilizumab. Wits J Clin Med. 2020; 2(1):47-52. [DOI:10.18772/26180197.2020.v2nSIa9] [PMCID]

85. Wang Y, Fei D, Vanderlaan M, Song A. Biological activity of bevacizumab, a humanized anti-VEGF antibody in vitro. Angiogenesis. 2004; 7(4):335-45. [DOI:10.1007/s10456-004-8272-2] [PMID]

86. Rosa SGV, Santos WC. Clinical trials on drug repositioning for COVID-19 treatment. Rev Panam Salud Publica. 2020; 44: e40. [DOI:10.26633/RPSP.2020.40] [PMID] [PMCID]

87. Ulrich H, Pillat MM. CD147 as a Target for COVID-19 treatment: suggested effects of azithromycin and stem cell engagement. Stem Cell Rev Rep. 2020; 1-7. [DOI:10.1007/s12015-020-09976-7] [PMID] [PMCID]

88. Bian H, Zheng Z-H, Wei D, et al. Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial. medRxiv. 2020 (In Press). [DOI:10.1101/2020.03.21.20040691]

89. Lequerré T, Quartier P, Rosellini D, et al. Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. Ann Rheum Dis. 2008; 67(3):302-8. [DOI:10.1136/ard.2007.076034] [PMID]

90. Monteagudo LA, Boothby A, Gertner E. Continuous intravenous anakinra infusion to calm the cytokine storm in macrophage activation syndrome. ACR Open Rheumatol. 2020; 2(5): 276-82. [DOI:10.1002/acr2.11135] [PMID] [PMCID]

91. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020; 146(1): 110-18. [DOI:10.1016/j.jaci.2020.04.006] [PMID] [PMCID]

92. Tursi A, Angarano G, Monno L, et al. Covid-19 infection in Crohn's disease under treatment with adalimumab. Gut. 2020; 2020:321240. [DOI:10.1136/gutjnl-2020-321240] [PMID]

93. Handoll HH, Farrar MJ, McBirnie J, Tytherleigh-Strong G, Milne AA, Gillespie WJ. Heparin, low molecular weight heparin and physical methods for preventing deep vein thrombosis and pulmonary embolism following surgery for hip fractures. Cochrane Database Syst Rev. 2002; 4:Cd000305. [DOI:10.1002/14651858.CD000305] [PMCID]

94. Agnelli G, Piovella F, Buoncristiani P, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. N Engl J Med. 1998; 339(2):80-5. [DOI:10.1056/NEJM199807093390204] [PMID]

95. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest. 2004; 126(3):188-203. https://doi.org/10.1378/chest.126.3_suppl.172S [DOI:10.1378/chest.126.3_suppl.188S] [PMID]

96. Mousavi S, Moradi M, Khorshidahmad T, Motamedi M. Anti-inflammatory effects of heparin and its derivatives: a systematic review. Adv Pharmacol Sci. 2015; 2015:507151. [DOI:10.1155/2015/507151] [PMID] [PMCID]

97. Thachil J. The versatile heparin in COVID-19. JTH. 2020; 18(5):1020-2. [DOI:10.1111/jth.14821] [PMID]

98. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. JTH. 2020; 18(5):1094-9. https://doi.org/10.1111/jth.14851 [DOI:10.1111/jth.14817]

99. Ozolina A, Sarkele M, Sabelnikovs O, et al. Activation of coagulation and fibrinolysis in acute respiratory distress syndrome: a prospective pilot study. Front Med. 2016; 3:64. [DOI:10.3389/fmed.2016.00064] [PMID] [PMCID]

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