Can Tocilizumab Reduce the Need of Invasive Mechanical Ventilator in COVID 19 Induced Cytokine Storm?

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SARS-CoV-2 may cause fatal clinico-pathological changes after replicating in the lower respiratory tract which may lead to wide spectrum of the disease severity including pneumonia, pulmonary edema/ARDS. While ARDS develops in 42% of patients presenting with COVID-19 pneumonia and 61 - 81% of those requires intensive care. According to researcher the intensive care unit and hospital mortality from typical ARDS is 35.3% to 40.0%, however for COVID-19 ARDS, mortality ranged between 26% to 61.5%, unfortunately if admitted in ICU and received mechanical ventilation, the mortality may exponentially increased to 65.7% to 94%, perhaps due to aggressive inflammatory responses [1]. Although COVID-19 pathogenesis is still not very clear to the scientific community, some patients with a severe disease have laboratory evidence of a sharp increase in large number of pro-inflammatory cytokines, including IL-6, which is secreted by various type of leukocytes, plays a decisive role in the inflammatory response. IL-6 can bind its mIL-6R at low concentration or, sIL-6R at higher concentration, creating the activated complex with gp130protein, facilitate signaling by Janus kinases (JAK) and Ras/mitogen-activated protein kinase (MAPK)/NF-B-IL-6 [2]. Though elevated levels of IL-6 not only associated with cytokine release syndrome but also attributed with a hypercoagulable state in humans, proposed to be associated with high risk of death in COVID 19 [3]. According to literature the optimum critical point of IL-6 was determined as 24.3 pg/ml in severe COVID-19 group with sensitivity and specificity of 73.3 and 89.3%, though along with D-Dimer, it reached to 93.3%, and 96.4% respectively [4].

Perhaps blocking the IL-6 pathway might reduce the vigorous inflammatory response in COVID-19, hence few researchers have endorsed the significant role of Tocilizumab in reducing mortality if administered timely in early state of impending cytokine storm. Tocilizumab is a recombinant humanized monoclonal antibody of the IgG1 class, which was introduced in the early 2000's for treatment of autoimmune disorders such as refractory rheumatoid arthritis and systemic juvenile idiopathic arthritis (sJIA), while approved by the FDA for the treatment of cytokine release syndrome (CRS) since 2017, which may act against both the soluble and membrane-bound forms of the interleukin-6 (IL-6) receptor [5].

Factually avert the mortality in cytokine storm is still challenge for global health community due to scarcity of evidences about the utility of recommended resources. Though on retrospective audit of ICU patients, we have experienced promising results of TCZ in 27 seriously ill patients admitted in the State of cytokine storm with viral pneumonia/ARDS caused by COVID 19, who were put on NIV/Mechanical ventilator in ICU with Pao_2/Fio_2 < 300, in which inflammatory markers were exponentially raised, Out of 27 patients, 21 (77.77%) were discharged uneventfully though 6 (22.22%) died during course of treatment after switching on invasive AC VC mode (Assist control) from NIV APRV Mode (Non-invasive; Airway Pressure release ventilation) or on HFNO (High flow nasal oxygen). IL6 and other inflammatory markers (Ferritin, CRP, LDH, D-Dimer) were significantly decline; 48 hour after TCZ infusion, besides this Pao_2/Fio_2 and Q SOFA score also improved in course of treatment among survivors (Table 1).

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Indices	Pre TCZ	Post TCZ (48 Hr)	P value
IL6 (pg/ml)	297.42 ± 549.82	266.87 ± 555.74	0.83
CRP (mg/L)	68.55 ± 52.59	32.64 ± 37.13	0.005
D Dimer (µg/ml)	124.60 ± 334.47	4.05 ± 3.76	0.00001
Ferritin (ngm/ml)	390.05 ± 238.72	264.47 ± 200.92	0.041
LDH (U/L)	690.84 ± 269.00	458.03 ± 296.52	0.0038
Q SOFA Score	1 ± 0.0	0.48 ± 0.84	0.0022
Pao_2/Fio_2	217.11 ± 63.86	377.51 ± 171.62	0.00003

Table 1: *Pre and post tocilizumab (TCZ) data of Inflammatory markers, QSOFA score and ABG indices in study subjects (N = 27).*
IL6: Interleukin 6; CRP: C-reactive Protein; LDH: Lactate dehydrogenase; QSOFA: Quick Sequential Organ Failure Assessment Score.

Similarly in retrospective cohort study conducted by Guaraldi., *et al.* by including 1351 patients; in which 179 were put on Tocilizumab in addition to standard therapy reveal that, Tocilizumab, whether administered intravenously or subcutaneously, might reduce the risk of invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia [6]. Moreover large cohort retrospective study by including 236 patients in Spain alleged that early use of Tocilizumab not only reduce mortality in severe cases of COVID 19 pneumonia but also reduce hospital stay [7]. According to recent study of Wuhan China, TCZ appears to be an effective treatment option in COVID-19 patients with a risk of cytokine storms [8]. In a single center observational cohort study by putting 22 patients on Tocilizumab in France observed that very few patients required mechanical ventilation in the TCZ group, especially among patients with more extensive CT lung damage, than in the control group and stated that TCZ showed significant control of the biological inflammatory syndrome and effective in the controlling of cytokine storm [9]. In other study conducted by Menzella F., *et al.* on Seventy-nine consecutive patients with severe COVID-19 pneumonia; received NIV at admission; 41 were treated with TCZ, shows that TCZ treatment may be effective in COVID-19 patients with severe respiratory impairment receiving NIV [10]. In a recently published systemic review and meta-analysis of 16 studies out of them 13 were retrospective and 3 were prospective highlighted that the addition of TCZ to the standard regimen might reduce mortality in severe COVID-19 [11]. Contrary to this Colanari M., *et al.* not much convinced with the TCZ in reducing mortality among ICU admitted patients in his study conducted on 112 patients, though serum IL 6 level was not measured before inclusion in TCZ group [12].

Cumulative worldwide evidences are in favor of early use of Tocilizumab in COVID 19 induced pneumonia/ARDS with standard management to reduce mortality in severely ill patients by the deferral of the requirement of invasive mechanical ventilator in the phase of cytokine storm, though it need more comprehensive research globally to consolidate the concept by further meta analysis. In addition to this minimum cut off value of IL6 titer in serum to commence TCZ therapy must also be explore in future research by the researchers to perceive optimum outcome in critical patients of COVID 19.

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