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Tocilizumab for treatment patients with COVID-19: recommended medication for novel disease

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Abstract

The coronavirus disease 2019 (COVID-19) virus has spread all over the world. Scientists are trying to discover drugs as effective treatment for patients with COVID-19. So far about 30 drugs have been introduced that one of them is Tocilizumab. Recently Tocilizumab has been introduced to treat patients with COVID-19 and researchers are investigating further the efficacy of this drug for different are patients. In Iran and China, some reports showed a positive effect of Tocilizumab on Saturation of Peripheral Oxygen (SPO2) but results of CT scan in patients in different. In some patients, CT scan showed reduced infiltration, however in other no change was observed. Unfortunately, until now there has been no definitive and effective treatment for patients with COVID-19. Although Tocilizumab has been accepted by China Health Commission to treat infected patients, its positive effects still cannot be predicted in all patients. Based on evidence of the Tocilizumab's effect on the SARS COV 2, researchers hope this drug will make effective and promising treatment to improve lung tissue inflammation in patients with the fatal COVID-19

virus. The present study provides an overview of respiratory inflammation with COVID-19 and probable effect of Tocilizumab on SARS-COV 2.

Key words: Tocilizumab, COVID-19, coronavirus disease, actemra

Background

Two known zoonotic coronaviruses, SARS-CoV and MERS-CoV, have been reported to damage the respiratory tract and cause severe outbreaks in the past decade (1-3). The coronavirus disease 2019 (COVID-19) virus, emerged in December 2019 in Wuhan, China (4). On Jan 30, 2020, WHO declared the current novel coronavirus disease 2019 (COVID-19) as the sixth public health emergency epidemic (5) This virus has rapidly spread in china, japan, South Korea and with cases now confirmed in many countries (4, 6).

Common symptoms at the onset of the disease include fever, cough, myalgia, fatigue, dyspnea and diarrhea (7). Most of the patients developed pneumonia, which can rapidly worsen into respiratory failure and develop Acute Respiratory Distress Syndrome (ARDS) (7, 8). Higher susceptibility and mortality was observed in elderly and patients with low immune function (9). According to a report, Yang X and colleague, the mortality for critical cases with ARDS increased and reached 60.5% (10).

Researchers are discovering new drugs to treat this emerging virus. So far about 30 drugs have been introduced to treat patients with COVID-19 such as Lopinavir, Ritonavir, Oseltamivir, and Ganciclovir (9). There is a classification of used drugs to treat respiratory infections from COVID-19 and stratified into three categories: 1. immune system enhancement (Interfron, Glubolin), 2.Chloroquine phosphate, 3. Antiviral components (11). Tocilizumab (a humanized anti-IL-6 receptor antibody) is one of drugs discussed for the treatment of these patients (12). Xiaoling Xu and colleagues conducted a clinical trial study in china and demonstrated that Tocilizumab is effective treatment in patients with severe COVID-19 (13). The current study reviews respiratory inflammation with COVID-19 and probable effect of Tocilizumab on SARS-COV 2.

What's the mechanism of respiratory inflammation with COVID-19?

Although, the exact mechanism of immunology that reinforces the potential damages of the respiratory system with COVID-19 has not been elucidated, but based on SARS COV, we can describe it (13). CD4^{+} T lymphocytes are rapidly activated and-differentiated into T helper and

generate granulocyte-macrophage colony-stimulating factor (GM-CSF). The cytokine environment provides inflammatory monocytes with a high production of inflammatory cytokines such as IL-6 (14). In the observations, large amounts of inflammatory cells infiltrate into the lungs of patients with COVID-19. This process may be responsible for an immune damaging and causing lung functional injuries and quick mortality (15).

According to the studies in ICU patients with COVID-19, higher plasma levels of cytokines including IL-6, IL-2, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), interferon-γ-inducible protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), and tumor necrosis factor alpha (TNF-α) were found (7, 16). This increase of inflammatory cytokine levels occurs as cytokine storm and is related to the severity and prognosis of the disease (16).

Role of IL-6 in lung fibrosis

IL-6 is produced in response to tissue injuries and various types of infections and contributes to host defense through activation of immune responses and stimulation of acute phase reactions. IL-6 is of great importance in the pathogenesis of various inflammatory diseases including infectious inflammations associated with tissue fibrosis and for this reason, tocilizumab, anti-IL-6 receptor antibody, has been developed. IL-6 binds to the membrane IL-6 receptor (IL-6R) which is only expressed on hepatocytes and some of the leukocytes and leads to classical signaling through the membrane-bound β-receptor glycoprotein 130 (gp130) (17, 18). There is another pathway, called trans-signaling, such that IL-6 binds to soluble forms of the IL-6R (sIL-6R), and this complex, IL-6/sIL-6R, can activate all of the tissue cells due to the expression of gp130 on all cells (17, 19). In this section, we review the role of IL-6 in lung inflammation and fibrosis.

