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A glance into the Pathology of Covid-19, Its Current and Possible Treatments; Interleukin Antagonists as an Effective Option; a Review

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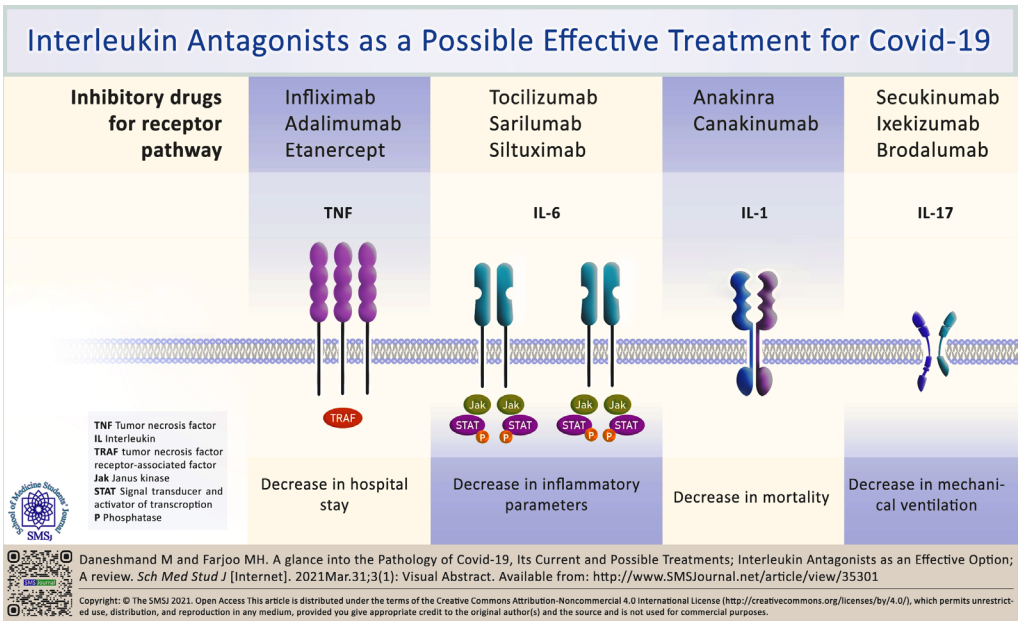
ABSTRACT

The outbreak of the novel SARS-COV-2 and its following complications has caused an almost unprecedented chaos throughout the world in recent years. Although a series of vaccines have been proposed recently in order to reduce the risk of mortality and morbidity of this disease, an ultimate and reliable cure has yet to be discovered. One of the major complications of Covid-19 is the outburst of a series of inflammatory responses in the respiratory system of the patients, which eventually causes a hypoxemic pneumonitis and accounts for most of the Covid-19 patients' mortality. It is suggested that a group of inflammatory cytokines such as different interleukins are responsible for this complication, therefore drugs which can influence this system may be useful in reducing this exaggerated inflammatory response which is dubbed the 'cytokine storm'. In this article we review potential treatment options for reducing the inflammatory response and discuss some clinical trials and case reports related to the drugs interfering with responsible interleukins in order to quench the cytokine storm.



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INTRODUCTION

The beginning of 2020 was heralded by an outbreak of a coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-COV-2). The current global pandemic of SARS-COV-2 has been spreading limitlessly throughout the world since December 2019. It primarily was observed in Wuhan city, China and to date, over 172 million confirmed cases and over 3 million deaths are reported by WHO [1]. Ever since there has been a significant effort for finding a treatment for this disease. Although a series of vaccines have been introduced among which some are FDA approved and are currently being injected, but a definitive cure is yet to be found [1, 2].

Various complications are attributed to this disease. Patients diagnosed with covid-19 often develop a hypoxemic pneumonitis with a profound inflammatory response which may be caused by elevated levels of inflammatory cytokines such as IL1 and IL6, interferon-γ inducible protein 10, and granulocyte-colony stimulating factor (GCSF) [3]. These cytokines increase the amount of cell adhesion molecules and vascular-endothelial growth factor (VEGF) in the lung and thereby increase the permeability in the lung epithelial cells and decrease barrier protection, which allows viral propagation and infiltration of neutrophils and inflammatory monocytes. These cytokines stimulate release of immature granulocytes from bone marrow which exacerbate the lung epithelium adherence and inflammation. This so called second loop in the lung leads to a series of systemic inflammations which culminate in what is known as cytokine storm syndrome [4]. This cytokine storm causes diffuse alveolar damage and acute respiratory distress syndrome and is the leading cause of mortality in the covid-19 patients (see below) [5].

