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Potential Immunological Treatments in COVID-19 Patients

COVID-19 Hastalarında Potansiyel İmmünolojik Tedaviler

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seemed in Wuhan, China in December 2019. SARS-CoV-2 infection in human was named as coronavirus disease 2019 (COVID-19). It has now infected more than 69 million people worldwide, becoming an epidemic responsible for more than 1,5 million deaths until 10th of December 2020. The epidemic still continues. This epidemic is the third epidemic caused by coronaviruses in the 21st century and may be the most important infectious disease representing a major public health threat to the whole world. Treatments against COVID-19 are constantly updated in the literature, based on evidence. Unfortunately, there is no definitive cure for COVID-19, and a number of drugs for use in severe cases of COVID-19 are now being studied in a number of nonrandomized or randomized trials. These include chloroquine, steroids, anti-inflammatory, and antiviral agents. Immunological treatments such as convalescent plasma, intravenous immunoglobulin, monoclonal antibodies (tocilizumab, eculizumab, itolizumab etc.), and anakinra treatments are tried in COVID-19 disease. Results from some trials look promising. Quite a few reports have also stood published so far on the use of immunological treatments for COVID-19 cases. In this review, we will discuss the key immunological treatments, mostly mentioned in the current literature, used in COVID-19 patients in detail.
Keywords: Anakinra; bamlanivimab; COVID-19; convalescent plasma; eculizumab; intravenous immunoglobulin; itolizumab; monoclonal antibodies; sarilumab; siltuximab; tocilizumab; svilobelimab.

ÖZ

Şiddetli akut solunum yolu sendromu koronavirüsü 2 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) Aralık 2019'da Çin'in Wuhan kentinde görüldü. İnsanlarda SARS-CoV-2 enfeksiyonu koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) olarak adlandırıldı. Şu anda dünya çapında 69 milyondan fazla insanı enfekte etti ve 10 Aralık 2020'ye kadar 1,5 milyondan fazla ölümden sorumlu bir salgın haline geldi. Salgın hala devam ediyor. Bu salgın, 21. yüzyılda koronavirüslerin neden olduğu üçüncü salgındır ve tüm dünya için önemli bir halk sağlığı tehdidini temsil eden en önemli bulaşıcı hastalık olabilir. COVID-19'a karşı tedaviler, kanıta dayalı olarak literatürde sürekli olarak güncellenmektedir. Ne yazık ki, COVID-19 için kesin bir tedavi yoktur ve şiddetli COVID-19 vakalarında kullanılmak üzere bir dizi ilaç şu anda bir dizi randomize olmayan veya randomize çalışmada incelenmektedir. Bunlar arasında klorokin, steroidler, anti-enflamatuar ve antiviral ajanlar bulunmaktadır. COVID-19 hastalığında konvalesan plazma, intravenöz immünoglobulin, monoklonal antikorlar (tocilizumab, eculizumab, itolizumab vb.) ve anakinra tedavileri gibi immünolojik tedaviler denenmektedir. Bazı çalışmalardan elde edilen sonuçlar umut verici görünmektedir. COVID-19 vakalarında immünolojik tedavilerin kullanımı hakkında şimdiye kadar çok az sayıda rapor yayınlandı. Bu derlemede, COVID-19 hastalarında kullanılan ve çoğunlukla güncel literatürde bahsedilen temel immünolojik tedaviler ayrıntılı olarak tartışılacaktır.
Anahtar kelimeler: Anakinra; bamlanivimab; COVID-19; konvalesan plazma; eculizumab; intravenöz immünoglobulin; itolizumab; monoklonal antikorlar; sarilumab; siltuximab; tocilizumab; svilobelimab.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seemed in Wuhan, China in December 2019. SARS-CoV-2 is a positive (+) sense, single-stranded, and enveloped RNA virus. SARS-CoV-2 belongs to the genus Betacoronavirus of the Coronaviridae family. It has a characteristic genetic property with two subtypes (S and L) and more than 140 mutation points. Four major proteins in the structure of SARS-CoV-2 are responsible for intracellular replication and human cell interaction: membrane (M), nucleocapsid (N), envelope (E) and, spike (S) proteins (1-4). The SARS-CoV-2 infection in human was named as coronavirus disease 2019 (COVID-19).

COVID-19 first started in Wuhan city with unidentified cases of pneumonia seen in some adults and become a global pandemic. It has now infected more than 69 million people worldwide, becoming an epidemic responsible for more than 1,5 million deaths until the 10th of December 2020. The epidemic still continues (5-6). This epidemic is the third epidemic caused by coronaviruses in the 21st century and may be the most important infectious disease representing a major public health threat to the whole world. Treatments against COVID-19 are constantly updated in the literature, based on evidence. Unfortunately, there is no definitive cure for COVID-19, and a number of drugs for use in severe cases of COVID-19 are now being studied in a number of nonrandomized or randomized trials. These include chloroquine, steroids, anti-inflammatory and antiviral agents (7-10).

Quite a little reports have also stood published so far on the use of immunological treatments in COVID-19 cases. In this review, we will discuss the key immunological treatments, mostly mentioned in the current literature, used in COVID-19 cases in detail.

CONVALESCENT PLASMA TREATMENT FOR PATIENTS WITH COVID-19

Since COVID-19 was first detected, we still have no definitive treatment options. Lately, the use of human convalescent plasma (CP) is considered a potential choice for the therapy of COVID-19 (11-12). CP has been successfully used in SARS-CoV, Ebola, MERS, and H1N1 viral infections (13). Quite a lot of works have been published in the past decade to assess the clinical helpfulness of CP in relation to respiratory coronavirus infections. Nowadays there is a snowballing interest in the use of passive immunotherapy through transfusion of CP originating from healed COVID-19 patients documented by numerous ongoing studies and daily reviews/perspectives/comments.

