

Tocilizumab in Patients Hospitalized with COVID-19 Pneumonia

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ABSTRACT

Background: Corona virus disease originated from Wuhan, China city of Hubei spreader all over world and immensely threatening people causing respiratory distress which has high mortality. SARS-CoV-2 causative agents enters human through inhalation of droplets leads to CD₄+T cell dependent immune response and increased antibody production along with immense cytokine release. COVID cases raises alarmingly reporting deaths in an alarming rate.

In the meantime interleukin-6 encourages endothelial damage and increases vessels permeability, interleukin-6 as cytokine plays a role in the vessels permeability related with the disease.

Summary: Heterogeneous clinical course ranging from asymptomatic via mildly symptomatic to a deadly acute severe respiratory syndrome leading to death. Patient main mortality factor is coagulation dysfunction thus all hospitalized critically ill COVID patient should receive pharmacological prophylaxis for thromboembolism. COVID is not always linked with superadded bacterial infection but serum procalcitonin is suggestive of bacterial pathogen that is if low procalcitonin suggest against bacterial superadded pneumonia.

Tocilizumab dampens down the risk of poor outcome and also decreases the hazard of minor infections in COVID-19 as super infection.

corona virus infection is cytokine storm during the major acute phase and the cytokine playing the major virulence is interleukin 6 causing inflammatory hazards in COVID infected critically ill patients

Various Meta analyses of studies under went to determine efficacy of tocilizumab but results leave the efficacy controversial

Key words: Mortality, Tocilizumab, Toxicity, Interleukin-6 blocker and cytokine storm

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INTRODUCTION

COVID patient, if asymptomatic or mildly infected recovers in weeks without hospitalization, and those affected patients showing symptoms of respiratory pneumonia and distress along with coagulation and sepsis requires hospitalization. Hyper inflammation with excessive synthesis of inflammatory cytokines including IL-6, IL-10, TNF α , and IF- γ cause deadly acute respiratory distress syndrome and coagulation dysregulation. Suppression of interleukin-6 is considered promising therapeutic plan against COVID. Tocilizumab, a recombinant, monoclonal antibody against interleukin-6 receptor. Tocilizumab was used to handle other auto immune ailments such refractory Rheumatoid Arthritis. Levels of interleukin-6 relates with COVID-19 severity which advises that the

immune dysfunction and respiratory distress might be prejudiced by interleukin-6 [1]. Aggregation of various white blood cells like lymphocytes and monocytes, endotheliosis, apoptosis, coagulation factors disturbance, and new blood vessels formation in the lung capillaries and vessels in people with COVID-19 proposes that vessels induced swelling and irregular functioning of vessels contributing to the pathological and patho physiological features of immense COVID-19 pneumonia [2-4].

Nidovirale family coronaviridae, the subfamily ortho Corneaviridae are all members of the order. In case of alpha and beta, virus will infect human, Corona virus with petal or club shaped leaves. They feature helical symmetry; highly pleomorphic, straight ssRNA and greatest positive sense size of undiagnosed RNA virus 26 to 32 KBP.

COVID cases rises alarmingly reporting deaths in a high rate, many measures has been taken like public health measures example social distancing, masks usage lockdown implementation, hand sanitization, decreasing social gatherings, forbidden public transport, mass closure

of various schools and institutions, local awareness, avoiding social meets along with vaccination in belief of a highly accurate and worthy quote "precaution is better than cure." Various vaccine campaign including all available vaccines like COVISHIELD and COVACCINE is distributed free of cost by government of India to mitigate the alarming increase in number of COVID-19 pneumonia cases. Symptoms of COVID includes fever, cough, anosmia, lack of taste, sore throat, myalgia, headache, vomiting along with nausea, sometimes complete gastro intestinal presentation, breathlessness and if the disease progressed to severe illness it includes breathing problems and severe hypoxemia.

Mainly in day 5 to day 10 of infection of COVID pneumonia the lung stage begins, and various measures and treatments can be implemented to prevent this stage and best being the combination therapy of Casirivimab and inevitable. Replication inhibitors such as Favipravin, zinc and hydroxyl Chloroquine should not be used. Specifically in first case group that is affected patients of COVID-19 pneumonia with neutropenia and second case group showing hypoxia with C reactive protein more than 75 mg/dl shows a promising therapeutic beneficial outcome by use of combination of tocilizumab and corticosteroids.