A considerable amount of researches and trials have been carried out about Covid-19 treatment and drugs which antagonize IL1 and IL6 receptors may be a promising approach for this purpose [6-10].

COVID-19 and Its Pathologic Respiratory Features

Corona virus is a positive-sense, single-stranded RNA virus which belongs to the family Coronaviridae with a genome size of approximately 30 kilobases. The virus encodes multiple structural and non-structural proteins. The former consist of: spike, envelope, membrane, and nucleocapsid protein, and the latter are responsible for corona virus RNA synthesis and processing. This is done by nonstructural protein (NSP) 7 to 16, which are cleavage products of two large replicase polyproteins translated from the coronavirus genome. [11]. The virus apparently triggers both humoral and cellular immune responses which may notoriously affect respiratory system. The severe lung injury in patients with covid-19 results from both direct viral infection and immune system overreaction [12, 13]. The detrimental changes consist of a constellation of pathologic processes occurring both in macro- and microenvironment. Hyaline membrane formation may cause vast alveolar damage which may be accompanied by pulmonary edema, and exudates of fibrin with subsequent aggregation of proteins. A reactive hyperplasia of type II pneumocytes also occurs with accumulation of different types of white blood cells such as monocytes, macrophages, and other mononuclear cells within alveoli. [14, 15]. Covid-19 attacks the respiratory system via invading epithelial cells and type 2 pneumocytes by attachment of the virus spike protein to the angiotensin converting enzyme 2 (ACE2) receptors [16]. The regulator gene of this receptor has shown a dose-dependent expression concomitant with the higher levels of SARS-CoV-2 virus, and is upregulated by interferon regulating genes such as Interferon Alpha Inducible Protein (IFI) 27, and IFI 6 [17]. This is while SARS-COVID-2 decreases surface expression of ACE2 receptors [18]. ACE2 acts via converting Angiotensin 2 into Angiotensin 1-7, and therefore has a vasodilatory effect. Moreover, it has a reducing effect on bradykinin expression, hence with the blockade of ACE2 receptors, high amounts of bradykinins can stimulate inflammatory response [19].

Cytokine Storm and Its Effects on Lung Pathology

Following entrance of SARS-COV2 into the respiratory epithelial cells, the virus provokes an immune response which leads to the production of plentiful amounts of inflammatory cytokines. Pathogenic T helper 1 (Th1) cells and intermediate CD14+, and CD16+ monocytes ignite a series of inflammatory immune responses which happen by the interaction between the membrane-bound immune receptors with antigens and the subsequent signaling pathways. This is followed by infiltration of macrophages and neutrophils into the epithelial cells of the lungs which provokes cytokine storm [12]. This happens when SARS-COV-2 stimulates Th1 cells to produce inflammatory mediators for instance different kinds of interleukins (e.g., IL1 and IL6), granulocyte-macrophage colony stimulating factor (GM-CSF) which stimulates CD14+, CD16+ monocytes to secrete massive amounts of other cytokines such as tumor necrosis factor α (TNFα) [12, 20]. The release of these types of cytokines is associated with a series of manifestations such as flu like symptoms, fatigue, cardio -myopathy and lung injury. IL6 can cause vascular leakage which activates complement and coagulation pathways that could cause diffuse intravascular coagulation. These clinical features are mostly seen in COVID-19 patients in severe condition and are major contributing factors to the mortality of this disease [21, 22].

Medications Effective in the Modulation of the Cytokine Storm

Considering the fundamental role of cytokine storm in severity of the COVID-19, anti-inflammatory drugs may be a potential therapy for reducing morbidity and mortality of this disease. The time period in which the anti-inflammatory drugs are used is of great importance, since there is a seven-day critical time between the onset of the symptoms and worsening of the patient's condition towards critical status [21]. This type of treatment has its own disadvan-

