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Not all Patients with Severe/Critical COVID-19 Pneumonia Benefit from Tocilizumab

Abdul Rehman Arshad, Bilal Saeed, Imran Khan

Department of Medicine, Combined Military Hospital, Peshawar/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To determine serum IL-6 levels predictive of death during hospitalization for severe COVID-19 pneumonia, to rationalize treatment in resource-limited settings.

Study Design: Prospective longitudinal study.

Place and Duration of Study: Combined Military Hospital, Peshawar Pakistan from Aug to Sep 2021.

Methodology: Patients with severe COVID-19 pneumonia, confirmed by a positive SARS-CoV-2 polymerase chain reaction, who received Tocilizumab between August 2020 and July 2021 were included. Patients with negative polymerase chain reaction for SARS-CoV-2, incomplete data, and those admitted before August 2020 were excluded. Paper medical records of eligible patients were scrutinized to record serum C-reactive protein, ferritin, procalcitonin, and interleukin-6 levels within the 24 hours preceding Tocilizumab administration (one or two doses left at the discretion of the treating physician). In-hospital mortality or discharge status was also noted.

Results: Out of 88 patients aged 59.21±14.10 years, 54(61.36%) were males. Twenty-five (28.41%) patients died in the hospital. Area under ROC curve for mortality associated with interleukin-6 levels was 0.719(95% confidence interval 0.603, 0.836; p=0.001). Serum interleukin-6 levels ≥60.28 pg/ml or greater had a sensitivity of 68.00% and specificity of 63.49% for predicting death in hospital. Two doses of Tocilizumab were required in 78(88.64%) patients, and the mortality rate was not different from those receiving only one dose.

Conclusion: Tocilizumab should preferably be avoided in patients with serum interleukin-6 levels ≥10 times the normal.

Keywords: COVID-19, Inflammation, Mortality, Pneumonia SARS-CoV-2, Tocilizumab.

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INTRODUCTION

The COVID-19 pandemic has been around for almost two years now, having played havoc with lives and lifestyles all over the world. So far, 276 million confirmed cases have been reported by the World Health Organization around the globe, with an overall mortality rate approaching nearly 2%.[1] A considerable proportion of these patients have required indoor care at some point during illness. This being a new disease, treatment guidelines have continued to evolve, commensurate with the increasing scientific evidence and experience.[2]

Replication of SARS-CoV-2 virus is mediated by RNA-dependent RNA polymerase. Antiviral agents such as remdesivir inhibit this enzyme and are thus helpful in the initial stages of the disease to control viral replication. The main pathophysiological process causing subsequent damage is the massive proinflammatory response commonly known as cytokine storm. The virus replicates in type 2 alveolar epithelial cells in the lungs, and the damage to these cells releases several cytokines and inflammatory mediators, including interleukin 6 (IL-6) and tumor necrosis factor-α.[2] These cause further damage to lung tissue, finally manifesting as acute respiratory distress syndrome. Steroids are the mainstay in the armamentarium to control this cascade, and the RECOVERY trial has elucidated the optimal dose of dexamethasone for patients with COVID-19 infection.[3] Despite the reduction in mortality and need for intensive care associated with aggressive use of steroids, many patients remain unwell with severe disease manifestations.[4] Tocilizumab, an anti-IL-6 receptor recombinant monoclonal antibody, is used to target inflammatory response in such cases. There is evidence to suggest a lower risk of mortality and need for mechanical ventilation in COVID-19 patients treated with Tocilizumab.[5] Cost and free availability of this drug are, however, a significant concern in our part of the world. These factors dictate the need for a more rational approach towards using this in routine clinical practice.[6]

Whereas the benefits of this drug are now clearly evident, we experienced many patients with poor

Correspondence: Dr Abdul Rehman Arshad, Department of Medicine, Combined Military Hospital, Peshawar Pakistan

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outcomes (especially in-hospital mortality) despite receiving Tocilizumab during the initial few weeks that we started administering it to our patients. We therefore sought to identify biomarkers predictive of a poor response. Identification of such patients helps in rationalizing treatment in resource-limited settings. Considering the mechanism of action of Tocilizumab and the practical reliance on IL-6 levels while deciding the need for Tocilizumab , we focused on serum IL-6 levels as a predictor of response to this novel therapeutic agent in this study.

