REVIEW ARTICLE

A Narrative Review on the Effectiveness of Tocilizumab in Reducing the Mortality Risk in COVID-19 Patients

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ABSTRACT

The novel coronavirus disease 2019 (COVID-19) has reached its pandemic scale within a short period of its first case reported in Wuhan, China in December 2019, leading to a great economic crisis all over the world. As of today, there is no clinically approved antiviral drug available for the treatment of COVID-19. Tocilizumab, a humanized monoclonal antibody against the interleukin-6 (IL-6) receptor, clinically approved for the treatment of rheumatoid arthritis, is one such drug used to manage the COVID-19 symptoms. The current study reviews the effectiveness of Tocilizumab as a treatment option for COVID-19. Research findings on Tocilizumab are effective in COVID-19 patients with the risk of cytokine storm and further complications. Nevertheless, this review also recommends further investigation on the effectiveness of this drug with a large group of patients for more accuracy in results with COVID 19 patients.

Keywords: COVID-19, SARS-CoV-2, Tocilizumab, Interleukin-6 inhibitors, Cytokine storm

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INTRODUCTION

In previous decades, there were two endemics of coronaviruses involving the transmission from animals to humans namely, the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). In late December 2019, another class of coronavirus outbreak that causes infectious respiratory disease from the human-to-human transmission and was first disclosed in Wuhan, China. This infectious virus has rapidly spread to other parts of the world and has caused a rise in cases of infections. The virus has caused a cluster of pneumonia cases from unknown aetiology. The pathogenic disease is then discovered to be caused by the new strain of coronavirus. The disease is now termed Coronavirus Disease 2019 (COVID-19). COVID-19 cases kept increasing in China and exported to outside of China when the first case of infection was detected in Bangkok, Thailand. On March 11, the World Health Organization (WHO) has announced it as a pandemic since the disease has spread across multiple continents. As of 25th December 2020, almost 78 million people were infected across 222 countries with the fatality of about 1735752 lives (1). In Malaysia, the total number of cases were about 101,565 with 445 deaths. (2).

An unknown β-coronavirus strain has been detected in all COVID-19 patients that were diagnosed with pneumonia following a virus genome sequencing. The separation of the β-coronavirus strain exhibited major similarities to two types of bat and pangolin-derived coronavirus strain which imitate the SARS-CoV-2 in about 96% match and about 92% respectively (RaTG13 and GD/P1L). Following that, the International Virus Classification Commission had decided to name the newly found strain of coronavirus with SARS-CoV-2. SARS-CoV-2 has a genome similar to the typical coronaviruses (3).

SARS-CoV-2 was revealed to have the initial clinical manifestations that affect the respiratory system and fever (4). An early report of pathological characteristics of a death case in a patient with severe SARS-CoV-2 infection revealed an elevation of increased concentration in proinflammatory cytokines (5). The over production of proinflammatory cytokines has been inducing the cytokine storm in a large population of patients that are critically infected with SARS-CoV-2 (6,7). Cytokine storm plays an important role in the development of disease aggravation (8). Currently, there are no clinically proven vaccines or antiviral drugs that are available as the standard treatment of this pathogenic COVID-19. Therefore, there is an urge to develop the potential effective therapeutic drugs to control the worsening condition of COVID-19 patients. The critically ill patients are given supportive treatments only since there is no standard treatment yet to be established. There

are clinical data on the surge of interleukin-6 (IL-6) in critical patients with COVID-19 and this elevation of IL-6, a pro-inflammatory cytokine is an important cause of the risk to develop cytokine storm. Cytokine storm induces acute respiratory distress syndrome (ARDS) or multiple organ failure which can collapse the immune system and lead to fatality (9,10).

Tocilizumab, which is a monoclonal antibody IL-6 inhibitor has its therapeutic effect on acting against IL-6 in case of a cytokine storm. Tocilizumab is the earliest recombinant humanized monoclonal antibody which inhibits the IL-6 receptor. Tocilizumab has been approved for the treatment of rheumatoid arthritis (RA), Castleman's disease, polyarticular juvenile idiopathic arthritis (PJIA), systemic juvenile idiopathic arthritis (SJIA), giant cell arthritis and chimeric antigen receptor(CAR) T cell therapy-induced CRS (11,12). It was first brought commercially under the trade name of RoActemra in the European Union and Actemra in the United States (13). Tocilizumab was synthesized by the graft of complementary determining regions of a laboratory mouse antibody of IL-6 receptor onto the IgG1 which was the human (14). Tocilizumab was involved in clinical trials in 1997 which began with the clinical trial for the use of Tocilizumab in RA.