tages, for instance a number of cytokines such as interleukins 1, 6, 10, 12 and 17 are necessary in the process of virus clearance and therefore anti-interleukin drugs could cause some complications. Furthermore, immune system deficiencies occurs in some patients suffering from COVID-19 and utilization of anti-inflammatory drugs such as glucocorticoids may exacerbate their situation [23]. Another option for COVID-19 treatment is administration of human immunoglobulin for intravenous use (IVIG). These molecules are natural antibodies with poly reactive properties with the ability to recognize and neutralize exogenous antigens of viral and bacterial origin, toxins and super antigens, or endogenous antigens like cytokines, chemokines and metalloproteases. IVIG molecules also depend on their Fc region interaction with the Fcγ receptors (FcγRs) to induce anti-inflammatory / immune-regulatory responses. Since FcγRs are expressed on cells involved in natural immunity (phagocytes), adaptive immunity (T cells, B cells), and also on antigen presenting-cells which connect both types of immunities, this interaction acts as a modifier for signaling through FcγRs and eventually may lead to strong anti-inflammatory responses [24]. Many studies have suggested that complement system becomes active during body exposure to SARS-CoV in humans and animals. It appears that a large amount of complement residues are dispersed throughout the bodies of patients, so finding a molecule with antagonistic potential against complement receptors could be promising in reducing the inflammatory response in these patients. Studies show that a humanized monoclonal antibody that works against complement receptor, C5a could reduce SARS-CoV-induced lung injury in mice and monkeys, therefore drugs with this mechanism such as [Eculizumab] might play a functional role [25]. Another important factor in inflammatory response is TNFα. It is mainly produced by macrophages and to a lesser extent by monocytes and B cells. TNFα stimulates IL1 and IL6 production and is vastly observed in the blood and tissues of COVID-19 patients. Therefore, anti TNFα drugs such as [Adalimumab] and [Infliximab] can be a logical option in the modulation of cytokine storm [26]. Calcitonin gene-related peptide (CGRP) is a potent vasoactive peptide and potential cardio-protective mediator. CGRP has also been found in pulmonary afferent nerve fibers and contributes to the vasodilation of pulmonary vasculature. Studies show that CGRP has an inducing effect on IL6 production; therefore, CGRP antagonists could have effects in treating cytokine storm [27].

Drugs in statin group are also considered potentially effective. Statins can be effective in the modulation of lipids, induction of autophagy, modulation of coagulation process, and regulation of NLRP3 inflammasome mediated inflammation. NLRP3 is a molecule belonging to NLR protein family and has a tripartite structure. It provokes immune system via activation of caspase-1 and IL1ß and IL18 [28, 29]. In another study, it was reported that Haloperidol decreased rate of mortality in patients on mechanical ventilation which might be due to its effect on lowering cytokine levels, therefore it can be potentially useful in combating the inflammatory response in COVID-19 [30, 31].

Role of Interleukin Antagonists in the Modulation of the Cytokine Storm

Several interleukins are involved in the inflammatory response of the cytokine storm such as IL-1β, IL-2, IL-4, IL-6, IL-8, IL-12, IL-13, and IL-17 [32]. One of the major interleukins responsible for the cytokine storm is interleukin 6 which is activated by leukocytes and promotes differentiation of B lymphocytes and secretion of acute phase proteins [33]. Interleukin 6 has an important role in the dendritic cell -T cell interaction which is crucial for the synthesis of T helper 17 cells along with other factors such as TGF-ß and IL-23. The T helper 17 cells secrete interleukin 17 which is responsible for the apoptosis of alveolar epithelial cells and progression to pulmonary fibrosis which compromises normal alveolar architecture, alveolar-capillary gas exchange, and eventually normal oxygenation in the lungs leading to the respiratory symptoms of the disease [32]. It seems that following the increase of IL-6 synthesis in COVID-19 patients, the number of T helper 17 cells escalates noticeably. There are various ways to inhibit IL-17 related pathways such as direct inhibitors, receptor antagonists, and direct pathway blockers [34, 32]. To date, there are three IL-17 blockers available: [Secukinumab]; an IgG 1, which directly binds to IL17A, [Ixekizumab]; an IgG4, which also directly binds to IL17A, and [Brodalumab]; an IgG 2, which binds selectively to IL17A receptor and inhibits its interaction with IL17A [35]. On the other hand, IL-6 acts through the Janus kinase-Signal Transducer and Activator of Transcription (JAK-STAT) signaling pathway to implement various immunological effects such as immune regulation, lymphocyte growth and secretion, and oxidative stress; consequently, finding a way to block the JAK-STAT pathways could actually have a role in reducing the cytokine storm severity [36], and [Ruxolitinib] and [Baricitinib] are drugs with JAK/STAT inhibition potency which could be helpful in this setting [36].