Saito and colleagues revealed the significance of IL-6 production in the infiltration of inflammatory cells in Broncho alveolar lavage fluid of wild-type and IL-6-deficient mice were treated with bleomycin. The number of neutrophils and macrophages decreased in BAL fluid in IL-6-deficient mice. In addition, lung pathology showed a decrease of the accumulation of inflammatory cells in IL-6-deficient mice compared with wild type. These findings revealed the significant role of IL-6 in the pathogenesis of bleomycin-induced lung injury and lung fibrosis (17).

Le and colleagues evaluated the importance of soluble IL-6Ra in idiopathic pulmonary fibrosis (IPF). The increase of soluble IL-6Ra was observed in mice during the onset and progression of fibrosis as well as patients with IPF. Neutralization of soluble IL-6Ra attenuated fibrosis in mice by a decrease in collagen, myofibroblasts and fibronectin in the lung. In addition, it has been shown that the production of soluble IL6Ra from macrophages interfere with IL-6 trans signaling and affect fibrosis in lung tissue. These results indicate the recovery of lung fibrosis by neutralization of soluble IL-6Ra (18). Another study was performed by Kobayashi et al. who investigated the neutralizing effect of anti-IL-6 antibody on lung injury induced by bleomycin in mice. Inhibition of the early increase of IL-6 by IL-6 neutralizing antibody promoted apoptosis of type 2 pneumocytes and infiltration of neutrophils and presented lung fibrosis. However, inhibition of the second increase of IL-6 by IL-6-neutralizing antibody recovered fibrosis in the lung. The results of this study showed that IL-6 could have a bidirectional role in the pathogenesis of lung fibrosis in animal models (19).

Tocilizumab

Tocilizumab known as traditional Actemra and Atlizumab is an immunosuppressive humanized monoclonal antibody drug (20-6). This drug is mainly used for the treatment of rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis (21, 22). Tocilizumab selectively and competitively binds to soluble expressing the IL-6 receptor (IL-6) and then blocking the signaling caused by IL-6 (21). This drug displays dose-dependent, nonlinear pharmacokinetics and has a long elimination half-life (22). Mechanism of Tocilizumab for inhibiting IL-6 receptors is shown in fig 1.

The elimination of Tocilizumab has been relatively slow and dependent on concentration. After saturating the IL6 receptors, clearance of dependent begins by the mononuclear phagocyte system. It has been shown that increase of the dose leads to prolongation of the half-life, but it should be considered that the elimination of Tocilizumab is capacity limited (6). In a review study of Sheppard and colleagues (2017), effects of gender, age, ethnicity, mild renal failure and treatment with methotrexate, NSAIDs or corticosteroids on the pharmacokinetics of Tocilizumab were unclear (22).

What is Tocilizumab medical use and side effect?

Tocilizumab is prescribed to treat moderate to severe active arthritis in adults, Giant cell arthritis, Polyarticular juvenile idiopathic arthritis and cytokine release syndrome in patients 2 years of age older with active disease (23, 24). The recommended dose of Tocilizumab is 4-8 mg/kg administered as a single 60- minute intravenous infusion every 4 weeks. This drug should be stored refrigerated at 2 to 8 c (36 to 46 F) (24).

Individuals with active infections should not be treated with Tocilizumab. There are no adequate studies of Tocilizumab in the pregnant women. Also, it is not known whether Tocilizumab is excreted in breast milk (23).

We can categories side effects into 1) common side effects (respiratory tract infections, headache, hypertension, elevation in liver test), 2) reactions of injection site (rash, redness, swelling, itching), 3) associated serious infection (tuberculosis, sepsis, fungal infection), 4) side effects reported in studies (hyper sensitivity reactions, developed cancer, reactivation of herpes zoster, gastrointestinal perforation in patients with diverticulitis) (22, 24).

About side effects of Tocilizumab in infected patient with coronavirus, initial researches did not reveal any side effects. Although may be reported longer time side effects.