A few years later, Tocilizumab was recognized to be introduced as the pioneer of a biologic drug to treat RA patients in moderate to severe cases and the only biologic drug in first-line therapy to treat SJIA (15). Randomized clinical trials have proven the therapeutic effectiveness of Tocilizumab in RA patients in single therapy or combined therapy together with Methotrexate (MTX) which is one of the disease-modifying anti-rheumatic drugs (DMARDs) if the patients have failed in response to TNF inhibitors (16). To date, Tocilizumab use is currently approved in 116 countries for the treatment of rheumatoid arthritis (RA). Tocilizumab is clinically administered via subcutaneous (SC) and intravenous (IV) routes. Tocilizumab molecular formula is C6428H9976N1720O2018S42 and exists molecularly with the mass of 145.0 kDa (17). Most mesenchymal and immune cells are involved in the production of IL-6 (18). In typical conditions, the amount of IL-6 is produced in small amounts and can be synthesized rapidly to improve the protective mechanism of the body when it is triggered by an infection or injury. An IL-6 cytokine-receptor complex will form when IL-6 binds to its target receptor. This in turn helps the cytokine-receptor complex to stimulate the signal transduction by binding to the glycoprotein gp-130. IL-6 receptors are available in two different forms which are the membrane-bound (mIL-6R) and a soluble form (sIL-6R). Both receptors involved in the transduction signalling mechanism by forming binding complexes with IL-6. Besides, the respective binding-complex will further attach to gp-130 and acts against the inflammation. Both receptors are distinguishable by the signalling effect that they are involved in, mIL-6 R involves in the classical signalling transduction mechanism while sIL-6 R plays a major role in intracellular signalling transduction (19). Other than that, IL-6 can work distinctly in different signalling pathways through separate mediators to generate acute reactive protein which is the Janus Kinases/Signal transducer and activator of transcription protein (JAK/STAT) tyrosine kinase pathway and MAPK/NF-κB-IL-6 pathway. To add on, IL-6 R has a low expression rate which causes most IL-6 to be unresponsive towards the signalling. However, some IL-6 can respond to the signalling by forming the respective binding complex and produce the desired signal transduction (20,21) In classical signalling, the activity is restricted to only for the immune cells that express mIL-6 R. Nonetheless, gp-130 is widely available and an elevation of IL-6 level in the immune system will cause a great expression of signalling activities of IL-6. The signalling activities will induce pro-inflammatory actions of the IL-6 (22). Tocilizumab works by inhibiting the classic and trans-signalling of IL-6 on immune effector cell by binding to both soluble and membrane-bound IL-6 receptor. Tocilizumab restrains the immune system (23). Fig. 1 illustrates the general mechanism of blocking IL-6 signalling by Tocilizumab (24).

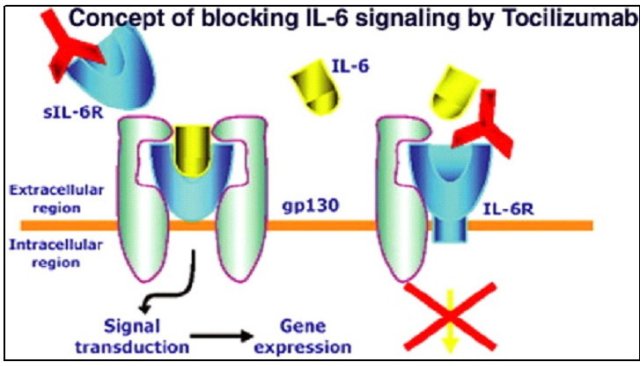

Figure 1: General mechanism of blocking IL-6 signalling by Tocilizumab

Cytokine release syndrome in covid-19

Cytokine storm occurs when the immune system becomes disoriented and the inflammatory response flares out of control. Cytokines are a group of small proteins that are product of secretion of cells and they are utilized for the signalling and communication process between cells (25). They have various biological functions such as balancing the innate immunity, adaptive immunity, haematopoiesis, involves in the growth and differentiation of cells, and bind to the receptors to repair damaged tissues (7). Different cytokines show different types of response by which their reaction depend upon the target cell through receptor binding. Each cytokine has different activities such as autocrine, paracrine, and/or endocrine activity. Among the various types of cytokines, they carry out functions such as control the cell proliferation and differentiation, balancing the angiogenesis and immune and response of inflammation (25). Interleukins are the cytokines that

are associated with the cytokine storm. Interleukins have various actions such as to balance the immune system by involving primarily in immune cell differentiation and activation. They possess both pro-inflammatory and anti-inflammatory properties. Cytokine storm is characterized by an inflammation that spreads to the systemic circulation and begins at a localized site.

Pathophysiology of Cytokine Release Syndrome in COVID-19

SARS-CoV-2 enter the cells via angiotensin-converting enzyme–related carboxypeptidase (ACE2) receptor (26). This receptor is mainly found in cardiopulmonary tissues and some haematopoietic cells (27).Infections of inflammatory cells such as monocytes, macrophages, and dendritic cells that are caused by beta-coronaviruses lead IL-6 to the activation and secretion of IL-6 and other inflammatory cytokines.