IL-6 effect can also be restricted through IL-6 receptor antagonists such as [Tocilizumab] and [Sarilumab], or by [Siltuximab] which binds directly to IL6 [37]. Tocilizumab has a long half-life and it is not easily available in clinic, therefore there is still a high demand for other potentially effective immunomodulatory drugs [10]. IL1 also plays a noticeable role, for example [Anakinra], a drug with antagonistic effect on IL-1 receptor, is commonly used in rheumatologic conditions and is of great importance in COVID-19 [38]. This is because IL1 is involved considerably in thrombotic complications and venous thromboembolism caused by COVD-19, and also induces the secretion of TNF which itself is a pro inflammatory cytokine. Both IL1 and TNF molecules are involved in the COVID-19 cytokine storm. When an inflammation happens, thromboxane A2, which is released by IL1, causes platelet vascular thrombogenicity both on endothelial and on non-endothelial cells. IL-1 is the most important immune molecule in inducing fever, since it has a role in the metabolism of arachidonic acid which is released from vascular

endothelial organs of the hypothalamus which function as a center for temperature control of the body. [Canakinumab] is another antagonist in this group which is a human monoclonal antibody against IL-1β and is used in the treatment of inflammatory diseases such as Familial Mediterranean Fever, and can have possible effects on COVID-19 related inflammatory response [39]. Hence, blockade or synthesis inhibition of IL-1 blocks all the pathological events, which can lead to death of the COVID-19 patient [40, 41].

Clinical Trials and Case Reports

Tocilizumab

Several studies are performed concerning the effectiveness of interleukin antagonists, among them Tocilizumab and Anakinra are the most worked on.

A clinical trial was performed among 255 COVID-19 patients. The patients were randomly given Sarilumab or Tocilizumab, an IL6 antagonist. Patients were divided into two groups: those requiring ≤45% fraction of inspired oxygen (FiO2) (termed stage IIB, 106 patients) and those requiring >45% FiO2 (termed stage III, 149 patients). Only one patient needed ventilation in group IIB, while 16 patients of group III required mechanical ventilation. Patients treated in stage IIB had lower mortality than those treated in stage III and also had shorter length of stay (mean days of stay 11.3 for IIB versus 15 for III). Hence, IL6 receptor inhibitor administration prior to entering stage III, was associated with improved COVID-19 outcomes [42].

Tocilizumab effects was assessed on 80 COVID-19 patients in a clinical trial. More than 88% of patients who were given IL-6 inhibitor did not need mechanical ventilator (MV). Moreover, Tocilizumab reduced the cytokine storm and inflammatory response in the majority of patients. This reduction in cytokine release appeared to be the cause of decrease in requiring mechanical ventilation of these patients and reduced the mortality and morbidity [6].

A comparative analysis was done on 74 recipients of Tocilizumab and 148 controls who were treated with hydroxychloroquine plus [Lopinavir/ritonavir] or [Remdesivir] as standard of care. In patients with severe disease, Tocilizumab did not seem to have any beneficial effect, while it exerted an obvious improvement in critical patients. A severe case was defined as the presence of respiratory distress, oxygen saturation in room air ≤93% at rest or P/F (arterial pO2 divided by the FIO2) ≤300 mmHg. A critical case was defined as the presence of respiratory failure which needs ventilation (either invasive or not), septic shock or any other organ dysfunction requiring ICU monitoring and treatment. Tocilizumab use was accompanied with a better overall survival compared to controls, but with a longer hospital stay mainly due to biochemical, respiratory and infectious adverse events. It is recommended to use Tocilizumab cautiously regarding its adverse effects, remarkable worsening of respiratory conditions, and bacterial infections. Shortly after Tocilizumab administration, the patients needed a transient ventilation, but they recovered. Since ventilation might compromise drug benefits and patients could proceed to critical state immediately after drug receiving, respiratory monitoring after drug administration is needed [43].

In a clinical trial, effectiveness of Tocilizumab was assessed on 64 COVID-19 patients. Since other factors affect survival rate as well, such as patients' comorbidities and the rate of demand for respiratory support, the study could not support effectiveness of Tocilizumab in modifying mortality of COVID-19 patients with hyper inflammation in 5 days, however, the study showed that it was effective on the survival of patients who stayed alive after 5 days and reduced the rate of mortality between days 6 and 30 on the second outcome, defined as incidence of invasive ventilation, thrombosis and hemorrhage [9].