Tocilizumab; treatment of COVID-19 infection

Tocilizumab inhibits IL-6- receptor, witch as described above is a key cytokine leading to an inflammatory storm which may result in increased alveolar-capillary blood-gas exchange dysfunction, especially impaired oxygen diffusion, and eventually lead to pulmonary fibrosis and organ failure. (25- 27) Based on some reports, Tocilizumab can be a suitable and effective drug for COVID-19 patients. (28-30)

As mentioned in table 1, to date some studies such as case reports, retrospective studies, and clinical trial about effectiveness of Tocilizumab in COVID-19 have been published in many affected countries i.e. China, France, Italy, Switzerland and Qatar (13, 30-39). However, still no evidence based study confirms efficacy of treatment with this drug. Some researchers have even criticized the use of this drug (40).

Toniati and colleagues in a single center study of 100 patients in Brescia, Italy prescribed 8mg/kg (max800mg) by two consecutive intravenous infusions 12 h apart. Based on the results of this study Tocilizumab was rapid, with sustained response and was associated with significant clinical

improvement in patients with COVID-19. (33) In a retrospective study conducted by Alattar and colleagues in Qatar, 25 patients with COVID-19 received one to three median doses 4.8mg/kg. Result of this study showed that Tocilizumab decreased the inflammatory markers, improved radiological outcomes and reduced needs for ventilator support (34).

In a case report study of 61-year-old man with COVID-19, who underwent kidney transplantation, it was observed that 324 mg Tocilizumab via subcutaneous with hydroxychloroquine can successfully manage the infection (35).

On the other hand, in another study that was recently published, new impact of Tocilizumab administration on mortality in severe COVID-19 was assessed. Patients received several doses of Tocilizumab including 400 mg (96%), followed by 800 mg (1%), 8 mg/kg (1%), and 4 mg/kg (1%). Based on the results of this study, current analysis does not support the use of Tocilizumab for the management of cytokine storm in patients with COVID-19 and use of this drug should be limited (40).

We estimate that many of studies haves mentioned positive effect of Tocilizumab in treatment of COVID-19 but recent studies doubt about its effects.

Expert opinion

The probable reason for the serious deterioration and the loss of some organs in coronavirus disease are cytokines, known as cytokine release syndrome (CRS) (1, 27). Therefore, drugs used in the past for the CRS have been considered as effective drugs for treating patients with COVID-19 (13). Recently Tocilizumab has been introduced to treat patients with COVID-19 and researchers are investigating further the efficacy of this drug for different patients (13).

There are multiple RCTs in progress to evaluate the efficacy of Tocilizumab include NCT04320615, NCT04317092 and NCT04363853. (41) Based on the results of reviewed studies, many patients observed positive effect after prescribing this drug (13, 30-38). However, we cannot claim that Tocilizumab has approved and confirmed positive therapeutic effect on this viral disease.

Initial studies has been shown that Tocilizumab had reduced mortality and improved clinical manifestation in patients infected with coronavirus. (30-40) But recently, Andrew Tsai and colleagues published an article that debates the use of Tocilizumab should be limited to the context of a clinical trial until more evidence is available (40). Indeed, the researchers claimed there was

no difference in mortality in patients treated with tocilizumab versus those receiving supportive care. However, a systematic review study conducted by Avi Kaye and Robert Siegel in Stanford University, investigating several other studies, concluded positive evidence for the potential efficacy of Tocilizumab resulting in less deaths. (42-44). According to the authors of this article, notable limitations such as different data of geographies, resources, demographics, and TCZ dosing amount, number and timing can affect the result of main conclusion. In this regard different studies have different participants, complementary drugs such as hydroxychloroquine, azithromycin, lopinavir/ritonavir, ribavirin, and/or interferon α2-a, Meropenem, Azithromycin and dexamethasone, different doses (4, 8 mg/kg), different time (1,2,3) and different route (IV, SQ). Therefore, we can assert that continuous accurate protocol and method of treatment with Tocilizumab is not found and physicians prescribe this drug with trial and error.

In some studies observed positive effect of Tocilizumab with combination of antiviral drugs such as lopinavir/ritonavir (400 mg/100 mg twice a day) or remdesivir 100 mg/day and corticosteroids able to improve clinical manifestations of patients. In this studies other drugs were different, for example in chinies and Italian clinical trials some drugs such as glucocorticoid, interferon α2, and antibiotic were used. Therefore, maybe antiviral drug, especially lopinavir/ritonavir (400 mg/100 mg twice a day) with Tocilizumab reduced mortality in severe COVID-19 patients.