Cytokine release syndrome (CRS) typically occurs following the effects of binding of the antibody or CAR T cell towards the specific antigen and its consecutive stimulation of bystander cells including both immune cells and non-immune cells. The stimulation of those cells will cause the widespread release of cytokines. The stimulation of CAR T cells may induce the exaggeration of activities in the cytokine pathway which triggers CRS-induced inflammation (28). Relating to the clinical treatment which involves T-cell activities, the overproduction of IFN-γ cytokine following the activation of T cells or tumour cells may cause CRS. The overproduction of IFN-γ cytokine may be indicated by the presence of fever, chills, headache, dizziness, and fatigue. Also, it could stimulate macrophages activity (25). Once the macrophages are active, they release a great number of cytokines including IL-6, TNF-α, and IL-10. The overproduction of TNF-α is highlighted by the exhibition of clinical manifestations very much alike to the ones that occur due to the overproduction of IFN- γ but it seems to be highly accountable for the occurrence of watery diarrhoea, vascular leakage, cardiomyopathy, lung injury, and acute phase proteins generation. A significant increase of IL-6 is highlighted in CRS patients and is believed to be one of the golden tickets to resolve CRS (29,30,31).

IL-6 which has notable proinflammatory properties can signal through two different signal transduction pathways which are acknowledged as classical cis-signal transduction and trans-signal transduction (32). IL-6 binds to its membrane-bound receptor (mIL-6R) in a complex with membrane protein gp130 and the mediator of downstream signal transduction is Janus kinases (JAKs) and signal transducer and activator of transcription 3 (STAT3) in cis-signal transduction (27). This will initiate the intracellular signal transduction (33). The membrane-bound gp130 is widely expressed compared to the expression of mIL-6R which it is mainly limited to immune cells. The activation of IL-6 via cis-signal transduction emerges the diverse effects on B and T cells and the innate immune system which lead to the development of CRS (32) In addition, IL-6R also exists in a soluble form(33). In trans-signal transduction, IL-6 makes binding to the soluble form of its receptor (sIL-6R) to form a complex with gp130 dimer on cell surfaces (34). The complex form via IL-6–sIL-6R–JAK-STAT3 signalling process is then activated in cells that particularly do not involve the expression of the membrane-bound IL-6 receptor (35). This activation leads to cytokine storm in the systemic circulation (27).

The signaling of IL-6 via the trans-signaling pathway triggers the severe clinical manifestations of CRS such as the vascular leakage and generation of overflow complement and coagulation which generates the disseminated intravascular coagulation (36). Cardiomyopathy is likely to occur due to the IL-6 action interrupting the normal condition of the muscular tissue of the heart (37). Moreover, CRS events can be marked by endothelial cell activity stimulation which is notable with the increase of Ang-2 and von Willebrand factor in serum. The endothelium has an important role in the intensification of inflammation and works as a target organ. This role can be proven by the prevalence of capillary leakage, hypotension, and coagulopathy that occur in severe CRS cases (38).

Referring to a research study that has been carried out on death of a CRS patient due to CD19-targeted CAR T cell treatment course, the endothelial cells have been discovered to provide a noteworthy amount of IL-6 in CRS condition (39). Another point to be taken seriously is that the activated endothelial cells and their consequence of the impaired vascular system could be the structural determinant of connecting the relationship of CRS with the consequence of neurotoxicity. This can be proven by a research study that has noted a neurotoxicity occurrence that followed after a therapy involving the immune system using CD19-targeted CAR T cells which were associated with the continuous findings of activated endothelium cells (40). In addition, other related cytokines such as IL-18, IL8, IP10, MCP1, MIG, and MIP1β shown a consequential increase in CRS cases accompanied with conditions similarto HLH/MAS (41)(41). IL-6 could be inducing the occurrence of HLH/MAS which accompanies the CRS by promoting the impairment inactivity of cytotoxic T and NK cells which these dysfunctionalities significantly indicate HLH and MAS (42).

Complications of Cytokine Release Syndrome

The complications of CRS usually have a significant risk of fatality. Some of the complications are acute lung injury (ALI), acute respiratory syndrome (ARDS), multiple organ failure, neurologic toxicity, and tumour lysis syndromes. ALI may be one of the resultant complications of cytokine storm in the alveoli in lung and systemic circulation. It is usually related to infections in the lungs or other organs

(43). ALI occurrence in humans is marked by acute mononuclear or neutrophilic inflammatory response before the chronic fibro proliferative phase which can be characterized by deposition of collagen in the lung. Injury of the lungs may develop into more severe form which is the acute respiratory distress syndrome (ARDS) as usually seen in SARS-CoV and influenza virus cases (25). Moreover, ARDS is associated with the inflammatory cytokine storm in which the patients have a significant elevation of serum cytokines level (23). Extrapulmonary organ failure can be characterized by clinical signs such as elevated liver enzymes and creatinine level which are present in some COVID-19 patients that have no respiratory failure condition (44). The high levels of cytokines in pro-inflammatory action which cause the cytokine storm can lead to shock, damage of extrapulmonary tissues and organs that lead to the risk of fatality (45,23). Cytokine storm also interferes with the extensive pulmonary pathology which contributes to the massive neutrophils and macrophages infiltration, diffuses alveolar damage and increases thickness of the alveolar wall. There are also possibilities of the development of spleen atrophy and lymph node necrosis as observed in some patients which signal the immune-immune- mediated damage (45). Neurologic toxicity associated by CRS is characterized with the neurologic symptoms which may present when other CRS symptoms coexist or getting resolved. Tumour lysis syndrome can occur coincidently with CRS due to hyperactivation of immune cells and the expansion is complement to antitumor efficacy (46).