Duan et al. (14) presented 10 serious COVID-19 patients who received a CP transfusion covering high neutralizing antibody titers (>1: 640) in the mean of 16.5th day (median) of admission/post-infection. Improvement in laboratory values and clinical symptoms were observed from the 3rd day after infusion. They observed improvement in oxygen saturation, neutralizing antibody titer, SARS-CoV-2 viral load, lung lesions, C-reactive protein (CRP), and lymphocyte count. Also, no serious side effects were observed in patients.

Shen et al. (15) reported a case series of 5 severely patients, all getting CP having SARS-CoV-2 antibodies (titer >1/1000) and a neutralization titer larger than 1:40, applied between day 10th and 22nd of admission. In 4 out of 5 patients, an increase in viral antibody titers, a decrease in SARS-CoV-2 viral loads, and an improvement in acute respiratory distress syndrome (ARDS) were observed. Zhang et al. (16) presented 4 critical patients transfused with 200-2400 mL CP from day 11 to day 18 of the admission. Improvement was observed in all patients including a pregnant woman. In two other studies evaluating CP treatment in COVID-19; Ye et al. (17) observed improvement in 6 patients and Ahn et al. (18) 2 patients after treatment.

The United States Food and Drug Administration (FDA) approved the use of CP on March 26, 2020. It triggered the planning of several trials regarding the use of CP to treat critical patients. When the search was conducted on the clinictrials.gov (https://www.clinicaltrials.gov) site on December 14th, 2020; 135 active ongoing studies were observed when the terms "convalescent plasma and COVID-19" were examined.

Rajendran et al. (19) studied five newly reported studies happening CP use in patients with COVID-19. The main results of this review observed that mortality was reduced in critical cases, SARS-CoV-2 RNA disappeared in most patients, clinical symptoms and radiological findings improved, and no significant side effects were seen secondary to CP treatment.

A systematic review and meta-analysis conducted in 2015 examined 32 studies on heavy influenza and SARS-CoV infection. These studies included 699 treated patient groups and 568 untreated control groups. In a pooled analysis of the data, the investigation revealed evidence of a reliable lessening in mortality in the group treated with CP compared to those who did not get a placebo (20).

In clinical situations characterized by hypercytokinemia, the timing of immunomodulatory treatments is very important, and early initiation of CP therapy seems to be associated with a better outcome. In heavy COVID-19 patients, inflammatory factors mainly associated with IL-6-related hypercytokinemia have been reported to increase significantly 7 to 14 days after onset, contributing to the aggravation of the disease (21). A study in 175 patients in China who improved from COVID-19 viral infection, obviously observes the formation of neutralizing antibodies specific for SARS-CoV-2 from 10-15 days when observed from infection. Peak neutralizing antibody levels were detected in all patients from 10 days and these antibodies remained stable thereafter (22).

The FDA classified the criteria for timing of COVID-19 CP collection as follows;

Scenario A (clinical results based): Donors' symptoms must have totally healed at least 28 days earlier donation.

Scenario B (clinical plus laboratory study based): Donors' symptoms must have totally healed at least 14 days earlier donation and COVID-19 PCR from nasopharyngeal swab must be negative.

The FDA suggests two clinical indications for the present usage of CP treatment in COVID-19 patients;

Scenario A (severe disease) is demarcated as one or more of the undermentioned: Dyspnea, blood oxygen saturation ≤93%, respiratory rate ≥30/min, PaO_2/FiO_2 rate <300, and radiological deteriorating with the dawn of lung infiltrates >50% within 1 to 2 days.

Scenario B (life-threatening disease) is demarcated as one or more of the undermentioned: Septic shock, respiratory failure, or multisystem dysfunction.
Additionally, CP could be used prophylactically in some cases, although it is not recommended by the FDA. These conditions are healthcare providers, individuals exposed to approved COVID-19 cases, and patients with multiple medical conditions (11).
CP therapy for COVID-19 patients, its schematic representation and the main steps are shown in Figure 1.

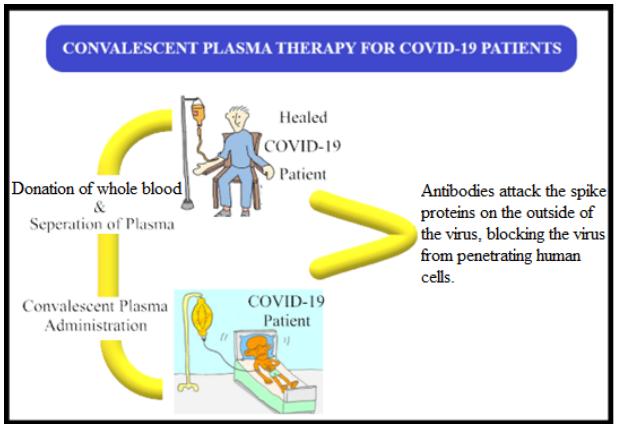

Figure 1. Schematic demonstration of convalescent plasma therapy in COVID-19 patients

Side Effects of Convalescent Plasma Treatment
Serious side impacts have not been reported in CP treatments for the Ebola infection, SARS, H1N1, and MERS outbreaks. The CP treatment was well tolerated in most cases. Some studies have reported minor side effects such nausea, chills, skin rashes, increased body temperature, and itching. These effects were solved spontaneously by symptomatic therapy or by dipping the transfusion ratio. Major side effects such as anaphylactic reactions, circulation overload, and transfusion-related acute lung injuries (TRALI) have also been reported in several cases. The incidence of TRALI is many rare (1 in 5000) and occurs only in severe cases (13,23).
General Warnings about Convalescent Plasma Treatment
The risk of transmitting hepatitis C virus, hepatitis B virus, and HIV from donated plasma must be fully examined. There is very limited information about the security of CP treatment in expectant patients; therefore, sufficient data are needed regarding the usage of CP treatment during pregnancy (13).
The amount and duration of treatment in the CP depends on the severity and viral load of COVID-19. It is trusted that virus-neutralizing antibodies, even in minor quantities, can be efficient when used for the avoiding or therapy of early symptoms of COVID-19. The resulting passive immunity can take weeks and months, but the exact duration needed is unknown. Antibodies should be used shortly after collection. CP treatment has the most potential to treat severe SARS-CoV-2 viral infections, as mutations that can change their properties may occur in the virus. Most of the previous studies were done with a small number of patients with co-morbidity such as diabetes or liver disease. Therefore, a larger scale of clinical studies are needed to produce statistically significant data in footings of the effectiveness of CP therapy and to study possible side effects united with it (13,23).
As a result, it is clear that until vaccines are available for COVID-19, new treatment options are urgently needed to reduce mortality and treat serious cases. CP should be imagined as a therapeutic option at the beginning of symptoms in severe COVID-19 patients.