A series of controversial results were observed in another study. In a retrospective case control study on 45 COVID-19 patients, 20 were treated with Tocilizumab, and 25 treated with standard care. Charlson comorbidity index (19 specific conditions like diabetes, MI, COPD, dementia, etc.) was higher than normal among Tocilizumab group, presented with more severe symptoms such as higher oxygen demand, and had poorer biological findings like severe lymphopenia and higher CRP level than patients without Tocilizumab (5.3 [±2.4] vs 3.4 [±2.6], p=0.014). However, Tocilizumab group accounted for less number of ICU admissions and/or death in comparison with the standard group. Despite the small sample size and the retrospective nature of the work, the study suggests that Tocilizumab may improve the conditions of the patients with severe SARS-CoV2 pneumonia [44]. In contrast, a retrospective study was performed among 224 patients hospitalized with COVID-19. Tocilizumab was administered to two groups of 57 non ICU and 167 ICU patients, and then the rate of fungal infections and in hospital mortality rates were assessed. Tocilizumab was administered to 28.1% of ICU patients and 4.2% of non ICU patients. Rate of fungal infections was significantly higher in patients who received Tocilizumab irrespective of being in ICU or non ICU group. Among the non ICU patients, Tocilizumab was accompanied with higher ratio of later ICU admission. Also in both groups, demand for invasive mechanical ventilation increased, and relatively higher in-hospital mortality rates were observed after Tocilizumab administration. Therefore Tocilizumab did not decrease in-hospital mortality in this cohort [45].

Effects of Tocilizumab was also assessed in a clinical trial among 42 COVID-19 patients in severe and critical stage. Severe stage is defined as chronic obstructive pulmonary disease and lower CRP levels, and critical status is defined as hypertension, diabetes, and higher CRP levels. Among 20 patients in severe conditions, only one patient died, and out of 22 critical patients, 6 patients died, and in general, conditions of 35 patients improved after Tocilizumab administration. Lung images related to the patients before and after receiving Tocilizumab were compared, and seven patients showed worsening pulmonary conditions in imaging, the same number did not represent considerable improvement,

and images of the remaining 28 patients showed noticeable changes in favor of healing. In this study, the mortality rate among patients receiving Tocilizumab in severe or critical status was reported to be 16% with a 6% reduction from 22% mortality rate observed in previous studies [46].

A retrospective analysis was done on 40 patients treated with Tocilizumab, most of whom had several comorbidities, and all had a series of biological abnormalities such as lymphopenia, increased CRP, ferritin, fibrinogen, D-dimer, and liver enzymes. Clinical state in 30 patients improved with Tocilizumab, but 10 patients died. Among the survivors, CRP levels dropped sharply as early as day 4 after Tocilizumab administration, and reached normal levels on day 6. Fibrinogen and lymphocyte count also returned to normal on day 6. Ferritin levels decreased significantly as well. The death of 10 patients a few days after Tocilizumab administration, may suggest that the treatment was too late, therefore it raised the notion "window of opportunity" for Tocilizumab. The dramatic reduction of serum CRP levels were observed both in patients successfully treated with Tocilizumab and in those who died after Tocilizumab administration. further investigations is needed on larger groups of patients for a more definite result [47].

In a multicenter observational study, the association between Tocilizumab exposure and hospital-related mortality among patients requiring intensive care unit (ICU) support for COVID-19 was checked in 13 hospitals. Tocilizumab decreased hospital-related mortality in patients who had CRP levels higher than 15 mg/dL. Additionally, a noticeable decline in mortality was found among patients who required mechanical ventilation and also in patients less than 65 years of age. It could be concluded that Tocilizumab has a suppressing effect on inflammatory stage of COVID-19 patients [8].

In another study the difference between single and multiple doses of Tocilizumab were compared as a single center experience. It appears that a single dose of Tocilizumab may have positive outcomes in critical patients even in those receiving glucocorticoids. Besides, repeated doses (even in lower doses) of Tocilizumab is also beneficial for critically ill patients. It is proven that repeated dosing of Tocilizumab at a frequency of daily, every other day, or every 3 days in various doses would be useful in critical patients, or even in patients whose IL6 levels are exceptionally high (90 times of normal levels). Tocilizumab has a long duration of action and its receptors have saturable binding properties, therefore the dose of Tocilizumab could be reduced with repeated use. Tocilizumab might be effective in the prevention or treatment of cytokine storms. After administration of Tocilizumab most patients recovered from acute phase and were stabilized following a later gradual fall in IL-6 levels [48].