METHODS OF DATA COLLECTION AND REVIEW

The focus of this review is to cover the indication on the use of Tocilizumab in reducing disease aggravation of severe COVID-19 cases and the mechanism of action of Tocilizumab in the occurrence of cytokine storm that affects the inflammatory reaction and immune response in COVID-19 patients. The different drug regimens that have been used were also analysed and compared. The articles collected consist of the recent findings on the effectiveness of the use of Tocilizumab that resulted in the resolution of symptoms of severe COVID-19 cases and they are published between December 2019 and July 2020. The findings from the multiple research studies included in this review will be a useful tool in delivering the importance of Tocilizumab in the treatment of COVID 19. The search results on pharmacological action of Tocilizumab will be used to investigate its properties as a potential drug in resolving disease aggravation and reducing the risk of fatality in patients with COVID-19. Moreover, this research study will be an aid for the ongoing antiviral drug research for this pandemic illness and for the future research community which is interested in this drug.

This review was performed based on the established and proven data collected from various literature sources through Scopus, PubMed, and Google Scholar databases. The literature search was carried out focused on the articles that have been published until July 2020 using the keywords such as “COVID-19”, “Tocilizumab”, “interleukin-6 inhibitors” or “IL-6”, cytokine storm.

The articles were collected and screened by reading the written titles, abstract and related keywords before the further selection process. The selection of the articles was carried out based on the inclusion and exclusion criteria that have been decided. The criteria were set to filter irrelevant and extraneous materials from being included in this review. The criteria that have been used for the selection of articles are such as they contain relevant data or studies involving the usage of Tocilizumab in humans as a treatment option to resolve disease aggravation of COVID-19 infection cases, published in the related databases with above said period and published in the English language. The articles would be excluded and considered inapplicable if they are found to be:

1. involving the usage of Tocilizumab in non-human studies
2. consisting pathological conditions not associated with COVID-19
3. published in non-English language having inadequate information to be used to be included in the review.

TOCILIZUMAB THERAPY IN COVID-19

Based on the findings in each study involving the Tocilizumab therapy in COVID-19 patients, 149 cases of COVID-19 patients who received the Tocilizumab therapy were analysed. The cases were extracted from grouped studies and individual studies of the patients. From the extracted cases, most studies have reported the severity of condition of the patients. The total number of cases with reported patients’ conditions is 114 cases. The conditions of the patients are classified into four categories which are mild, moderate, severe, and critically severe based on the guidelines of diagnosis and treatment of pneumonia infected by Novel Coronavirus issued by the National Health Commission of China (47). There were no mild cases reported. There were 3.5% of moderate infection of COVID-19 cases, 81.60% of cases of severe patient condition, and 14.90% of critically severe COVID-19 cases. Most patients were associated with comorbidities including hypertension, diabetes mellitus, stroke, cardiovascular diseases, cancer, rheumatologic diseases, and anaemia. Moreover, most of the studies have reported the use of Tocilizumab therapy in detail for any concomitant use of other therapy in patients’ treatment courses with an exception of the study that was reported by Giamarellos-Bourboulis et al., (48), which brings the total of reported cases respective to the Tocilizumab therapy details to 95 cases. About 93% of the cases have been reported to include other therapies in the treatment course for COVID-19 patients and 7.37% of the total

cases used Tocilizumab in monotherapy. Each case which includes the combined therapies used a different therapy approach based on each patient's condition. The combined therapies include the use of Lopinavir, Lopinavir/Ritonavir, and Hydroxychloroquine therapies specifically to resolve COVID-19 symptoms. The details of a retrospective analysis of patient conditions are summarised in two tables. Table I comprises of the demographic information, comorbidities, and severity of condition of patients in grouped studies and Table II includes the clinical manifestations, treatment details and the condition of the patients following Tocilizumab treatment course. Table III highlights the demographic information, comorbidities, symptoms condition severity, therapy details and condition of patients following Tocilizumab therapy in individual studies.

IMPROVEMENTS ON IMMUNE DYSREGULATION

Zhang et al. have reported a reduction of serum IL-6 level in their case study. The patient involved in their case report, has received IV Tocilizumab for 8 mg/kg due to the high level of serum IL-6 on day 9 of his hospitalization. Not long after, his serum IL-6 level showed a significant reduction from 121.59 to 20.81 pg/ml in the following 10 days. Nonetheless, it accelerated to the peak, to 317.38 pg/mL, and then successfully declined to 117.10 pg/mL. Besides, an improvement in the expression of HLA-DR was detected after Tocilizumab therapy as it increased significantly due to the inhibition of IL-6 receptor. This was proven by Giamarellos-Bourboulis et al. in a clinical report. They reported that peripheral blood mononuclear cells (PBMCs) from COVID-19 patients with immune dysregulation were taken for sampling and cultured overnight with the patients' IL-6-rich plasma. The results showed that the expression of HLA-DR on CD14 monocytes was inhibited by the IL-6 in plasma. The inclusion of Tocilizumab to block the IL-6 pathway was successful as it has partly improved the expression of HLA-DR on monocytes. Moreover, the administration of Tocilizumab in six COVID-19 patients with immune dysregulation has elevated the plasma lymphocyte count within the first 24 hours. The absolute lymphocyte count has supported that Tocilizumab has a clear potential to treat COVID-19-induced immune dysregulation.