INTRAVENOUS IMMUNOGLOBULIN TREATMENT FOR PATIENTS WITH COVID-19
Intravenous immunoglobulin (IVIG) was first licensed in the USA in 1980. It is a very effective treatment for preventing life-threatening infections in cases with primary and secondary immune deficiencies. IVIG has also been administered as adjuvant therapy for critically ill patients. A blood product purified off mixed plasma of healthy individuals, globulins is the parent component and wealthy in anti-bacterial and anti-viral IgG antibodies (24-27).
IVIG is a pool of IgG from thousands of healthy donors and exposed individual donors to endemic infectious illness, vaccines, and ubiquitous microorganisms contributing to the manufacture of IgG antibodies versus distinct microorganisms and their antigens (28-31). IVIG from healthy donors is used not only to treat autoimmune diseases such as vasculitis, ITP, Guillain Barrè Syndrome, and Kawasaki but also some difficult, bacterial, and viral infections.
IVIG infusion can effectively neutralize pathogens in the respiratory tract by increasing the serum IgG level, thus promoting improvement from disease and shortening the duration of the illness. IVIG can also cure the body's defenses, block target cell-related host receptors, and avert the pathogen from more damaging the target cell (24). In supplement, the usage of IVIG may also affect the differentiation and maturation process of lymphocytes, inhibit the immune reply of white blood cells, inhibit the manufacture of inflammatory factors, and thus decrease the inflammatory lesion met by the sick. Lately, it has been reported to be involved in improving the hyperinflammatory condition as well as coagulation abnormity in septic cases (32-36).
Various mechanisms of action have been attributed to the beneficial effects of IVIG. Thus, these therapeutic properties of IVIG appear to be particularly suitable for COVID-19 severe infection, where inflammation with an untargeted adaptive immune activation and resulting clotting abnormalities playing a role in the pathogenesis of the disease (37,38).
Virgo (S) glycoprotein forms a homotrimer protruding off the viral surface. The angiotensin-converting enzyme 2 (ACE2) receptor is highly expressed on the apical surface of many cell types, including airway epithelium. The S protein mediates the entry of SARS-CoV-2 into host cells by binding to the ACE2 receptor. Although the mechanisms by which IVIG acts against COVID-19 are not fully understood, two mechanisms are being discussed (Figure 2). First, neutralizing antibodies prevent the binding of the SARS-CoV-2 spike protein at the ACE2 receptor, preventing viral inlet into the cell. Second, IVIG is thought to have an anti-inflammatory effect by binding the FCy receptor (39-40).

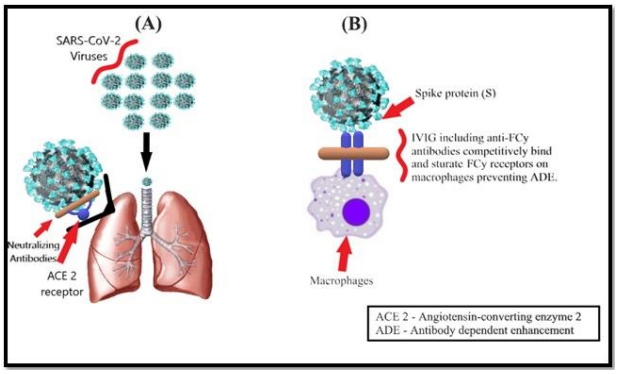

Figure 2. (A) Neutralizing antibodies prevent SARS-CoV-2 spike protein from binding to the ACE2 receptor, preventing viral entry into the cell. **(B)** Among the proposed mechanisms by which IVIG exerts an anti-inflammatory effect, the binding of the FCγ receptor is shown

A meta-analysis of the use of IVIG in SARS infection finalized that it is not net whether it improves prognosis. When we look at the literature regarding the use of IVIG in MERS infection, there is no evidence that IVIG has anti-MERS efficacy has not been reported. Investigations on infection with influenza viruses such as H1N1 have shown that IVIG can prohibit a serious infection with pandemic influenza. In 2009, a multicenter, randomized, double-blind, controlled hyperimmune globulin used to treat cases with heavy H1N1 infection found that the use of hyperimmune globulin in the therapy of heavy H1N1 within 5 days of start of symptoms was associated with a decline in viral burden and death rate (35,41).

There are some studies on COVID-19 patients treated with IVIG reported. Cao et al. (42) reported remission in 3 severe cases of COVID-19 after IVIG treatment. Lin et al. (43) recommended early initiation of high-dose IVIG associated with anticoagulant therapy. Quinti et al. (44) demonstrated that the patients were protected with IVIG therapy in seven patients with primary immunodeficiency. Lanza et al. (45) successfully treated a 42-year-old patient with heavy COVID-19 pneumonia with IVIG infusion. In a study conducted by Xie et al. (46) with 58 severe COVID-19 cases who received IVIG therapy followed in the ICU, initiating IVIG as adjuvant therapy for COVID-19 pneumonia within 2 days after acceptance to the ICU reduced the usage of mechanical ventilation, shortened the time of hospital remain and significant clinical efficacy was found. Mohtadi et al. (47) observed improvement in all patients after high-dose IVIG (0.3-0.5 g/kg) treatment for 5 alternate days in 5 severe COVID-19 patients who failed standard treatments.