Timing for prescribing Tocilizumab and selecting suitable patients for treatment is also an important question. All of the reviewed studies included patients in severe phase of disease. Some researchers claim that the optimal time to prescribing Tocilizumab is in beginning of inflammation and first steps of dropping O2 saturation. But still accurate time and infection stage to start this drug is unclear.

Comparison the clinical differences between effective (30-40) and ineffective (47) treatments revealed the importance of time of administration and combination therapy with antivirals and Tocilizumab. In one clinical trial show ineffective treatment, Tocilizumab administer before the progression of respiratory failure and in patients who met the aforementioned criteria for disease severity. In this trial patient didn't received any antiviral drug (47). Administration of Tocilizumab in the studies with effective results were combined with an antiviral drug and for patients with severe COVID-19.

There have been few reports about side effects after use of Tocilizumab. For example study of Campochiaro and colleagues Bacterial/fungal infection showed side effects only in 13% of patients

who received this drug (42).In another study, Rojas-Marte and colleagues, reported bacteremia, fever, cough and shortness of breath (45). Majority of studies did not find any side effects after use of Tocilizumab in patients affected with COVID-19 until with twice prescribing (46, 48). Due to the current pandemic situation and three speed of resource dissemination, there may be side effects but they are not reported. On the other hand, taking drugs at the same time makes it difficult to judge the side effects.

We should know that Tocilizumab is not an anti-viral drug and may only be effective in a group of patients with inflammation and lung damage caused by the coronavirus. Another important point is that excessive production and activity of Tocilizumab can cause autoimmune diseases and damage body tissues (26-29). This drug is very sensitive and can be used in a specific age and certain patients. As a result of review of the published data and based on the mechanism of action of Tocilizumab, we may be able to claim that this drug can be a better or more suitable choice to be used for in patients with higher IL-6 level than normal.

Although Tocilizumab has been accepted by China Health Commission and also recommended by some other health commissions all over the world, its positive effects cannot be predicted in all patients.

Conclusion

Tocilizumab may have a positive effect on improving immune damaging, lung functional injuries and arterial oxygen saturation. Researchers who had the successful experience of using this drug for treating inflammation lungs diseases, hope it will make effective and promising treatment to improve lung tissue inflammation in patients with fatal COVID-19 virus. However, further accurate clinical trial studies are needed to determine its efficacy in patients with specific characteristics such as age, level of IL-6, and different clinical symptoms.

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- Tocilizumab is a suggested anti-inflammatory drug to treatment COVID-19
- Our study is immunopharmacology review that can be suitable for now
- Tocilizumab is effective treatment in patients with severe COVID-19
- Still accurate time and infection stage to start this drug is unclear
- Accurate clinical trial studies are needed to determine Tocilizumab efficacy

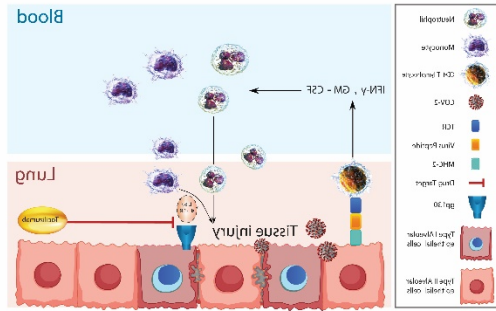|	Table 1: Clinical outcomes of patients with Covid-19 after Tocilizumab therapy					
References cited in the text	**Title**	**Country**	**Patient no**	**Study design**	**Dose of Tocilizumab**	**Other drug**
13	Effective treatment of severe COVID-19 patients with tocilizumab	China	21 Patients with severe COVID-19 ranged from 25 to 88 y	Clinical trial	4–8mg/kg (one dose) and 400 mg through an IV drip up to a maximum of 800 mg (3 dose)	antiviral therapy of lopinavir/ ritonavir (200/50 mg per tablet for adults twice a day, IFN-α (5 million U each time for adults or equivalent dissolved in 2 mL of sterilized water and aerosol inhalation twice a day, ribavirin (recommended for use with IFN or lopinavir/ritonavir, 500 mg per dose for adults glucocorticoid (use for a short period of time, range 3 to 5 d, as appropriate, at a dose not exceeding the equivalent of 1 to 2 mg/kg per day methylprednisolone
31	Tocilizumab, an anti-IL6 receptor antibody, to treat Covid-19-related respiratory failure: a case report	France	42 year patient with COVID-19	Case report	8 mg/kg IV for each dose, 8 hours apart	lopinavir-ritonavir 400 mg-100 mg orally
32	Tocilizumabtreat mentinCOVID-19 :A single center experience	China	15 patients with severe COVID-19	Retrospective study	80 to 600mg per time	Unclear
33	COVID-19 in a patient with systemic sclerosis treated with	Switze rland	57- year- old woman with systemic sclerosis	Case report	8 mg/kg IV every 4 weeks	Unclear