Furthermore, there is also a potential for the reduction of the CRP level. Xu et al. have successfully identified that there was notable improvement in the C-reactive protein (CRP) level which 16 patients out of 19 patients had restored their CRP levels to a normal level and Tocilizumab addition to antiviral therapy has proven it (11,49). In addition, Zhang et al. have detected a remarkable response of restoration of normal T cells post-Tocilizumab therapy to a patient in their case report. The patient that was involved in their case report has received IV Tocilizumab for 8 mg/kg due to the high level of serum IL-6 on day 9 of his hospitalization. After several days, his serum IL-6 level showed an inconsistent

Table I: Demographic details, comorbidities, and severity of condition of COVID-19 patients.

Author	Population (n)	Mean age	Gender		Comorbidities						Severity of condition			
			Male (%)	Female (%)	HTN (%)	DM (%)	Str. (%)	CVD (%)	Cancer (%)	Others (%)	Mild (%)	Moderate (%)	Severe (%)	Critically severe (%)
Morena et al., 2020	51	60	78.4	21.6	29.4	11.8	-	49.0	5.9	CLD: 9.8 RD:5.9 Oth-er:5.9	-	3.9	84.3	11.8
Giamarellos-Bourboulis et al., 2020	54	64	74.0	26.0	-	18.5	-	26.0	0	-	-	-	52.0	-
Xu et al., 2020	20	56.8	85.7	14.3	-	-	-	-	-	-	-	-	81.0	19.0

HTN, hypertension; DM, diabetes mellitus; Str., stroke; CVD, cardiovascular diseases; CLD, chronic lung disease; RD, rheumatologic diseases.n grouped studies.

Table II: Clinical manifestations, treatment details and the condition of the patients following Tocilizumab treatment course in grouped studies.

Author	Clinical manifestations						Combined therapy	Initiation dose of TCZ (mg)	Condition status Post-TCZ Therapy		
	Fever (%)	Cough (%)	Fatigue (%)	Dyspnea (%)	Chest pain (%)	Others (%)			Discharged (%)	Hospital-ized (%)	Death (%)
Morena et al., 2020	74.5	62.7	-	54.9	-	-	Lopinavir/ritonavir (400 mg/100 mg) Hydroxychloro-quine (200 mg BID)	400 8 mg/kg (in patients with body weight ≥ 60 kg)	61.0	12.0	27.0
Giamarel-los-Bourboulis et al., 2020	-	-	-	-	-	-	-	-	-	100	N/A
Xu et al., 2020	100.0	66.7	28.6	28.6	-	Nausea: 19.0	Lopinavir MP	400	90.5	9.5	-

TCZ, Tocilizumab; MP, Methylprednisolone.

Table III: Demographic information, comorbidities, symptoms, condition severity, therapy details and condition of patients following Tocilizumab therapy in individual studies.

Case	Author	Age	Gender	Comorbidities	Symptoms	Severity of condition				Combined therapy	Initiation Dose (mg)	Initiation dose of TCZ (mg)	Condition status post-TCZ therapy
						Mild	Moderate	Severe	Critically severe				
1	(Luo et al., 2020)	73	M	HTN	-				Yes	MP	40	480	Death
2		62	M	-	-				Yes	MP	40	600	Death
3		62	M	HTN	-				Yes	MP	80 (BID)	320	Death
4		74	M	HTN Stroke history	-				Yes	-	-	480	Stabilized
5		72	M	HTN	-				Yes	-	-	100	Stabilized
6		73	M	-	-				Yes	-	-	80	Stabilized
7		65	M	HTN Stroke history	-				Yes	MP	40	480	Worsen
8		66	F	Stroke history	-			Yes		MP	80	480	Stabilized
9		73	M	HTN Diabetes	-			Yes		-	-	480	Stabilized
10		77	M	HTN Diabetes	-			Yes		-	-	400	Stabilized
11		65	F	HTN Diabetes	-			Yes		MP	40	400	Stabilized
12		77	M	HTN Diabetes	-			Yes		-	-	400	Improved
13		75	M	-	-		Yes			MP	40	480	Stabilized
14		77	M	-	-		Yes			-	-	80	Stabilized
15		80	F	-	-			Yes		MP	40	240	Worsen
16	(Radbel, Narayanan, & Bhatt, 2020)	40	M	-	Fever Dry cough Dyspnea	-	-	-	-	Hydroxy-chloroquine Azithromy-cin Bumetanide Norepi-nephrine	-	400 mg	Death
17		69	F	Diabetes Rheumatoid arthritis Aplastic anaemia	Produc-tive cough Pleuritic chest pain Fever Fatigue Abdomi-nal pain	-	-	-	-	Hydroxy-chloroquine Azithromy-cin Norepi-nephrine	-	560	Death
18	orrison et al., 2020	65	M	-	-	-	-	-	-	Lopinavir/ ritonavir Ribavirin Hydroxy-chloroquine Propofol	-	-	Hospitalized
19		43	M	-	-	-	-	-	-	Lopinavir/ ritonavir Ribavirin Hydroxy-chloroquine Propofol Midazolam	-	-	Hospitalized
20	(Zhang et al., 2020)	60	M	Multiple myeloma	Chest tightness Dyspnea	-	-	-	-	MP	40	8 mg/kg	Discharged
21	(Michot et al., 2020)	42	M	Metastatic sarcomatoid clear cell renal cell carcinoma	Fever Mild cough	-	-	-	-	Lopinavir/ ritonavir	400/100	8 mg/kg	Fully recov-ered
22	(Di Giam-benedetto et al., 2020)	71	M	HTN	Flu-like symptoms Dyspnea	-	-	-	-	Lopinavir/ ritonavir Hydroxy-chloroquine	-	-	Improved
23		45	M	-	Fever Dyspnea Chest pain	-	-	-	-	Lopinavir/ ritonavir Hydroxy-chloroquine	-	-	Improved
24		53	M	HTN		-	-	-	-	Lopinavir/ ritonavir Hydroxy-chloroquine	-	-	Improved

