Use of Tocilizumab in COVID-19 Infection

Pranjal Toshniwal, Shiv Joshi*

Department of Community Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Demmed to be University), Sawangi (Meghe), Wardha, Maharashtra, India

ABSTRACT

Background: Cytokine storm is one of the severe clinical outcome of COVID-19 which is indicate the patient's critical condition. The progression of cytokine storm is extremely fast and needs to be control any how in order to prevent the patients from meeting with fatal clinical outcome.

Summary: The novel Coronavirus created so much havoc because of two reasons. First the high transmissibility of the novel Coronavirus makes it extremely difficult to contain in certain geographical extent. Second is its capacity to create unmanageable medical complications which can give rise to fatality figures. Repurposing of drugs to treat the patients of COVID-19 was inevitable as no course of treatment or medications were viable. Till date no definite treatment is available for COVID-19 and ad hoc administration of drugs according to the condition of patient and its clinical history is being done. The efficacy of the tocilizumab has been an issue of discussion all over the world as various studies has indicated different suggestion regarding the administration of drugs.

Conclusion: Efficacy of the tocilizumab has been tested for quite some time and international cohort is needed to authenticate the results coming from the different pockets of the world. The patients obtaining fatal clinical outcome post administration of tocilizumab must be examined for the necessary reason. This can create a negative list for the health care professional among which administration of tocilizumab is prohibited. The efficacy in many patients must also be studied in detail to list all the positive outcome of the administration of drugs.

Key words: COVID-19, Tocilizumab, Dexamethasone, Methyl prednisolone, Cytokine storm, IL-6

INTRODUCTION

Coronavirus disease 2019 or COVID-19 is the continuously evolving pandemic which has adverse affected the entire world. For past more than one an half years, the COVID-19 has creating destruction of such massive scale as no other event in recent past of human history can replicate such destruction. The initiation of COVID-19 which is caused by the novel Coronavirus, latest entrant in the Coronaviridae virus family which had MERS-CoV-2 and SARS-CoV-2 as its members. Since its inception in the city of Wuhan situated inside the Hubei province in China, it had rapidly spread its devastating effects all round the world creating ripples everywhere. Till December 3, 2021, 263,536,622 infection cases pertaining to COVID-19 has been registered and 5,232,562 mortalities due to COVID-19 related compilations has been reported from all across the world [1]. The mutation in the virus id the natural phenomenon and are most of the times minor in nature. But drastic behavior change in the virus manifestation can be termed as major mutation and it can create havoc of another scale. The latest variant of concern named Omicron (B.1.1.529) is the talk of the town as it can reportedly infect many people in less time as compared to its highly contagious predecessor, delta variant [2]. The omicron, which started its journey from southern part of the African continent few days ago, has now reach almost every part of the world creating a wave of panic. Various vaccine candidates got approval from drug controlling agencies around the world and till now more than seven billion jabs has been administered all over the world [3]. The concerns regarding efficacy of the vaccines around mutant version of novel Coronavirus and its waning nature is another topic for research. The cytokine storm is the over activation of the cytokines mainly interleukins which generates over inflammatory response in order to fight the exterior aggression by some pathogens. It can create complications as inflammations in vital organs such as heart and blood vessels can obstruct the functioning of the vital organs leading to multi organ failure and eventually fatal clinical outcome. Tocilizumab is one of the repurposed drugs which are being used to treat the patients of COVID-19. It is basically used in rheumatoid and juvenile arthritis to suppress the immune system response. The cytokine storm in severe COVID-19 patients

presents the same condition and the usage of tocilizumab was found viable alternative as the therapy. But not all the patients shown improvement after the administration of the tocilizumab and some of them even met with lethal clinical outcome [4].