METHODOLOGY

The prospective longitudinal study was carried out at the Department of Medicine, Combined Military Hospital, Peshawar, from August to September 2021. The research protocol was approved by the Ethics Review Committee of the hospital beforehand, (Approval No. 341, dated 14 July 2021). Sample size calculation was done using EasyROC: a web-tool for receiver operating characteristic (ROC) curve analysis (ver. 1.3.1). For this purpose, we assumed an expected area under ROC curve of 0.7 for Tocilizumab failure (Mussini, et al.6) and an anticipated mortality rate of 44%, corresponding to an allocation ratio of 2.25.[6,7] Using a consecutive sampling technique, patients were included in this study.

Inclusion Criteria: Patients with severe or critical COVID-19 pneumonia confirmed by a positive RT-PCR for SARS-CoV-2 and suggestive high-resolution CT scan chest findings, were included.

Exclusion Criteria: Patients not receiving Tocilizumab , patients with negative polymerase chain reaction for SARS-CoV-2, incomplete data, and those admitted before August 2020, since we were not routinely checking serum IL-6 levels in our hospital laboratory at that time, were excluded.

The minimum criteria required for classification as severe disease were respiratory rate ≥30 per minute, oxygen dependency, PaO2/FiO2 <300 mm Hg, and infiltrates involving more than 50% lung fields on high-resolution CT scan of the chest. Standard treatment protocols were followed for the management of all patients. Our institutional policy for administering Tocilizumab is summarized in Table-I. All patients had serum C-reactive protein (CRP), ferritin, IL-6, and procalcitonin levels checked not more than 24 hours before administration of Tocilizumab. The standard dose was 600mg intravenous infusion (8mg/kg, rounded off to the nearest vial strength), repeated once after 18 hours if no significant clinical improvement occurred. Assessment for this was left to the discretion of the consultant in charge of the case, per the policy of our hospital.

Documents were reviewed to record baseline demographic data of the patients and their clinical status, including duration of hospital stay and in-hospital outcomes. Severity of radiological changes was also noted. Laboratory Management System software of the hospital was used to trace reports of serum IL-6, CRP, ferritin, and procalcitonin levels, if not clearly endorsed in papers.

Data analysis was done with Statistical Package for Social Sciences (SPSS) for Windows, Version 20.0 (IBM Corp, Armonk, NY). All quantitative data were described as Mean±SD. Receiver operating characteristic (ROC) curve analysis was used to determine the sensitivity and specificity of IL-6 levels within the 24 hours preceding Tocilizumab administration for predicting in-hospital death and to determine the best cut-off value using the curve coordinates. Different outcomes were compared among dead patients and survivors using an independent samples t-test for continuous variables with parametric distribution, and an independent samples Mann-Whitney U-test for continuous variables with non-parametric distribution. The level of significance was set at 5% for these comparisons.

RESULTS

There were a total of 88 patients aged 59.21±14.10 years included in this study. Out of them, 54 (61.36%) were males, and the rest were females. Median duration of hospitalization was 8 days (interquartile range 6-12 days), whereas median stay in hospital at the time of Tocilizumab administration was 2 days (interquartile range 2-3 days). Twenty-five (28.41%) patients died in the hospital. Comparison of different parameters between patients dying in the hospital and those leaving the hospital alive is shown in Table-II. A vast majority (78; 88.64%) of the patients required two doses of Tocilizumab , whereas 10(11.36%) received only a single dose. There was no difference in mortality amongst patients receiving one or two doses of Tocilizumab (30.00% and 28.21% respectively; *p*: 0.91)

Area under ROC curve for mortality associated with IL-6 levels was 0.719 (95% confidence interval 0.603, 0.836; *p*=0.001). Details are shown in Figure. Further analysis showed that serum IL-6 levels of 60.28 pg/ml or greater within 24 hours of Tocilizumab

administration had a sensitivity of 68.00% and specificity of 63.49% for predicting death during subsequent stay in hospital.