A systematic review was performed on studies about treating COVID-19 patients with Tocilizumab. Total number of 29 patients were enrolled in these studies. IL-6 levels in these patients were elevated initially after Tocilizumab therapy which is in favor of cytokine storm and may persist in a number of patients which was seen among 2 of these patients. However, after initiation of Tocilizumab, C reactive protein levels declined sharply, which shows that this drug is capable of reducing hyper-inflammation but due to the mentioned complications, further investigation is required [7].

Two cases of patients with COVID-19, who received Tocilizumab, complicated with cytokine release syndrome and its fatal correlate, secondary hemophagocytic lymphohistiocytosis (sHLH), were studied. In spite of the medication, they both progressed to sHLH and one of them developed viral myocarditis. Therefore the safety of this drug and the timing for its use should be taken into consideration [49].

Anakinra

In a retrospective cohort study, the effectiveness of Anakinra was evaluated among 36 COVID-19 patients with acute respiratory syndrome. Patients were divided into two groups receiving high dose and low dose of Anakinra and results were compared with a group of patients with standard treatment. Prior to study, 16 patients had received only mechanical ventilation and standard therapy and comprised the study's control group. 29 patients formed the high dose Anakinra group and 7 patients received low dose of Anakinra. In Anakinra group, low dose of Anakinra was not associated with a significant difference in CRP levels or changes in clinical status. However, high-dose drug on 21 patients were associated with reduction in serum CRP and progressive improvement in respiratory function, five patients required mechanical ventilation and the remaining three died. Totally 90% of patients survived in the high dose Anakinra group and 56% in the standard treatment group. Rate of survival without mechanical ventilation was 72% in the high dose Anakinra group versus 50% in the standard treatment group. This study showed that treatment with high-dose Anakinra was safe and associated with better clinical outcomes [10].

A clinical trial was done on nine COVID-19 patients who were all older than 18 years old and their chest CT scans were compatible with COVID-19-pneumonia. After initiation of Anakinra, only one out of nine patients showed acute respiratory failure after 6 hours of drug initiation which demanded discontinuation of therapy. All of the other eight patients showed good clinical and biological outcomes after three days of Anakinra administration. CRP levels decreased steadily during six days of therapy and was normalized on day 11. In all patients, an early chest CT scan between days 5 to 8 showed no more abnormalities. All nine patients were alive at the last follow-up [50].

The efficacy of Anakinra on preventing mechanical ventilation was assessed in a case series among 11 patients with severe COVID-19. Seven of the patients did not require mechanical ventilation, and all of them were discharged. Four patients who received Anakinra in more than 4 days after onset of acute hypoxemic respiratory failure required mechanical ventilation, three of whom were eventually ex-

tubated (2 discharged and 1 remained hospitalized), and 1 died. All 3 patients who were eligible for Anakinra administration (such as documented SARS-CoV-2, fever, and ferritin >1,000 ng/mL with one additional laboratory marker of hyper-inflammation) but did not receive the drug, required mechanical ventilation. Ultimately this study suggests that Anakinra may be a potential option in treating COVID-19 patients with cytokine storm syndrome [51].

Effectiveness of Anakinra; an interleukin 1 inhibitor; was assessed in a case report study among 5 patients with hematological diseases, severe SARS-CoV-2 infection and hyper-inflammation following Tocilizumab treatment. Despite the previous use of Tocilizumab, all patients showed minimal improvement, as they needed higher oxygen aid with progressive elevation of inflammatory markers. After administration of Anakinra, patients' clinical condition continued to deteriorate, as predicted by progressive worsening of radiology images accompanied by continuous rise in inflammatory markers. Moreover, an increase in IL-10, the most immunosuppressive cytokine, was observed after the administration of Anakinra. It seems that Anakinra could not improve clinical status of these patients [52].

The efficacy of Anakinra was studied as a sole treatment on a 47-year-old man with no history of smoking and no noticeable medical history except for well-controlled and untreated asthma, and possible allergy to glucocorticoids. He was primarily treated with hydroxychloroquine, azithromycin, and oxygen but no significant change was observed in the patient symptoms. Following Anakinra administration, an abrupt and progressive improvement occurred in respiratory condition, the patient's fever faded, clinical stabilization was achieved and inflammatory parameters were normalized after 10 days. Also the chest x-ray at this time showed noticeable improvement of the pulmonary infiltrates. Therefore this study reported a well-tolerated case of COVID-19 treated with Anakinra [53].