Among all patients organ that is most affected by infection is the lung as the spike protein which is present in virus bonds to ACE-2 after which uncoated takes place which proceeds with replication of viral genomic RNA by RNA dependent RNA polymerase.

COVID-19 infection involves dyspnoea which is due to inflammation of lungs that is asthma also involves inflammation of lungs and thus it is cited as most important risk factor for COVID-19 pneumonia

LITERATURE REVIEW

Mechanism of action and pharmacological action of tocilizumab

- Tocilizumab competitively inhibits attaching of interleukin 6 to its receptor interleukin 6 receptor inhibiting the entire complex prevents interleukin 6 inflammatory chain that summon t and b cells.
- Circulating interleukin-6 activates Janus kinase and it contributes to organ damage such as maturing T cells into effector T cells and increasing vascular permeability and reducing myocardial contractility.
- Interleukin 6 increases production of C reactive protein, serum fibrinogen and amyloid a and decreases the production of serum albumin this altogether causes amyloidosis, cardiovascular disorders, anaemia and edema thus interleukin 6 inhibitor tocilizumab is very beneficial [5].
- Tocilizumab decreases angiogenesis, blood vessel permeability and decreases synthesis of vascular endothelial growth factors thus beneficial in rheumatoid arthritis [6].
- **Pharmacokinetics:** Clearance of tocilizumab depends on 2 paths:

- First is nonlinear clearance at high doses and
- Second is linear clearance at low doses.
- Tocilizumab has very long and dose dependent half-life.
- **Doses:** fixed drug administration for treatment of COVID-19 suggest dosage of 8 mg/kg IV and not exceed 800 mg/dose, one more IV infusion 8 hours after first infusion if required.
- Subcutaneous administration not authorized.
- **Baricitinib** and non-invasive orally managed selective prevent or of jak 1 and jak 2 remained originated to be real in dropping recovery time of COVID-19.
- **Adverse effect of Tocilizumab**
 - Hyper cholesterolemia
 - Hypertension
 - Increased levels of alanine transferase and aspartate transaminase
 - Upper respiratory tract infection
 - Gastritis
 - Hypothyroidism
 - Injection site local reaction
 - Anaphylaxis
 - Gastrointestinal perforation
 - Mouth ulcers
 - Diarrhoea
 - Weight gain
 - Stomatitis
 - Neutropenia
 - Thrombocytopenia
 - Leukopenia
 - Chronic bronchitis
 - Cough
 - Conjunctivitis
 - Herpes simplex infection
 - Nasopharyngitis
 - Dizziness

Drug interactions

- Decreased blood plasma levels of simvastatin
- Normalizes cytochrome levels

Indications of tocilizumab

FDA approved

- Cytokine release syndrome
- Giant cell arteritis
- Juvenile idiopathic poly-articular arthritis
- Systemic juvenile idiopathic arthritis
- Systemic sclerosis associated lung disease [7].

Non-FDA approved

- COVID-19 (respiratory distress)
- Cytokine release syndrome

Randomized controlled trial

It was performed with study title as tocilizumab to prevent the progression of hypoxemic respiratory failure in hospitalised non-critically ill people with COVID-19

A Parallel assignment, prospective multi centric and randomized double blind study including 243 participants was conducted in 2020 with double masking (subjects who meet inclusion criteria and none exclusion criteria will be randomized 2:1 to tocilizumab)

Using methods, randomization was in 2:1 ratio and was stratified accordingly to age and country.

- One or two doses of IV TOCILIZUMAB 8 mg/kg to max 800 mg/dose is given to patient
- If a patient clinical signs and symptoms worsened, another infusion is given 8-24 hours apart
- Efficacy is evaluated at day 28th and follow up for total 60 days

Two types of outcomes

In the follow up period measurement of CRP levels, ESR and biochemical levels of AST and ALT along with adverse effect should be carried out.

Study suggesting criteria's for tocilizumab infusion

Inclusion criteria

- Radiographic evidences which are suggestive of COVID-19 infection
- Hospitalized affected patients who are suffering
- Confirmed SARS COVID illness
- Non pregnant female and male
- CRP>50 mg/lit with respiratory rate >25, SPO₂<93%, PAO₂<65 mm of hg and increasing dyspnoea on dyspnoeic scale

Exclusion criteria:

- Age more than 80
- Intensive care is required
- Uncontrolled bacterial super infection
- History of severe allergy to tocilizumab
- History of colonic perforation
- History of diverticular disease
- History of chronic liver and renal disease
- History of primary immunodeficiency

Earlier authors concluded that there is in sufficient proofs and results depicting efficacy and clinical safety of tocilizumab, as time passes then various multiple randomized control trials took place which helped to study the efficacy and clinical benefits of tocilizumab.