HTN, hypertension; MP, Methylprednisolone.

result which indicates the process of restoration of the normal T cells (50).

RESOLUTION OF PRESENTING SYMPTOMS

The administration of Tocilizumab as an additional therapy has produced significant outcomes in alleviating the symptoms of COVID-19. Common presenting symptoms such as fever, shortness of breath, chest tightness, and flu-like symptoms have been proven to be diminished or reduced following the administration of Tocilizumab. These clinical outcomes have been proven in several clinical reports involving patients that were admitted to the hospital due to the presence of the respective symptoms and positive testing of SARS-CoV-2 infection. Twenty-one COVID-19 patients have restored their body temperature to normal on the day after Tocilizumab was administered and maintained in a stable condition and all febrile patients recovered. Those with presenting shortness of breath had resolved (11,49). In addition to that, Michot et al. reported that a 42-year-old patient that had developed sudden dyspnoea and low oxygen saturation was further administered with two doses of IV Tocilizumab (8 mg/kg) for 8 hours apart on the eighth day of admission. He showed good clinical response as his fever rapidly resolved.

The most significant improvement was the clearance of abnormalities of the chest in COVID-19 patients diagnosed with pneumonia. Tocilizumab therapy has been proven to work well to reduce or diminish the abnormalities such as fluid filtrates, lesions, and ground-glass opacities appearance in the pneumonic patients of COVID-19. In patients with abnormal chest lesions, 19 patients from 21 patients showed improved chest condition in which the lesions were absorbed (7). According to Zhang et al., on the nineteenth day of hospitalization, a patient with previous ground glass opacities had miraculously resolved (50). The pulmonary infiltrates and ground-glass opacities showed partial relapse following Tocilizumab therapy (51).

Di Giambenedetto et al. have reported a symptom treatment success for shortness of breath as they observed that two patients with serious dyspnoea had recovered (49). Furthermore, Zhang et al. stated that the patient that was involved in their case report had received IV Tocilizumab for 8 mg/kg due to the high level of serum IL-6 on day 9 of his hospitalization. Three days after, he showed a remarkable response of disappearance of his chest tightness (50).

ALLEVIATION OF RESPIRATORY PROBLEMS

Regarding the oxygen intake, several scientists have reported that Tocilizumab has contributed to improving the oxygen intake of the infected patients by reducing their oxygen supplementary therapy and promoting restoration of the respiratory system. The finding was supported by a clinical report that stated the peripheral oxygen saturation has progressed following Tocilizumab administration and resulted in no further need of oxygen therapy which 15 patients had reduced the intake of oxygen and a patient who previously had tracheal extubation successfully awaken on the fifth day after therapy (7). Moreover, it is reported that a patient that had developed low oxygen saturation was further administered with two doses of IV Tocilizumab (8 mg/kg) for 8 hours apart on the eighth day of admission. His condition improved as his oxygen consumption level has reduced (51). Di Giambenedetto et al. has contributed to the findings on the improvement of oxygen intake too. They stated that Tocilizumab was prescribed and administered to three selected COVID-19 patients as an addition to the antiviral therapy initiated to the patients. One patient had shown improvement in partial pressure to fractional inspired oxygen ratio (49).