LITERATURE REVIEW

Epidemiology of COVID-19

Novel Coronavirus or SARS-CoV-2 is the latest entrant in the Coronaviridae family which is infamous for their deadly and lethal viruses. Previously SARS-CoV-2 which is the predecessor of the SARS-CoV-2 and MERS-CoV-2 has caused the outbreaks of Middle Eastern Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) [5]. The case fatality rate among these outbreaks was higher than COVID-19 but the geographical extent to which these infection spread was confined to small portion of the world. The SARS-CoV-2 virus has proven that it is far more destructive than its previous counterparts. SARS-CoV-2 or the novel Coronavirus belongs to the beta Coronavirus type, other being alpha, gamma and theta. The Coronavirus is virus which was identified way back in the 1960's. It is infecting humans for more than 50 years [6]. Initially it was spread through Europe as the unidentified flu which was completely harmless only hand full of people needed medical attention. Then the genome sequencing of the virus revealed about it and it was named Coronavirus. The shape of the virus and spike proteins on it is such that it resembles the shape of crown hence named Coronavirus. After more than four decades past from the initial identification no major infection had caused due to Coronavirus and then the study on the Coronavirus made no progress due to natural attitude. But as the 21st century started and a major outbreak in the form of Severe Acute Respiratory Syndrome (SARS) infected south east and southern parts of Asian continent affecting thousands of people and proved fatal for considerable amount of people in less number of days. Then it was identified that there is virus named SARS-CoV-2 which is behind the outbreaks. The viruses are quasi living organism which is inactive outside the host and becomes only active when they enter into the host body [7]. Many animals other than human Coronaviruses exist and they already accustomed to the virus. For humans the transition is difficult and immune system will take time to notice and produce antibodies and memories against the virus. Also viruses are notorious to mutate themselves in such a way that they can survive the host body for longer duration. Meanwhile they can restructure themselves to evade the immune system response which is targeted against them. Sometimes vaccines also rendered ineffective by the virus and viruses can override the protective cover provided by the vaccine. The novel Coronavirus created so much havoc because of two reasons. First the high transmissibility of the novel Coronavirus makes it extremely difficult to contain in certain geographical extent. Second is its capacity to create unmanageable medical complications which can give rise to fatality figures. These factors made it

one most destructive virus and causing havoc of unprecedented scale in past hundred years of human history. No other event in the human civilizational past had caused destruction on such massive scale as COVID-19 has caused. The clinical manifestation of COVID-19 is still evolving and by each passing day adds more to its details. The incubation period for the virus is 4 to 12 days and symptoms starts to show generally after 4 to 6 days [8]. In some cases symptoms will never appear and person needs no medical attention as their immune system adapts with the pathogenic invasion and destroys the virus on its own. The person with high viral loads needs medical attention and show symptoms which are of various kinds. The general and widespread symptoms which are most seen among the patients of COVID-19 are cough, cold and fever along with fatigue and headache. The symptoms are not limited to these and varies according to the patients clinical history, viral load present etc. Diarrhea and dyspnea along with loss of taste and smell has been seen among mild to moderate patients while acute respiratory distress syndrome and other severe symptoms were found among severely affected patients [9]. Need of sophisticated medical care arises in some of the patients which are termed as critically ill patients and needs constant medical attention. They comprise most of the case fatalities happening due to COVID-19 related complications. Hence large spectrum of the symptoms has been shown among the patients with different anatomical status.

Over activation of cytokines

Cytokine storm also identified as hypercytokinemia is the human anatomical response to the exterior viral infection and it attempts to gain command on the disease causing virus by releasing cytokines. Cytokines are mainly tiny protein molecules which are created in the human's body [10]. Numerous kinds of proteins and enzymes are produced in the body to carry out the daily operation of the body. Protein synthesis occurs in cell. They have a crucial function in cell signaling. Cell signaling is the capacity of the cell to interact with them self and neighboring location to obtain, transfer and process the inward and outward signals. Signals can be from outside the cell also known as extracellular that is generated due to events occurred exterior of the cell. Interleukins like IL-6, chemokine's and interferons are few of the cytokines. They are usually made by B and T lymphocytes, macrophages. Cytokines are generally pro inflammatory molecules used to nudge when body identifies the outside viral infection and requirement to regulate it rises. But occasionally these cytokines are produced in tremendous quantity saturating the system with it, resulting a huge inflammation all over the body and on various organ systems. This can result into cell injury and multiple organ failure. Macrophage Activation Syndrome (MAS) sometimes interchangeably used in place of cytokine storm but they have divergences in there terms. Cytokines storm was reason for the massive number of case mortalities from the young adult age group in the pandemic of Spanish Flu in the year 1918. Many kinds of other viral diseases like swine flu have been initiating the cytokine reaction after arriving into