The effectiveness of Anakinra on a 37 year old male with COVID-19 was studied in a case report. The drug was started with a dose of 100 mg/day. After 7 days of treatment, the patient's retrosternal chest pain was relieved, CRP and D-dimer values, as well as echocardiogram normalized. Anakinra was discontinued 7 days later and the patient was discharged in good clinical condition. He had no problem in his follow-up visit 2 weeks after the hospital discharge, while other treatment options like colchicine and indomethacin did not affect the patient's symptoms considerably prior to the administration of Anakinra. This study suggested that Anakinra may be effective in alleviating COVID-19 inflammatory symptoms [54].

In another case report, the effect of Anakinra on a 57 year old man with COVID-19 was assessed for reducing inflammatory responses caused by the disease. The patient received Anakinra for 7 days along with Tocilizumab and a group of antibiotics. During the follow up, inflammation was diminished and body temperature became normal. By day 16, the patient faced noticeable improvement in respiratory system, in which the oxygen saturation rose to 92% using Venturi mask, but a series of adverse reactions were reported following this study like elevation of procalcitonin, and lung consolidation which was detected on day 10 and could probably be due to persistent viral infection and inflammation. Since Anakinra has a short duration of action, its administration could be discontinued as soon as adverse reactions appear, a property in contrast to long acting medications such as Tocilizumab [38].

Canakinumab

In a prospective study, effectiveness of Canakinumab was evaluated among 150 Covid-19 patients, out of whom 88 patients received Canakinumab. Patients were compared according to changes in oxygen support, duration of hospitalization, and blood factors. In 61.4% of patients, Canakinumab significantly decreased oxygen support requirement. Median range of hospitalization was 24 days in the entire population and 6 days following Canakinumab administration. Also a significant increase in lymphocyte count and decrease in CRP levels were observed among patients who received Canakinumab. [55]

In a study among 48 patients, effects of Canakinumab was assessed on hospitalization duration, survival rate, and oxygen status in a clinical trial. 33 patients received Canakinumab and the rest received standard therapy (antivirals, antibiotics and Hydroxychloroquine). Median age, comorbidities and presenting symptoms were relatively similar between two groups. On day 10 after Canakinumab administration, a 63.2% decrease in supplemental oxygen was observed and ventilation improved significantly. Regarding survival rate, Canakinumab group outnumbered the standard group with 90% survival rate versus 73.3%. The hospitalization rate for less than 21 days was 63% in Canakinumab group, whilst in the standard group all patients were hospitalized more than 21 days [56].

In a study 34 patients were enrolled in a clinical trial to observe the effectiveness of Canakinumab on ICU patients with Covid-19. Effectiveness of this drug was evaluated monitoring inflammation indices and oxygen demand. Patients were divided into two groups of 17 individuals. One group received Canakinumab and the other group received the standard therapy for Covid-19 (Hydroxychloroquine or Lopinavir/Ritonavir). The groups were observed on day zero (before drug administration), day 3 and day 7 of drug administration. Inflammation indices such as D-dimer and fibrinogen dropped significantly, P/F (arterial pO2 divided by the FIO2) ratio increased, and oxygen flow decreased in Canakinumab group on day 3 and 7 versus day zero. On the other hand, supply of oxygen increased in the standard group on day 3 versus day zero, but decreased in day 7 versus day zero. Another finding was the reduction in the lactate levels in Canakinumab group which is a solid sign of reduced respiratory fatigue in this group of patients.[57]

Effects of Canakinumab was evaluated among ten hospitalized COVID-19 patients as a clinical trial and the results were compared with another ten hospitalized COVID-19

patients who did not receive this drug. There were no recorded adverse reactions such as site injection reactions. Following its administration, serum CRP was decreased rapidly and lung oxygenation improved. 45 days after hospitalization, all ten patients in Canakinumab group were discharged from the hospital with no need for oxygen or physical complications related to COVID-19 and no neutropenia or bacterial sepsis was seen. By contrast, the patients on the control group had slower improvements in serum CRP and oxygenation. After 45 days of hospitalization, in non-Canakinumab group, one patient deceased and the others were discharged, among whom one patient required oxygen therapy [58].

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