	tocilizumab for SSc- ILD		(SSc) and COVID-19		
34	Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatorysyndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy	Italy	100 patients with severe COVID-19	Clinical trial	8mg/kg (max800mg) by two IV infusions 12 h apart	antiviral drugs (lopinavir 400 mg + ritonavir 100 mg twice a day or remdesivir 100 mg/day), antibiotic prophylaxis (azithromycin, ceftriaxone or piperacillin/tazobactam), hydroxychloroquine400mg/day and dexamethasone20mg/ day
35	Tocilizumab for the treatment of severe coronavirus disease 2019	Qatar	25 patients with severe COVID-19	Retrospective study	4.8mg/kg (range, 2.7-7.5mg/kg) (one to three doses)	hydroxychloroquine, azithromycin, lopinavir/ritonavir, ribavirin, and/or interferon α2-a
36	COVID-19 pneumonia in a kidney transplant recipient successfully treated with tocilizumab and hydroxychloroquine	Italy	61-year-old man, who underwent kidney transplantation	Case report	324 mg SC	Meropenem, Azithromycin was administered orally for 3 days, Hydroxychloroquine, IVIG
37	Off-label useoftocilizumabinpatientswithSARS-CoV-2 infection	Italy	Three patients with COVID-19	Case series	8mg/kg IV with a second dose 12hours after the first and a possible third dose after further 24-36 hours (three dose)	Unclear
38	Rapid and Severe Covid-19 Pneumonia with Severe Acute Chest Syndrome in a Sickle Cell Patient Successfully Treated with Tocilizumab	France	One patient with Severe Acute Chest Syndrome in a Sickle Cell	Case report	8 mg/kg IV (one dose)	Hydroxychloroquine

39	Favorable changes of CT findings in a patient with COVID-19 pneumonia after treatment with tocilizumab	Italy	A 64 old man with	Case report	8 mg/kg (two doses)	Unclear
40	Hydroxychloroquine and Tocilizumab Therapy in COVID-19 Patients - An Observational Study	US	198 patients	Observational Study	400 mg (96%), followed by 800 mg (1%), 8 mg/kg (1%), 4 mg/kg (1%)	Unclear
41	Impact of tocilizumab administration on mortality in severe COVID-19	New Jersey	132 patients	Cohort study	10 patients (15.1%) received 800 mg of tocilizumab, 3 patients (4.5%) received 600mg of tocilizumab, and 53 patients (80.3%) received 400 mg	Unclear
46	Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study	Italy	32 patients	Cohort study	400 mg IV	hydroxychloroquine 400 mg daily, lopinavir/ritonavir 400/100 mg twice daily, ceftriaxone 2 gr for 6 days, azithromycin 500 mg daily
47	Outcomes in patients with severe COVID-19 disease treated with tocilizumab: a case–controlled study	USA	96 patients	Case–control	Unclear	Hydroxychloroquine, Azithromycin, Corticosteroids, Remdesivir, Vitamin C, Zinc

48	Tocilizumab for Treatment of Severe COVID-19 Patients: Preliminary Results from SMAtteo COvid19 REgistry (SMACORE)	Italy	21 patients	Clinical trial	8 mg/kg IV (up to a maximum 800 mg per dose)	hydroxychloroquine (200 mg bid), azithromycin (500 mg once), prophylactic dose of low weight heparin, and methylprednisolone (a tapered dose of 1 mg/kg up to a maximum of 80 mg)
49	Improved survival outcome in SARs-CoV-2 (COVID-19) Acute Respiratory Distress Syndrome patients with Tocilizumab administration		44 patients	Case- control	Unclear	Hydroxychloroquine, Azithromycin, Steroids - hydrocortisone/ methylprednisolone/ dexamethasone
	COVID-19: corona virus disease -19 , TCZ: Tocilizumab, CRP: C-reactive protein, IVIG: intravenous immune globulin, SPO2:Satu Computed tomography, SSc: systemic sclerosis, IV: Intra venous, SC: Subcutaneous					