the human body. Cytokine storm manages to make patients critically ill. Patients admitted with severe pneumonia along with COVID-19 and Acute Respiratory Distress Syndrome (ARDS) are the result of the over activation of pro inflammatory cytokines which is causing lung injury hurting the alveolar tissues which further obstructs the flow of the oxygen to various parts of human body. Controlling cytokine storm in time is the key to reduce the mortalities linked to COVID-19. C Reactive Protein (CRP) levels were also found to be elevated resulting into inflammatory response by the body [11].

Repurposing the existing drugs

As the pandemic of COVID-19 struck the whole world, all were taken aback considering the novelty of the disease. No scientific and genomic data was present with the scientific community and they did not know how viral behavior will pan out in coming times. As there was no past history of infection from such virus, the medical fraternity was completely clueless about how to treat the infected patients. Curative measure needs to be in place to fight off the virus. But health care professionals along with the rest of the whole world were new to this new pandemic. Therefor there was no established course of treatment available with the health care professional and scientific [12]. But the patient of COVID-19 has to be treated in order to control the pandemic. Therefore health care professionals started to use the existing drugs to curb the novel Coronavirus causing COVID-19. Symptom wise and patient wise treatment was given and the experience of the health care professional helped to select the medication. Several available drugs were repurposed as they were being produced to cure ailments other than COVID-19. The health care professionals started giving medications according to the ailments. For example if someone tested positive for COVID-19 and has only cough, cold and fever then existing drugs for the same is prescribed for the patient along with continuous update on medical status of the patient for checking any kind of deterioration in the health status. Starting from basic antibiotics and antivirals, patients started feeling improved clinically. Health care professionals then extrapolated the inference in case of moderate to severely ill patients as there was no other way to stop the spread of the viral infection. Various existing drugs such antimalarial, antivirals, antibiotics; corticosteroids which are used for treatment of the disease other than COVID-19 are now being used to treat COVID-19 [13]. Drugs such as remdesivir, favipiravir, dexamethasone, chloroquine, hydroxy-chloroquine, tocilizumab etc. are being used to treat the COVID-19 patients as they have shown some efficacy while the course of treatment. In fact certain immune modulatory drugs such as tocilizumab and remdesivir were found to have been saving the patients which are critically ill due to hyper activation of immune system generating pro inflammatory molecules called cytokines in extremely large amount crating inflammation on various vital organs and organ systems inside the body. Cytokine storm can result into heart failure which can further leads to other organ failure

resulting into multi organ failure as the supply of oxygen along with other vitals is obstructed [14].

DISCUSSION

Tocilizumab and COVID-19

Tocilizumab basically is a drug which is in the form of monoclonal antibodies which prohibits the receptors of the interleukins especially IL-6. It is basically an immunosuppressive drug which is used for the treatment of rheumatoid arthritis and juvenile arthritis. In rheumatoid arthritis which generally manifests as the person ages, the IL-6 levels become extremely high hence joints become inflamed and rigid. tocilizumab which was licensed in 2003 is used since to treat the rheumatoid arthritis [15].