Based on the data collected from the patients' case studies, it is reported that 82.93% of the patients had positive clinical outcomes. The positive clinical outcomes include resolution of initial symptoms of COVID-19 infection and improvements in the immune system to combat infections and disease aggravation. These factors highly contributed to the tendency of a patient to be completely healed from the viral infection. From the said percentages, the studied patients had better health outcomes and most of them have been discharged from the hospital. In contrast, there are 17.07% of patients failed to recover from the infection following Tocilizumab therapy. Two patients had deceased as their conditions deteriorated and unfortunately developed secondary hemophagocytic lymphohistiocytosis (sHLH) (52). There were three critically ill patients further treated with a single dose of Tocilizumab. However, they had failed the treatment and the other two patients had aggravation of disease following the therapy (47).

IMMUNE SYSTEM DISRUPTION OF COVID-19

Failure to antiviral therapy in COVID-19 patients poses a high risk of fatality associated with immune dysregulation induced by SARS-CoV-2. The immune dysregulation may contribute to severe respiratory failures such as ARDS and cytokine release syndrome. Patients presenting with pneumonia symptoms such as ground-glass opacities appearance and lesions in the lung due to SARS-CoV-2 viral attack have been shown to have high potential to develop severe respiratory failure. Patients with COVID-19-induced pneumonia who had clinical aggravation to severe respiratory failure exhibited hyper-inflammatory activities. These over-inflammatory responses are contributed by immune dysregulation of macrophage activation syndrome. Both conditions are featured by the increase of activities of the immune system associated with overproduction of pro-inflammatory cytokines. The immune dysregulation may be dependant on

the IL-6 whereas the IL-1b plays an essential role in macrophage activation syndrome (53). Along with that, the exaggeration of immune responses that are caused by pathogenic T cells and inflammatory monocytes may contribute to the deterioration of disease state to severe lung impairment (54). These findings simply contributed to the idea that SARS-CoV-2 infection has promoted the immune disruption in infected patients and exposed them to a high potential of complications with increased activity of cytokines mainly the IL-6.

Immune dysregulation can be mainly characterized by the hyper-activity of pro-inflammatory cytokines and impairments on the production or functioning of the lymphocytes. The lymphocyte abnormalities are characterized by the presentation of lymphopenia which may cause by the atypical levels of CD4 cells and B cells (55). In addition, the presence of comorbidities in the COVID-19 patients especially in severe and critical patients also poses a high risk to the development of immune dysregulation. This is because the immune system has the possibilities to keep deteriorating as the involved body system is already impaired. Therefore, patients with comorbidities have a high potential to develop most of the disease aggravation states, not mainly focused on the immune dysregulation. The immune dysregulation is just the trigger that could further depress the body system and impose a worser condition.

Moreover, severe respiratory failure can be characterized by having a significant reduction in the HLA-DR on CD14 monocytes. The decrease of the HLA-DR is mainly to be caused by the overproduction of IL-6 in the immune system. IL-6 is found to effectively hinder HLA-DR expression (56). This indicates that the overproduction of IL-6 is an intervention to the decrease in HLA-DR expression on CD14 monocytes of COVID-19 patients. This could induce the depression of the immune system and deteriorate the patient condition to sepsis events. Therefore, any therapy that could inhibit IL-6 towards its binding to the receptor would pose a positive effect as it can improve the expression of HLA-DR on the monocytes. Tocilizumab seems promising to this hypothesis.

On a serious note, Radbel, Narayanan, and Bhatt have reported a finding on two COVID-19 cases involving COVID-19-induced CRS and its deterioration to sHLH regardless of the administration for Tocilizumab. This deterioration to sHLH highlights that overproduction of IL-6 is essential to be inclusive in promoting CRS in COVID-19 (26). Besides, patients with a severe infection of SARS-CoV-2 present with high counts of IL-2, IL-10, and TNF-α. Both IL-10 and TNF-α are mainly involved in both CRS and sHLH (52).

TOCILIZUMAB APPROACH IN MANAGING OF DISEASE IN COVID-19

Most findings have supported positive clinical outcomes on the use of Tocilizumab in COVID-19. Tocilizumab is mainly used as an add-on therapy to the existing therapies such as Lopinavir, Ritonavir, Methylprednisolone, and Hydroxychloroquine.

Methylprednisolone is a corticosteroid agent that is the potential to combat cytokine storms benefiting from its anti-inflammatory properties. However, corticosteroid therapy requires administration in high dose and extension of the period of therapy. It is also associated with consequences potentials of side effects. Tocilizumab was added in Methylprednisolone therapy for closer monitoring of the potential of CRS in COVID-19 patients. The relevance of this treatment regime was based on the understanding of the importance of IL-6 in COVID-19 and the previous notable experience on the pharmacological action of Tocilizumab in the treatment of CRS which can be triggered by the chimeric antigen receptors redirect T-cell (56).