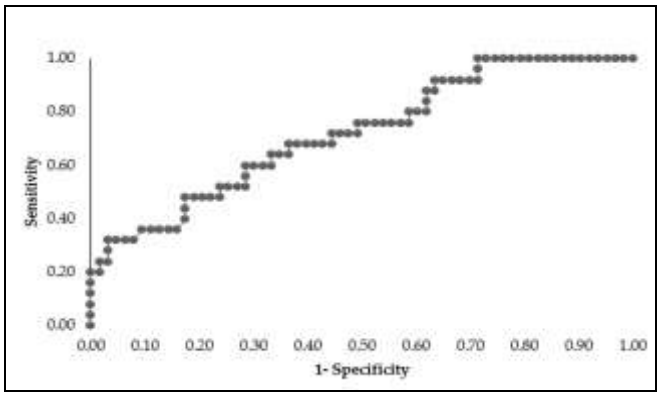

Figure: ROC Curve for IL-6 levels Predicting in- Hospital Mortality

Table-I: Criteria for Tocilizumab in COVID-19 Pneumonia

Indications	**All of the Following**
	Serum IL-6 >3x ULN Normal serum procalcitonin levels Use of steroids for a minimum of 24 hours
	Plus, any two of the following:
	Temperature >100oF Hypotension or decrease in MAP ≥10 mmHg Requirement of high flow oxygen (≥6 L/min) Sustained Respiratory rate ≥30/ minute
	Plus, any of the following:
	CRP ≥100mg/l Ferritin ≥600ng/ml
Contraindications	Absolute neutrophil count <1000/µl Platelets <50000/µl ALT >5 times ULN Pregnancy and breast feeding Structural sequelae of previously treated pulmonary tuberculosis

ULN: upper limit of normal; MAP: mean arterial pressure; ALT: alanine transaminase, CRP: C Reactive Protein

DISCUSSION

The major finding in our study was a significantly high mortality amongst patients with severe/critical COVID-19 infection, approaching nearly one in every three to four patients. Results from systematic reviews and meta-analyses are consistent with a reduction in the need for mechanical ventilation and improvement in short-term mortality with the use of Tocilizumab for COVID-19 infection.[7] However, we looked at an important clinical problem from a different perspective. We identified serum IL-6 levels, almost ten times the upper limit of normal, beyond which administering Tocilizumab was generally futile. This is a significant finding considering the limited resources we work with and the inability of our patients to afford expensive medical treatment.

Direct comparison of the cut-off for IL-6 levels with other studies is difficult because of complex heterogeneities. A cohort study on 901 patients in China documented IL-6 levels >37.65 pg/ml to be predictive of in-hospital mortality with a sensitivity of 91.7% and a specificity of 95.7%.[8] This cohort was fundamentally different from ours, since only about 60% of them had severe or critical disease, 21.4% had elevated IL-6 levels at baseline, and Tocilizumab was administered to 16 patients only. Similarly, another study on 50 patients from Spain revealed a sensitivity of 71% and a specificity of 89% for IL-6 levels ≥34.94 pg/mL as a predictor of mortality.[9] This set of patients was also different from ours, since the vast majority had moderate disease and only 12% had severe disease as defined by the CURB-65 score. However, all of them received Tocilizumab in addition to standard of care. Yet another study involving 41 patients

Table-II: Comparison of Outcomes between Dead Patients and Survivors (n=88)

Variables	Total	Death	Alive	*p*-value
Age (years)	59.21±14.10	65.03±10.55	56.91±14.72	0.005
Duration of Total Hospital Stay (days)	8.00(6.00-12.00)	11.00(7.00- 15.00)	8.00(5.90-10.08)	0.078
Duration of Stay at the Time of Tocilizumab Administration (days)	2.00 (2.00- 3.00)	3.00(2.00-5.00)	2.00(2.00-3.00)	0.001
CT Severity Score	32.21±3.42	31.64±2.92	32.43±3.60	0.287
IL-6 (pg/ml)	54.05(16.49- 111.78)	88.90 (34.63-252.20)	39.10 (11.00- 86.39)	0.001
CRP (mg/l)	218.62±50.82	221.99±53.99	217.28±49.88	0.708
Ferritin (ng/ml)	730.49±91.85	769.06±101.81	715.18±83.60	0.024
Procalcitonin (ng/ml)	0.76±0.10	0.76±0.13	0.76±0.09	0.854