Early usage of IVIG as an adjuvant therapy aimed at COVID-19 pneumonia in selected patients may decrease the rates of mechanical ventilation and hospitalization. Although a definitive treatment for COVID-19 is not available, the combination of IVIG and other alternative therapeutic modalities such as dexamethasone can be used as a treatment protocol against COVID-19.

MONOCLONAL ANTIBODY TREATMENT FOR THE PATIENT WITH COVID-19

Monoclonal antibodies (MAB) are antibodies that react against only one epitope and are derived from only one B-lymphocyte-based cell clone. The method of obtaining MABs was described by César Milstein, Georges Köhler, and Niels Jerne in 1975. MABs are especially used to avert and treat diseases from the immune system and cancer illnesses. Only seven out of 100 licensed MABs are for treating and preventing infectious diseases. MABs are not chemical mixes like most drugs. It is based on natural antibodies, which are proteins that the body breeds to advocate itself against illnesses. However, it is constituted in the laboratory and mass-produced in factories. Because of these properties, they are named "designer antibodies" (48,49).

It is being tested whether various MABs licensed for other diseases or under development have an impact on COVID-19 cases. Researchers have besides been swiftly detecting MABs that particularly goal SARS-CoV-2. More than 70 MAB products are currently under progress for COVID-19. MAB agents that have been tried in the literature to treat COVID-19 so far are tocilizumab (a MAB against IL-6), siltuximab (a MAB against IL-6), sarilumab (a MAB against IL-6), eculizumab (anti-C5 MAB), bamlanivimab (LY-Cov555), vilobelimab (Anti-C5a antibody IFX- 1) and itolizumab (Anti-CD6 MAB) (49-56).

Tocilizumab

Interleukin-6 (IL-6) is a cytokine that moves significant role in inflammatory reaction and immune reply. New clinical experience shows that IL-6 is one of the greatest significant cytokines involved in COVID-19 induced cytokine storms. Therefore, tocilizumab (TCZ), a recombinant humanized anti-human IL-6R monoclonal antibody of the IgG1 subtype, is being tested in the therapy of COVID-19 cases. TCZ is soluble and specifically binds membrane connected IL-6 receptors (mIL-6R and sIL-6R) and inhibits mIL-6R and sIL-6R mediated signal transduction. It is certified for the therapy of systemic juvenile idiopathic arthritis and rheumatoid arthritis. It has withal been reported to show part in Crohn's disease and Castleman disease (57-61).

Let's evaluate the results of the studies with TCZ in order. Luo et al. (50) included 15 patients diagnosed with COVID-19 in the study. While 10 patients showed a reduction in IL-6 levels and clinical improvement, 4 patients did not show a reduction in IL-6 levels or clinical recovery. In addition, 1 patient also aggravated the clinic. No adverse drug reactions were reported during TCZ treatment. Xu et al. (62) included 21 severe COVID-19 patients in the study. The body temperature of all patients returned dramatically to normal on the first day after taking TCZ and remained stable thereafter. In the following days, clinical symptoms improved simultaneously. After TCZ treatment, 13 patients recovered within 2 weeks and were discharged. 6 patients recovered between the 2nd and 3rd weeks and were discharged. No death was reported. Toniati et al. (63) included 100 severe cases of COVID-19 pneumonia in the study. 24-72 hours after TCZ treatment, 58 patients presented a fast recovery in the respiratory tract and clinical, 37 patients were stabilized compared to the pre-TCZ status, and 5 patients deteriorated. 77 patients improved on the 10th day; 61 of them were observed that diffuse two-sided opacities disappeared significantly on lung X-ray, and 15 were discharged from the hospital. In addition, 20 patients died and 3 patients' clinic

deteriorated. Serious adverse events in three patients were observed during the 10-day follow-up; two patients improved septic shock and one died. One patient developed gastrointestinal perforation necessitating emergency surgery.

Sciascia et al. (64) enrolled 63 patients with COVID-19 in the study. In this study, the cases were treated with intravenous (IV) and subcutaneous (SC) routes. There was no difference between the routes of administration in terms of mortality. Fever regressed in the first 24 hours in 24 of 25 patients who had fever after TCZ treatment. An improvement was observed in clinical and laboratory values. Seven patients died. In this study, TCZ application within 6 days after hospitalization was found to be associated with an increased probability of survival. Campochiaro et al. (65) enrolled 65 cases with COVID-19 in the study. Thirty two patients were followed with TCZ and 33 cases with standard therapy. Although mortality was determined as 15% in the TCZ group and 33% in the standard therapy group, there was no statistically significant difference between the two groups in terms of clinical recovery and mortality. Klopfenstein et al. (66) enrolled 45 cases with COVID-19 in the study. Twenty cases were followed up with TCZ and 25 cases with standard therapy. As a result of the study, they found that TCZ can reduce the number of admissions to the ICU and/or mortality in cases with severe SARS-CoV-2 pneumonia. Tleyjeh et al. (67) evaluated the results of 11,775 patients in their meta-analysis with the data of 24 studies. As a result of the meta-analysis, it was determined that TCZ decreased the risk of mechanical ventilation in hospitalized COVID-19 cases and did not decrease short-term mortality in randomized controlled studies. On the other hand, a relationship between TCZ and low mortality was found in cohort studies.

When the results of the studies in the literature were evaluated, it was observed that TCZ prevented the fever seen due to COVID-19 disease for the first 24 hours. Respiratory and clinical recovery has been observed in many patients. It is not known exactly how much TCZ prevents mortality. Although TCZ did not provide definitive treatment for COVID-19 patients, it was observed that the rate of recovery was high in patients. A clinical trial with TCZ according to current data in patients who do not respond with standard treatments may be promising.