According to Luo et.al., a clinical study revealed that a single dose of Tocilizumab may pose a therapeutic failure to reduce the severity of disease in SARS-CoV-2 critically infected patients. The failure managed to happen although the therapy was in the combination with Glucocorticoid. In contrast, a frequent dose of Tocilizumab seems promising to improve their disease state. According to that finding, it is relevant to indicate repeated doses of Tocilizumab in critical COVID-19 patients which seem to exhibit more effectivene and safer compared to the use of Glucocorticoid. This also works in treating patients with the moderate conditions. Also, Tocilizumab with the indication of single dose can benefit COVID-19 patients in serious conditions which the presentation of high IL-6 level up to 10 times of escalation. However, the repetition of dosing should be decided cautiously considering the pharmacokinetic properties of the drug. The dose of Tocilizumab should be adjusted accordingly as it has a long half-life time and it is potential to saturate the binding activities towards the IL-6 receptor. A recommended safe intervention on dosing would be at a daily basis frequency, every other day, or every three consecutive days. Administration of Tocilizumab in two to three doses are reasonable for critical patients and can be considered in the therapy for patients with elevated IL-6 level too (47).

RISK ADVERSE EVENTS ASSOCIATED WITH TOCILIZUMAB

There are two cases of COVID-19 patients in critical condition that have been reported to develop

hypertriglyceridemia (57). This points up that Tocilizumab administration in COVID-19 critically ill patients may trigger the metabolic response of the patients too. It is reported that IL-6 can act as an immunomodulator and has direct effects on metabolism. An increase in IL-6 level deploys the free fatty acids (FFA) through the fat-storing cells, adipocytes (58). The respective interleukin will then trigger the glucose and FFA uptake from the serum by the skeletal muscle (59).

Based on the finding, the precise mechanism of the increase in triglyceride level induced by Tocilizumab use is still unclear and still needs to be explained in detail (60). The resultant elevation of triglycerides level may be influenced by the blockade of both membrane-bound and soluble receptors of the IL-6. Referring to both cases, the patients receive propofol infusion for sedation purposes. From previous studies, propofol infusion can elevate triglycerides secondary to the vehicle of lipid emulsion.

In addition, this propofol-induced hypertriglyceridemia is common within 2.25-7 days after Tocilizumab therapy is started with stabilization taking place within 72 hours (58,61,62). Patients with propofol sedation may pose a greater risk to develop hypertriglyceridemia when co-administered with Tocilizumab. This adverse effect should be monitored closely and continuously for better insight.

Furthermore, few more authors have expressed their concern on another adverse effect of Tocilizumab use in critical COVID-19 patients which is the intestinal perforation. Its mechanism remains unclear but there is a possible risk factor that has been recognized which is the preceding diverticulitis (63,64). There is a high expression of ACE 2 in the intestines which the ACE 2 plays the main role in SARS-CoV-2 infection in becoming the human host receptor (65).

Thus, this provides a suitable medium of SARS-CoV-2 to replicate considering the high expression of the receptor and leads to gastrointestinal such as abdominal pain(66). From these findings, an imbalance or changes in haemodynamic may cause low blood flow to the intestines and weaken the lining of the intestines. As Tocilizumab can weaken the response in the acute phase, intestinal perforation may present without serious escalation of CRP level and can be overlooked in patients with sedation and ventilation (64).

According to these findings, Tocilizumab has revealed significant potential adverse events from its administration to critically ill COVID-19 patients. It is vital to observe the essential specified monitoring parameter for critical COVID-19 patients that are treated using Tocilizumab therapy, evaluate the therapeutic outcomes and be attentive towards any possible adverse effects of Tocilizumab which also may be influenced by the activity of concomitant drugs.

CONCLUSION

Inflammatory response at optimal dose is essential to guarantee relief to COVID-19 patients and to promote viral clearance. A well-functioning inflammatory response surely leads to a favorable immune system. The intervention of the immune system in infection will work on clearing the pathogens and induce the resolution of any inflammations, impairments, or presenting symptoms to combat infection. It will also result in return to a normal homeostasis state and prevent disease aggravation. The known cytokine storm or the CRS which is induced by SARS-CoV-2 can potentiate other severe conditions and organ or systemic failures resultant in death. Therefore, we need to cater to this problem by having effective and beneficial treatment to reduce the mortality risk of COVID-19 patients associated with the respective conditions.

To achieve this target, Tocilizumab is promising to suppress the pro-inflammatory cytokines that degenerate the immune system and improve the clinical conditions of patients. The symptoms associated resolve rapidly and the immune system hasrestored to normal condition well in most cases. Nonetheless, it also poses adverse effects that can challenge the patient's immune system's ability to recover normally. Several studies have demonstrated positive and negative findings on the use of Tocilizumab as a therapy for this fatal infectious disease. Tocilizumab is acceptable for off-label use for its hypothetical clinical benefits during this pandemic due to its benefits outweighing the risk of adverse effects.

However, the limitation of this review is the number of cases involved in each research study is small. The results on the use of this drug need can be evaluated more accurately if there is a larger number of cases.Therefore, more cases need to be included. Nevertheless, this flaw of studies is relevant and acceptable as there are many studies involving COVID-19, and potential therapies are still being conducted and not published yet during the period of this narrative review is carried out. There are more clinical trials being performed involving larger subjects. From these clinical trials, thorough studies on the effectiveness of Tocilizumab can be recognized along with its reasonable indicated dose in the initiation of therapy, contraindications, clearer points of side effects throughout complete studies on its pharmacological details in COVID-19.

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