CT: Computed tomography; IL-6: Interleukin 6; CRP: C Reactive Protein

admitted to an intensive care unit in Belgium showed that IL-6 >406 pg/mL had a 75% sensitivity and 64% specificity to predict mortality.[10]

Tocilizumab is a humanized monoclonal antibody that competitively and selectively blocks the IL-6 receptor. Clinically meaningful results can be seen if this drug is administered within ten days of symptom onset in selected patients.[11] The United States FDA previously approved it for different rheumatologic conditions, such as rheumatoid arthritis, giant cell arteritis, and cytokine release syndrome seen with chimeric antigen receptor-T cell therapy. The FDA issued emergency use authorization in June 2021 for patients with COVID-19 infection who require supplemental oxygen or ventilatory support in addition to steroids.[12] Its use is not entirely safe from significant side effects.

Tocilizumab has been utilized as a therapeutic option for COVID-19 pneumonia in other parts of Pakistan as well. In a retrospective review of 40 patients from Karachi, the majority of whom had critical/severe disease, clinical, biochemical, and radiological improvement was seen in 77.5% of patients after Tocilizumab administration, followed by successful discharge to home.[13] In another study done in Peshawar by Amin *et al*., amongst 45 patients with severe COVID-19 infection, serum CRP levels reduced with Tocilizumab , but there was no significant change in serum LDH and d-dimers.[14] Changes in inflammatory markers did not predict mortality at day 28. It is interesting to note that Tocilizumab was used at a lower dose (4mg/kg) in this cohort. Hassan *et al.,* have reported a more encouraging experience from Islamabad.[15] Amongst 120 patients with severe/critical disease, only 36 required a second dose of Tocilizumab , and the mortality rate was much lower at 15%. This is all the more important since all of these patients had received standard of care for at least seven days before Tocilizumab was administered. This was in contrast to the generally recommended time frame of up to 3 days of hospital admission.[16] One of the significant landmark trials for Tocilizumab use in COVID-19 infection, REMAP-CAP, also reaffirms the fact that an earlier administration might be the optimum strategy.[17]

Our patients exhibit distinct behaviors compared to those in the developed or Western world due to multiple factors. Thus, the results of trials conducted elsewhere cannot be easily extrapolated for better management decisions in our settings. This study has provided an opportunity for regional physicians to draw inferences about how patients from Khyber Pakhtunkhwa would behave in a real-world scenario and thus improve prognostication and use available resources more effectively. The interpretation of our results may be limited by the retrospective nature of data collection in this study. We did not evaluate the effectiveness of Tocilizumab in preventing the need for invasive mechanical ventilation in terms of serum IL-6 levels. One of the reasons for this was that a small percentage of patients were already receiving ventilatory support at the time of Tocilizumab administration. Moreover, we did not record possible side effects of Tocilizumab and thus could not compare the frequency of the same between patients with IL-6 levels above or below the identified threshold. Differences in patients' characteristics and outcomes have been observed in different waves of COVID-19 infection internationally.[18] Similarly, differences in clinical characteristics of multiple SARS-CoV-2 variants are also well documented.[19] Considering this, we would be interested in knowing whether the results of this study hold for the successive waves of COVID-19 infection in Pakistan. More studies on this topic are thus recommended in the future.

CONCLUSION

Elevated serum IL-6 levels guide the use of Tocilizumab amongst COVID-19 patients with a compatible clinical picture. However, many such patients did not benefit from this intervention and died in the hospital. Considering the cost and limited availability, the use of this novel drug should be rationalized for patients with levels greater than ten times the upper limit of normal.

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Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

ARA & BS: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

IK: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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