Siltuximab

Siltuximab is an anti-IL-6 chimeric MAB, used in Castleman disease. It can be considered as a therapeutic strategy for treating severe cases of SARS-CoV-2 infection, as it benefits COVID-19 patients with TCZ therapy. Currently, there are no studies with completed data for COVID-19, the drug is in the trial phase (51).

Sarilumab

Another anti-IL-6 MAB is sarilumab. Right now, information on the usage of sarilumab in COVID-19 is limited. Let's evaluate one by one of the studies performed with sarilumab treatment in COVID-19 cases. Della-Torre et al. (68) administered sarilumab to 28 cases with heavy COVID-19 pneumonia and inflammatory phenotype in addition to standard treatments. Patients who were given sarilumab were compared with 28 patients with similar demographic, laboratory, and respiratory parameters who received only standard therapy. The mortality rate was lower in the sarilumab group (2/28 patients, 7%) compared to the standard treatment group (5/28 patients, 18%), but this difference was not statistically significant. Treatment with sarilumab in this study was associated with a significantly earlier reduction in serum CRP and fever.

Benucci et al. (69) gave sarilumab treatment to eight patients hospitalized for COVID-19. Aggressive and early treatment with sarilumab resulted in discharge within 14 days of hospital admission, with seven of eight cases showing negatory results on the molecular test. One case died. Montesarchio et al. (70) enrolled 15 laboratory-confirmed COVID-19 cases in the study. After administration of sarilumab, fast healings in respiratory parameters were reported in 67% of cases and 34% died. Nine of the eleven cases with CT findings replied to the therapy. However, all cases, with the inclusion of those who responded to sarilumab, referred with serum IL-6 levels at least ten times the top limit of normal.

Considering the available data, more randomized controlled works are needed to understand whether sarilumab treatment is effective in COVID-19.

Eculizumab

Eculizumab is anti-C5 (fifth element of complement pathway) MAB. It is a drug used to cure neuromyelitis optica, atypical hemolytic uremic syndrome, and paroxysmal nocturnal hemoglobinuria. There are studies that have been treated with eculizumab in COVID-19 patients, the data of these studies are evaluated below one by one.

Diurno et al. (52) successfully treated four COVID-19 cases admitted to the ICU for heavy pneumonia or ARDS with eculizumab. The average disease duration was observed as 12.8 days. Laurence et al. (71) administered eculizumab therapy to three critical COVID-19 patients. It resulted in a significant decrease in neutrophil and D-dimer levels in all three patients, and normalization of creatinine and liver function values in two patients. One case with heavy cardiac insufficiency had a whole remission. Partial remission was observed in the other two cases. Annane et al. (72) compared the data of 35 cases who received eculizumab and 45 cases who received standard treatment. The mortality rate was found inferior in the eculizumab group (17.1%) compared to the standard treatment group (37.8%). Cases treated with eculizumab had a meaningfully faster fall in total and conjugated bilirubin, blood urea nitrogen, and lactate levels compared to patients receiving standard therapy. A significantly faster rise in prothrombin time, platelet count, and oxygen saturation was observed. In this study, it was concluded that eculizumab could reduce hypoxia and improve survival in patients with severe COVID-19.

When the available data were evaluated, it was observed that eculizumab treatment was effective compared to standard therapy. More randomized controlled studies are needed to make a decision on this treatment.

Bamlanivimab

Bamlanivimab (LY-CoV555) has been authorized by the FDA for emergency use for mild to moderate COVID-19 therapy in adults and children who are not admitted to the hospital. It has been stated that bamlanivimab reduces the rates of hospitalization with early treatment in COVID-19 patients with chronic illness (53). But for now, there are no

studies with finalized data for COVID-19, the drug is in the trial phase.

Vilobelimab

Vilobelimab is anti-C5a is IFX-1 MAB. Vlaar et al. (55) among whole data of 15 patients with COVID-19 who received vilobelimab and 15 patients who received standard therapy were compared. Six patients died out of 30 patients comprised in the work. Two patients were in the group receiving vilobelimab, the other 4 patients were in the group receiving standard therapy. Considering the available data, more randomized controlled studies are needed to understand whether vilobelimab treatment is effective.

Itolizumab

Itolizumab is anti-CD6 MAB. Atal et al. (73) conducted a multi-center, two-arm, open-label, randomized, phase II, and pivotal clinical trial in 30 cases in India. While 20 patients were treated with itolizumab and supportive care, 10 patients in the control group received only supportive care. In this way, the study was performed with a 2:1 randomization. All patients who received itolizumab fully recovered and were discharged from the hospital, while three (30%) of ten cases in the control group died. All patients who received itolizumab were weaned from oxygen on the 30th day, and unlike the control group, none of them needed ventilator support. Clinical markers of inflammation such as CRP, lactate dehydrogenase (LDH), D-dimer, serum ferritin, TNF-a, and IL-6 presented clinically significant normalization after itolizumab administration and correlated well with radiological and clinical recovery in symptoms. In another investigation, the authors deduced that in 19 senior COVID-19 cases who were moderately ill, itolizumab therapy was associated with an importantly cut risk of ICU admission and a 10-fold lower death risk (74).

When current studies are evaluated, it is seen that itolizumab treatment will give promising results in severe COVID-19 disease. It can be said that itolizumab is the second most effective MAB agent used in the treatment of COVID-19 after TCZ, which is observed to be the most effective. However, randomized controlled studies are required to obtain a clear conclusion on itolizumab treatment.