Various randomized controlled trials that took place such as:

- The bacterial double blinded type of multi centric randomized controlled trial and the study depicts safety of tocilizumab with less infection.
- The convactrial double blinded placebo controlled randomized controlled trial type of multi centric randomized controlled trial included the COVID infected hospitalized affected patients with severe bi lateral lung infiltrates depicting lung involvement showing pneumonia and hypoxia and this study depicts that tocilizumab reduces the hospital stay for

a patient and reduces time of discharge of that patient.

- **The corimuno toci 1 trial:** It is a small sample sized randomized controlled trial suggesting tocilizumab gives a benefit to slow down or by dampening the progression of patient of severe COVID-19 pneumonia to mechanical ventilation or death
- **The impact trial:** It is a randomized controlled study design which includes reverse transcriptase polymerase chain reaction confirmed in COVID infected hospitalized affected patients who were already hypoxemic but not on non-invasive or invasive ventilation or requiring respiratory support, same as CORIMUNO-TOCI this study also depicts probability of progression to mechanical ventilation or invasive ventilation or death.
- **Remap cap trial:** It is an international trial that studied other drugs belongings to same class group as of tocilizumab that is interleukin 6 inhibitor example sarilumab and the trial depicts tocilizumab is better efficated for affected patients with highest C reactive protein
- **Lastly the recovery trial:** It is a randomized controlled trial which includes 3 groups of affected patients that is
 - Affected patients receiving invasive mechanical ventilation
 - Affected patients receiving non-invasive respiratory support
 - Affected patients receiving no respiratory support

Recovery trial states the inexpensive and widely available steroid dexamethasone reduces the death of COVID-19 affected patients and the group of affected patients shows significant results and got discharged very likely.

DISCUSSION

Thromboembolic events are high in SARS-COV-2 infected individuals, COVID-19 pneumonia morbidity and mortality is significant in today's world with alarming rising infection rates. Not only the respiratory system involvement contributes to the mortality of COVID-19 pneumonia but also disturbance in coagulation and vascular system contributes to mortality in affected patients of COVID-19 pneumonia.

COVID is a prothrombotic state and thus prothrombotic state is a result of platelets activation, immobilization and mechanical ventilation along with the use of central venous catheter and this prothrombotic state will further leads to coagulation dysfunction, coagulopathy and development of thromboembolism in COVID-19 pneumonia affected patients with increased risk of death. Thrombosis along with vascular inflammation and lung infiltration by SARS COV-2 virus is the main cause for multi organ failure in case of COVID-19 thus to mitigate the thrombo embolism state and to reduce the prothrombotic state in COVID-19 pneumonia prophylactic dose of low molecular weight heparin *i.e.* LMWH is administered in all affected patients if respective of critical illness and this prophylactic

administration is done only in absence of any contraindications. Paediatric and COVID infection

Another topic that is being considered is breast feeding it's unclear that virus whether passes from mother to child through breast milk or breast feeding, babies can be nursed if the mother's breast milk is determined to be free of 2019 COVID pneumonia. During breast feeding there is still probability of droplets being transmitted through intimate contact thus it is critical to take precautions while breast feeding like good respiratory hygiene, use a mask and wash their hands before and after contacting the infection to avoid infection to the patient.

The interleukin 6 signalling hazardous pathway activation further causes varied cellular functions which includes differentiation of plasma cells to increase production of antibodies and other reacts like acute phase proteins which includes C reactive protein, bone homeostasis and lipid metabolism

Tocilizumab is a monoclonal antibody which inhibits the pleiotropic cytokine signalling pathway and the major cytokine responsible is interleukin 6 and its creates havoc thus an interleukin 6 inhibitor called tocilizumab is repurchased for use in COVID-19 pneumonia

Various randomized controlled trials have been performed and a result of various randomized control trials have been mixed but in total suggests potential benefit when used early in severe COVID-19 pneumonia disease.