It its relevance as various drug controlling agencies grants it emergency use authorization as everyone is desperately looking for the possible cure for the deadly and lethal disease like COVID-19. The property of tocilizumab to bind the IL-6 receptor which is one of the leading cytokine causing harm is extremely beneficial as one gets rid of the over activated cytokines. A single center study which includes 15 patients of which 12 are males and rest are females suggests insights after administering tocilizumab along with other anti-inflammatory drugs [16]. The median age was 73 years. 7 patients were critically ill while rests were seriously to moderately ill. Heart related ailments were common among the patients and more than ten patients were suffering from one or more than one underlying medical illness along with COVID-19. Comorbidity is yet another worse thing to have during COVID-19 infection as the chance of patient slipping into critical state increases along with each comorbidity. The dose quantity was fixed between 80 mg to 600 mg per time and 5 of them got it twice or more. In all the patients the CRP levels were elevated by considerable amount of number which was a serious cause of concern as the elevated CRP levels is closely linked with the COVID-19 related mortalities. But after the administration of dosage of tocilizumab according to the patient's condition and in the range of 80 mg to 600 mg, the CRP levels were found to be lowered by considerable margin and patients were relived from the mishaps occurring due to elevated CRP levels. The drop from 126.9 to 11.2 is extremely commendable and administration of tocilizumab was found to be successful in some aspect. Although four patients met with fatal clinical outcome as their CRP levels did not came down even after the administration of tocilizumab. In remaining 11 patients from the study, the patients were in manageable situation within a week from the administration of the said medication. The study indicates a mixed results and still one cannot confirm that tocilizumab is the panacea for the patients suffering from over activation of the inflammatory response which is generally used to protect the body from the external pathogenic aggression. In case of IL-6 levels it was found that these enzymes are up to 90 times higher than their actual figure which stands at 627.1 pg/ml. There was a

peculiar trend seen after the administration of tocilizumab among the study cohort. The levels of the IL-6 was found to be spiking after the initial administration of the dose then after some time it starts to decrease. The tocilizumab was administered along with methyl prednisolone as efficacy of the both the drugs thought to have been increasing if administered at the same time. The IL-6V levels of four deceased patients rose tremendously after administration of the drugs and no signs of improvement. Hence it is concluded that not all the patients are suitable for the administration of the methyl prednisolone and tocilizumab as the cytokine storm controlling drug. The prevention as well as treatment of the cytokine storm must be considered for severely ill patients who can show certain reactions. Certain biomarkers such as D dimer, CRP, IL-6 levels indicate the wellbeing of the body. If these levels are not at their normal standings then health care professionals must monitor continuously these patients as these patients can show aggravated cytokine reaction in coming time. Anticipation of cytokine storm can have beneficial impact on the course of treatment and prevent large number of case fatalities happening due to cytokine distress [17].

However some concerns are attached to the administration of tocilizumab as a blanket therapy. A study has shown that there can be certain amount of risk factors associated with tocilizumab. A cohort of studies which had 3080 patients of which 1538 were administered tocilizumab as the treatment drug and rest were administered etanercept. There was an average follow up of the said patients for 3.2 years. 83 cases among the 1538 cases reportedly develop adverse cardiovascular outcome while in etanercept it was 78. The hazard ratio was 1.05. The cardiovascular risk was found to be higher in tocilizumab than etanercept. But contradictory study outcome was noted when tocilizumab was compared with Tumor Necrosis Factor Inhibitors (TNFi) [18]. It was found that cardiovascular adverse outcome was higher among TNFi administered patients than tocilizumab indicating the efficacy of the tocilizumab over TNFi. In other study patients who did not need any kind of sophisticated medical care like mechanical ventilation or oxygen support system, tocilizumab reduced the chances of disease progression and the chance of fatal clinical outcome was also lowered [19].

CONCLUSION

The cytokine storm is by far established itself as the adverse clinical outcome of the COVID-19 and is the reason behind the many fatalities around world happening due to COVID-19 which is caused by the latest entrant in the Coronaviridae family, novel Coronavirus. By controlling and preventing the cytokine storm from progressing into severe and unmanaged symptom it must be controlled by any means. Efficacy of the tocilizumab has been tested for quite some time and international cohort is needed to authenticate the results coming from the different pockets of the world. Certain patients showing adverse reaction or no improvement at all after the administration of tocilizumab must be profiled and checked for the common thread which links all of them. They can be avoided from the adverse impact presented by the tocilizumab. As the novel Coronavirus is highly unpredictable and has capacity to mutate itself to evade the immunity and vaccine cover and can re infect the patients, every person must focus on the preventive and precautionary measures which are extremely effective while dealing with highly contagious pandemic like COVID-19. These measure not only prevent us from getting infected but if infected can only progress to mild symptoms which are easier to manage clinically. Vaccination must be promoted to every age group as it can mellow down the impact of the novel Coronavirus even if it infects post vaccination. No severe reaction has been seen post vaccination and provides considerable amount cover against the severe symptoms of the disease.

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