ANAKINRA

Anakinra is a human recombinant IL-1 receptor (IL-1R) antagonist. It is used as a second-line therapy to manage rheumatoid arthritis symptoms after treatment with a disease modifying anti-rheumatic drug (DMARD) has failed. It is used to treat anyone from infants to adults with periodic syndrome associated with cryopyrin, including neonatal-onset multisystem inflammatory disease. It also appears to be forceful in the therapy of macrophage activation syndrome (MAS), a type of cytokine storm. It has been shown to aid the treatment of secondary hemophagocytic lymphohistiocytosis (HLH), especially in pediatric patients with other rheumatologic disorders. Coronaviruses can induce the manufacture of tumor necrosis factor, IL-6, IL-1β, and other cytokines related in autoinflammatory disorders. It has been suggested that anakinra, may help neutralize the hyperinflammatory state associated with COVID-19, which is considered to be a reason for ARDS (75-79).

Cavalli et al. (80) compared the data of 29 patients diagnosed with COVID-19 treated with anakinra and 16 patients treated with standard therapy. A decrease in serum CRP and progressive improvement in respiratory parameters were observed in 21 (72%) of 29 cases who received anakinra treatment on day 21. The 3 (10%) patients died and 5 (17%) cases were due to mechanical ventilation. In the standard of therapy arm, 8 (50%) of 16 cases presented respiratory parameters recovery; one (6%) case was on mechanical ventilation and seven (44%) cases died. Mortality was inferior in the anakinra arm (10%) compared to the standard treatment arm (44%) on day 21. Survival without mechanical ventilation was 72% in the anakinra arm and 50% in the standard therapy arm. Huet et al. (79) compared the data of 52 cases with COVID-19 treated with anakinra and 44 cases on standard therapy. Thirteen (25%) cases in the anakinra arm and 32 (73%) cases in the standard therapy arm had a history of acceptance to the ICU for death or invasive mechanical ventilation. As a result of this study, in severe forms of COVID-19-related pneumonia necessitating oxygen treatment, a 10-day therapy with SC anakinra was associated with a decrease in both the necessity for mechanical ventilation and death rate compared to an arm receiving standard therapy with like features.

Navarro-Millán et al. (81) examined the data of 14 patients diagnosed with COVID-19 who were given anakinra therapy. Seven of those who received anakinra therapy within 36 hours after the onset of ARDS did not need mechanical ventilation and all were discharged home. As a result of this study, it was concluded that anakinra, when introduced early after the inception of ARDS, may be useful in COVID-19 cases with signs of cytokine storm syndrome.

CONCLUSION

CP and IVIG could open a new window to the method of COVID-19 treatment, especially applied at the beginning of the disease at accurate doses, according to current literature. To decide on the role of MAB therapy in COVID-19, it seems to require further randomized controlled clinical trials.

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REFERENCES

1. who.int [Internet]. World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 32. [Cited: 2020 June 27]. Available from: https://www.who.int/docs/default-

source/coronaviruse/situation-reports/20200221-sitrep-32-covid-19.pdf?sfvrsn=4802d089_2.
2. Gasparyan AY, Misra DP, Yessirkepov M, Zimba O. Perspectives of immune therapy in coronavirus disease 2019. J Korean Med Sci. 2020;35(18):e176.
3. She J, Liu L, Liu W. COVID-19 epidemic: disease characteristics in children. J Med Virol. 2020;92(7):747-54.
4. Ahmed SF, Quadeer AA, McKay MR. Preliminary identification of potential vaccine targets for the COVID-19 coronavirus (SARS-CoV-2) based on SARS-CoV immunological studies. Viruses 2020;12(3):254.
5. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020;395(10223):514-23.
6. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382(8):727-33.
7. Franchini M. Why should we use convalescent plasma for COVID-19? Eur J Intern Med. 2020;77:150-1.
8. Özdemir Ö. Coronavirus disease 2019 (COVID-19): diagnosis and management. Erciyes Med J. 2020;42(3):242-7.
9. Özdemir Ö, Pala A. Diagnosis, treatment and prevention methods of pediatric COVID-19 infection. J Biotechnol and Strategic Health Res. 2020;1(Special Issue):14-21.
10. Kılıçaslan Ö, Sav NM, Erişen Karaca S, Kocabay K. COVID-19 disease in children: clinical course, diagnosis and treatment overview and literature data compilation. Konuralp Med J. 2020;12(2):316-25.
11. Sahu KK, Jindal V, Siddiqui AD, Cerny J, Gerber JM. Convalescent plasma therapy: A passive therapy for an aggressive COVID-19. J Med Virol. 2020;92(11):2251-3.
12. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. J Clin Invest. 2020;130(4):1545-8.
13. Pawar AY, Hiray AP, Sonawane DD, Bhambar RS, Derle DV, Ahire YS. Convalescent plasma: A possible treatment protocol for COVID-19 patients suffering from diabetes or underlying liver diseases. Diabetes Metab Syndr. 2020;14(4):665-9.
14. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci USA 2020;117(17):9490-6.
15. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA. 2020;323(16):1582-9.
16. Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, et al. Treatment with convalescent plasma for critically ill patients with severe acute respiratory syndrome coronavirus 2 infection. Chest. 2020;158(1):e9-e13.
17. Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol. 2020;92(10):1890-901.
18. Ahn JY, Sohn Y, Lee SH, Cho Y, Hyun JH, Baek YJ, et al. Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. J Korean Med Sci. 2020;35(14):e149.
19. Rajendran K, Krishnasamy N, Rangarajan J, Rathinam J, Natarajan M, Ramachandran A. Convalescent plasma transfusion for the treatment of COVID-19: systematic review. J Med Virol. 2020;92(9):1475-83.
20. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis. 2015;211(1):80-90.
21. Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, et al., Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). MedRxiv. 2020. doi: 10.1101/2020.02.10.20021832.
22. Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. MedRxiv. 2020. doi: 10.1101/2020.03.30.20047365.
23. Hendrickson JE, Hillyer CD. Noninfectious serious hazards of transfusion. Anesth Analg. 2009;108(3):759-69.
24. Nguyen AA, Habiballah SB, Platt CD, Geha RS, Chou JS, McDonald DR. Immunoglobulins in the treatment of COVID-19 infection: Proceed with caution. Clin Immunol. 2020;216:108459.
25. Özdemir Ö, Arsoy HEM. Convalescent (immune) plasma therapy with all aspects: Yesterday, today and COVID-19. Erciyes Med J. 2020;42(3):252-9.
26. Özdemir Ö, Erkun O. Solving puzzle of the immunopathogenesis for management of COVID-19 disease. MOJ Immunol. 2020;7(1):13-5.
27. Arsoy HEM, Özdemir Ö. Current therapeutic interventions for COVID-19. Bezmialem Science. 2020;8(Supplement 3):105-16.
28. Jawhara S. Could intravenous immunoglobulin collected from recovered coronavirus patients protect against COVID-19 and strengthen the immune system of new patients? Int J Mol Sci. 2020;21(7):2272.
29. Diep BA, Le VT, Badiou C, Le HN, Pinheiro MG, Duong AH, et al. IVIG-mediated protection against necrotizing pneumonia caused by MRSA. Sci Transl Med. 2016;8(357):357ra124.
30. Gauduchon V, Cozon G, Vandenesch F, Genestier AL, Eyssade N, Peyrol S, et al. Neutralization of Staphylococcus aureus Panton Valentine leukocidin by intravenous immunoglobulin in vitro. J Infect Dis. 2004;189(2):346-53.
31. Krause I, Wu R, Sherer Y, Patanik M, Peter JB, Shoenfeld Y. In vitro antiviral and antibacterial activity of commercial intravenous immunoglobulin preparations--a potential role for adjuvant intravenous immunoglobulin therapy in infectious diseases. Transfus Med. 2002;12(2):133-9.
32. Scopetta C, Gennaro GD, Polverino F. High dose intravenous immunoglobulins as a therapeutic option for COVID-19 patients. Eur Rev Med Pharmacol Sci. 2020;24(9):5178-9.