Various comorbidities are present associated with COVID pneumonia are diabetes mellitus, hypertension, chronic pulmonary disease, breathlessness, asthma which if associated with COVID-19 pneumonia further increases the mortality and leads to death

Other similar pathogenic corona virus such as acute severe respiratory syndrome CoV is SARS-CoV and Middle East respiratory syndrome CoV is MERS-CoV, this above corona virus variants also cause severe pneumonia like illness leading to ACUTE respiratory distress syndrome.

Combination therapy with steroids

Steroids and tocilizumab both as combination is approved for cytokine release syndrome, but this combination needs to be validated in a randomized controlled trial.

Dexamethasone lowers 28th day mortality among severe acute respiratory distress syndrome but some authors also mentioned and depicted that glucocorticoid at high and wrong route of administration delays viral clearance.

Contraindications of tocilizumab

- Hypersensitivity reactions
- Pregnancy
- Renal impairment
- Liver dysfunction

Other interleukin 6 targeted biologics includes

- Olokinumab
- Sarilumab
- Sirukumab
- Clazakizumab

These biologics are in development in this constantly changing field; however tocilizumab and sarilumab is approved for treatment of rheumatoid arthritis. Sarilumab can be used now a day. In 2020 spread of COVID brought unexpected health care and financial burden and illness yearly.

Main cause of death in COVID is disseminated intravascular coagulation and acute respiratory distress syndrome. Some studies also reports that tocilizumab given to severe COVID PTS is linked to reduced death rate and lesser intubation period.

Preventive measure

As the transmissibility of the novel coronavirus has been tremendously increased after the double mutation in the viral strain, it also became more deadly. More and more people are severely ill, especially those who escaped the second wave [8]. There is a deficiency of health care infrastructure and workforce in the medical field. Also, COVID-19 is associated with the post recovery illness where many of the affected patients complained about the persistence of the symptoms after recovering. Reduced physical capacity and weakened muscles of vital organs like heart and damaged alveolar tissue can pose serious threats, and there is a need for rehabilitative care for COVID-19 affected patients. All these tedious tasks can be avoided by taking proper preventive care. Also, now preventive measures got their power multiplier in the guise of a vaccine. Vaccines and all preventative measures are the best to avoid all these menaces [9]. Preventive measures updated by WHO include wearing a double mask, avoid going out, sanitization of hands at proper timing, maintaining physical distancing, and avoiding touching public surfaces should be followed at any cost by each individual to avoid the risk of COVID infection. Vaccination should be a compulsion everywhere to all ages to prevent further waves of this ill-severe threat. As the collapsing health care infrastructure is evident that preventive health care is always better than curative health care, thus the Vulnerable population must be vaccinated on a mission mode to lower the burden on sophisticated healthcare infrastructures like oxygen support systems and intensive care unit beds.

CONCLUSION

- COVID-19 is related to a dysregulated immune response and hyper inflammatory condition in human body, exacerbating critical breathing pain set of symptoms and multi organ catastrophe.
- Raised heights of interleukin six are predictive of probability of mechanical aeration
- Tocilizumab adds benefit to against viral agent and glucocorticoid therapy. Corona virus is a moderately

new infection and little in thought concerning what is means for kids and pregnant ladies, anybody of all ages might become contaminated and spread infection. Overall, there is no mortality benefit in affected patients receiving Tocilizumab. The higher but statistically insignificant mortality in Tocilizumab may be due to a 2:1 randomization, a beta error, and a higher incidence of sepsis in affected patients receiving Tocilizumab.

Limitations

- Affected patients in this trial were chosen based on race and ethnicity, which shows that the affected patients might not have been consecutive.
- The excellent benefit of Tocilizumab may be biased based on race and ethnicity and thus non reliable. Conclusively, there is NO mortality benefit in affected patients receiving Tocilizumab.
- The higher but statistically insignificant mortality in Tocilizumab may be due to a 2:1 random, a beta error, and higher incidence of sepsis in affected patients receiving Tocilizumab.

COVID-19 is not going anywhere in near future as various news from across the world reporting the resurgence in cases of it. Therefore the demand of prospective gear such as hand glove, personal protective equipment's kits, facial masks, head and foot cover will remain high. The production facility must ensure the materials used in COVID must be recyclable, ecosystem should be maintained.

Furthermore Tocilizumab infusion increases the infection of pulmonary aspergillosis called as COVID associated pulmonary aspergillosis.

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