33. Keitel WA, Voronca DC, Atmar RL, Paust S, Hill H, Wolff MC, et al. Effect of recent seasonal influenza vaccination on serum antibody responses to candidate pandemic influenza A/H5N1 vaccines: a meta-analysis. Vaccine. 2019;37(37):5535-43.
34. Tout I, Loureiro D, Mansouri A, Soumelis V, Boyer N, Asselah T. Hepatitis B surface antigen seroclearance: immune mechanisms, clinical impact, importance for drug development, J Hepatol. 2020;73(2):409-22.
35. Bissett SL, Godi A, Jit M, Beddows S. Seropositivity to non-vaccine incorporated genotypes induced by the bivalent and quadrivalent HPV vaccines: a systematic review and meta-analysis. Vaccine. 2017;35(32):3922-9.
36. Cagigi A, Cotugno N, Rinaldi S, Santilli V, Rossi P, Palma P. Downfall of the current antibody correlates of influenza vaccine response in yearly vaccinated subjects: toward qualitative rather than quantitative assays. Pediatr Allergy Immunol. 2016;27(1):22-7.
37. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect. 2020;9(1):727-32.
38. Ferrara G, Zumla A, Maeurer M. Intravenous immunoglobulin (IVIg) for refractory and difficult-to-treat infections. Am J Med. 2012;125(10):1036.e1-8.
39. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020:181(2):281-92.e6.
40. ter Meulen J, van den Brink EN, Poon LL, Marissen WE, Leung CS, Cox F, et al. Human monoclonal antibody combination against SARS coronavirus: synergy and coverage of escape mutants. PLoS Med. 2006;3(7):e237.
41. Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? Nat Rev Immunol. 2013;13(3):176-89.
42. Cao W, Liu X, Bai T, Fan H, Hong K, Song H, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. Open Forum Infect Dis. 2020;7(3):ofaa102.
43. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect. 2020;9(1):727-32.
44. Quinti I, Lougaris V, Milito C, Cinetto F, Pecoraro A, Mezzaroma I, et al. A possible role for B cells in COVID-19? Lesson from patients with agammaglobulinemia. J Allergy Clin Immunol. 2020;146(1):211-13.e4.
45. Lanza M, Polistina GE, Imitazione P, Annunziata A, Spirito VD, Novella C. Successful intravenous immunoglobulin treatment in severe COVID-19 pneumonia. IDCases. 2020;21:e00794.
46. Xie Y, Cao S, Dong H, Li Q, Chen E, Zhang W, 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.
47. Mohtadi N, Ghaysouri A, Shirazi S, Ansari S, Shafiee E, Bastani E, et al. Recovery of severely ill COVID-19 patients by intravenous immunoglobulin (IVIG) treatment: A case series. Virology. 2020;548:1-5.
48. Köhler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature. 1975;256(5517):495-7.
49. gavi.org [Internet]. Gavi, The Vaccine Alliance. What are monoclonal antibodies - and can they treat Covid-19? [Cited: 2020 December 12]. Available from: https://www.gavi.org/vaccineswork/what-are-monoclonal-antibodies-and-can-they-treat-covid-19.
50. 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):814-8.
51. Palanques-Pastor T, López-Briz E, Poveda Andrés JL. Involvement of interleukin 6 in SARS-CoV-2 infection: siltuximab as a therapeutic option against COVID-19. Eur J Hosp Pharm. 2020;27(5):297-8.
52. Diurno F, Numis FG, Porta G, Cirillo F, Maddaluno S, Ragozzino A, et al. Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience. Eur Rev Med Pharmacol Sci. 2020;24(7):4040-7.
53. Mahase E. Covid-19: FDA authorises neutralising antibody bamlanivimab for non-admitted patients. BMJ. 2020;371:m4362.
54. fda.gov [Internet]. Food and Drug Administration. Bamlanivimab EUA Letter of Authorization, November 10, 2020. [Cited: 2020 December 12]. Available from: https://www.fda.gov/media/143602/download.
55. Vlaar APJ, de Bruin S, Busch M, Timmermans SAMEG, van Zeggeren IE, Koning R, et al. Anti-C5a antibody IFX-1 (vilobelimab) treatment versus best supportive care for patients with severe COVID-19 (PANAMO): an exploratory, open-label, phase 2 randomised controlled trial. Lancet Rheumatol. 2020;2(12):e764-73.
56. Díaz Y, Ramos-Suzarte M, Martín Y, Calderón NA, Santiago W, Viñet O, et al. Use of a humanized anti-CD6 monoclonal antibody (itolizumab) in elderly patients with moderate COVID-19. Gerontology. 2020;66(6):553-61.
57. Kaur S, Bansal Y, Kumar R, Bansal G. A panoramic review of IL-6: structure, pathophysiological roles and inhibitors. Bioorg Med Chem. 2020;28(5):115327.
58. Navarro G, Taroumian S, Barroso N, Duan L, Furst D. Tocilizumab in rheumatoid arthritis: a meta-analysis of efficacy and selected clinical conundrums. Semin Arthritis Rheum. 2014;43(4):458-69.
59. Yokota S, Miyamae T, Imagawa T, Iwata N, Katakura S, Mori M, et al. Therapeutic efficacy of humanized recombinant anti-interleukin-6 receptor antibody in children with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum. 2005;52(3):818-25.
60. Nishimoto N, Kanakura Y, Aozasa K, Johkoh T, Nakamura M, Nakano S, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. Blood 2005;106(8):2627-32.
61. Ito H, Takazoe M, Fukuda Y, Hibi T, Kusugami K, Andoh A, et al. A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. Gastroenterology. 2004;126(4):989-96.
62. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with

tocilizumab. Proc Natl Acad Sci USA. 2020;117(20):10970-5.
63. Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmun Rev 2020;19(7):102568.
64. Sciascia S, Aprà F, Baffa A, Baldovino S, Boaro D, Boero R, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. Clin Exp Rheumatol. 2020;38(3):529-32.
65. Campochiaro C, Della-Torre E, Cavalli G, De Luca G, Ripa M, Boffini N, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. Eur J Intern Med 2020;76:43-9.
66. Klopfenstein T, Zayet S, Lohse A, Balblanc JC, Badie J, Royer PY, et al. Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. Med Mal Infect. 2020;50(5):397-400.
67. Tleyjeh IM, Kashour Z, Damlaj M, Riaz M, Tlayjeh M, Altannir M, et al. Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis. Clin Microbiol Infect. 2020;[Epub ahead of print]. doi: 10.1016/j.cmi.2020.10.036.
68. Della-Torre E, Campochiaro C, Cavalli G, De Luca G, Napolitano A, Marca SL, et al. Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: an open-label cohort study. Ann Rheum Dis 2020;79(10):1277-85.
69. Benucci M, Giannasi G, Cecchini P, Gobbi FL, Damiani A, Grossi Vet al. COVID-19 pneumonia treated with Sarilumab: A clinical series of eight patients. J Med Virol. 2020;92(11):2368-70.
70. Montesarchio V, Parrela R, Iommelli C, Bianco A, Manzillo E, Fraganza F, et al. Outcomes and biomarker analyses among patients with COVID-19 treated with interleukin 6 (IL-6) receptor antagonist sarilumab at a single institution in Italy. J Immunother Cancer. 2020;8(2):e001089.
71. Laurence J, Mulvey JJ, Seshadri M, Racanelli A, Harp J, Schenck EJ, et al. Anti-complement C5 therapy with eculizumab in three cases of critical COVID-19. Clin Immunol. 2020;219:108555.
72. Annane D, Heming N, Grimaldi-Bensouda L, Frémeaux-Bacchi V, Vigan M, Roux AL, et al. Eculizumab as an emergency treatment for adult patients with severe COVID-19 in the intensive care unit: A proof-of-concept study. EClinicalMedicine. 2020;28:100590.
73. Atal S, Fatima Z, Balakrishnan S. Approval of itolizumab for COVID-19: A premature decision or need of the hour? BioDrugs. 2020;34(6):705-11.
74. Díaz Y, Ramos-Suzarte M, Martín Y, Calderón NA, Santiago W, Viñet O, et al. Use of a humanized anti-CD6 monoclonal antibody (itolizumab) in elderly patients with moderate COVID-19. Gerontology. 2020;66(6):553-61.
75. fda.gov [Internet]. Food and Drug Administration. US Anakinra label, May 2016. [Cited: 2020 December 14]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103950s5175lbl.pdf.
76. Singh JA, Hossain A, Tanjong Ghogomu E, Kotb A, Christensen R, Mudano AS, et al. Biologics or tofacitinib for rheumatoid arthritis in incomplete responders to methotrexate or other traditional disease-modifying anti-rheumatic drugs: a systematic review and network meta-analysis. Cochrane Database Syst Rev. 2016;5:CD012183.
77. Canna SW, Behrens EM. Making sense of the cytokine storm: a conceptual framework for understanding, diagnosing, and treating hemophagocytic syndromes. Pediatr Clin North Am. 2012;59(2):329-44.
78. Gusdorf L, Lipsker D. Schnitzler Syndrome: a review. Curr Rheumatol Rep. 2017;19(8):46.
79. Huet T, Beaussier H, Voisin O, Jouveshomme S, Dauriat G, Lazareth I, et al. Anakinra for severe forms of COVID-19: a cohort study. Lancet Rheumatol. 2020;2(7):e393-400.
80. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheumatol. 2020;2(6):e325-31.
81. Navarro-Millán I, Sattui SE, Lakhanpal A, Zisa D, Siegel CH, Crow MK. Use of anakinra to prevent mechanical ventilation in severe COVID-19: A case series. Arthritis Rheumatol. 2020;72(12):1990-7.