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ORIGINAL ARTICLE

Assessment of Predictors of Mortality in COVID-19 Patients Treated with Tocilizumab

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ABSTRACT

Background: A hypersensitivity condition called cytokine storm is the main cause of death in COVID-19 patients. A monoclonal antibody called tocilizumab may be able to suppress the Interleukin-6 receptors (IL-6R) and lessen the likelihood that the body would have a hypersensitive immune response.
Aim: To evaluate the mortality advantages of tocilizumab in individuals with COVID-19.
Study design: Retrospective study.
Place and duration of study: Bahria Town International Hospital Lahore from 16th June 2020 to 17th September 2021.
Methodology: Patients with 96 confirmed instances of COVID-19 were enrolled. Two groups of patients were created. A single dosage of tocilizumab was administered to 52 participants in the first group, referred to as the survivors, and 44 patients in the second group, who passed away within 14 days. From the patients' medical records, the demographic information, co-morbid conditions, and laboratory values were obtained. The hospital's institutional review board and ethics committee (IRBEC) gave its approval for this study. The permission was ignored because this was a retroactive analysis.
Results: 54.24 16.58 was the average age, and 54 (56.25%) of the population were men. 52 (54.16%) patients were survivors, compared to 44(45.83%) patients in the non-survivor group. In non-survivors compared to survivors, the older age group was shown to be statistically significant (62.78±12.86 vs. 51.65±11.68, p=0.003). Additionally, non-survivors had a greater BMI (p=0.006). In our study, hypertension and diabetes were the two co-morbid conditions that were most frequently detected (35.24% and 28.94%, respectively). The mortality rates among patients with diabetes, asthma, COPD, and cancer were all considerably higher (P=0.01, 0.006, and 0.004, respectively). Cancer and type-2 diabetes patients had death rates that were considerably higher (p=0.05 and p=0.01, respectively). C-reactive protein (CRP), D. Dimer, procalcitonin (PCT), and IL-6 were discovered to be the significant predictors of mortality (p 0.0001, 0.05, 0.001, and 0.004 respectively).
Conclusion: Even though tocilizumab is authorised and has been shown to have positive results, people with diabetes, COPD, and asthma are more likely to experience negative results even after getting a single dosage of the medication. Similar to CRP, D. Dimer levels are reliable indicators of death.
Keywords: Tocilizumab, Motility predictors, Co-morbid conditions, COVD-19, Procalcitonin, D. Dimer

INTRODUCTION

Because it often attaches to the respiratory system and depresses the respiratory system, this virus is also known as the severe acute respiratory distress syndrome-2 (SARS-CoV-2) coronavirus.[1] Acute respiratory distress syndrome symptoms and those of this virus are similar (ARDS)[2]. The increased production of several cytokines in response to this virus infection is reported to be the most frequent cause of respiratory depression, according to literature. The term "cytokine release syndrome" refers to this condition (CRS). According to recent studies, patients who suffer from COVID-19 resistance and cytokine release syndrome have worse results[3]. The production of cytokines such interleukin-6 (IL-6), IL-2, IL-7, TNF-Alpha, IP-10, and granulocyte colony stimulating factor is uncontrolled in cytokine release syndrome.[4] Biochemical indicators such ferritin, D. Dimer, procalcitonin, and reactive protein C have also been linked to inflammatory cytokines[5]. Based on these signs and the body's oxygen level, we may identify the coronavirus infection (COVID-19) and describe its level of severity. Elevated levels of interleukin-6 in CRS and also found in the Middle East Respiratory Syndrome (MERS), are a defining feature of infection by the respective virus. More CD14+, CD16+ and inflammatory monocytes are likely to have been the source of the first cytokine spike. Increased SARS-2 coronavirus (SARS-CoV-2) viral load protracted viral ribonucleic acid (RNA) desquamation, gradually or sudden transition to mechanical ventilation, and demise have all been associated with higher blood IL-6 concentrations[6]. These results suggest that if we block the interleukin-6 receptor (IL-6R) it may be able to halt the inflammatory response at a crucial stage of the invasion process.

Interleukin-6 (IL-6) is prevented from competitively attaching to its receptor by a novel monoclonal antibody named tocilizumab (IL-6R). The complete receptor complex must be blocked to stop IL-6 from signalling to inflammatory mediators that attract B and T cells. Tocilizumab has a nonlinear pharmacokinetic profile. As shown by one Phase III and two Phase II clinical trials that showed a significant reduction in disease activity and the acute-phase response, tocilizumab's capacity to target and block IL-6R can result in a significant improvement in the signs and symptoms brought on by the cytokine release syndrome in a variety of inflammatory diseases like rheumatoid arthritis (RA). Tocilizumab appears to be generally well tolerated when given either by itself or in combination with methotrexate. Adverse events occurred in almost equal amounts across all groups, and they were not dose-related. Tocilizumab may be an alternative for those who do not adequately respond to methotrexate. Because IL-6R inhibition has a distinct mechanism of action, some individuals who do not respond to anti-tumor necrosis factor drugs or who only have a partial response may respond to tocilizumab[7]. The Food and Drug Administration (FDA) has therefore approved tocilizumab for use in a number of conditions where there is an excessive production of cytokines[8]. As we predicted, several tocilizumab non-randomized and open-label studies have shown conflicting findings. Tocilizumab and sarilumab, two immunosuppressive IL-6 inhibitors, have been demonstrated to reduce mortality in critically

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ill patients, including those on ventilators, by 8.5%. Furthermore, it is still unknown what factors led to a favourable tocilizumab response in COVID-19[9,10]. Asians have a high incidence of sickness and are prone to illness.

Asian nations have greater rates of heart disease, diabetes, and hypertension than other ethnic groupings. Tocilizumab has been widely used in CRS during the current pandemic, although there is no proof of its effectiveness in Asians, with only a few case series and scant observational data[11]. The goal of this study is to find out how to predict death in patients who have been given tocilizumab.

MATERIALS AND METHODS

Between 16 June 2020 and 17 September 2021, this research was conducted retrospectively at the Bahria Town International Hospital in Lahore using the descriptive methodology. The trial comprised all confirmed COVID-19 infections on RT-PCR treated with a single dose of tocilizumab and admitted to the COVID-19 ICU Bahria town International Hospital Lahore. The age range of the research was 18 to 80. Both gender (male and female) was included in the study after taken the informed consent. The study excluded subjects whose biochemical variable records were missing or whose follow-up 14-day outcomes were not followed after all data was gathered retrospectively from patient records. This study was approved by the Institutional Review Board and Ethical Committee (IRBEC). The participants were divided into two groups after administered the single dose of tocilizumab. The dose was given intravenously once a day at 8 milligrams per kilogramme of body weight rate. Both groups were given the same standard treatment protocol, which includes low molecular weight heparin, dexamethasone antibiotic, and antiviral software. Non-survivors were assigned to the first group, while survivors were assigned to the second group. Serum ferritin, CRP, D. Dimer, PCT, and other laboratory data were assessed on the third day following tocilizumab administration. Co-morbid diseases such as diabetes mellites (DM), hypertension (HTN), asthmatic status, and chronic obstructive pulmonary disease (COPD) were also identified for future research in both groups.

Data was analysed by SPSS 24.0. For normally distributed continues variable mean with standard deviation (S.D) was used and categorical variables were represented as frequencies. The chi-square test, exact, student t-test, and Wilcoxon-Mann-Whitney test were used to compare the "Deceased vs. Recovered".

RESULTS

The average age of the patients was 54.24 ± 16.58 years, with 54(56.25%) being male. In our study, there were 52(54.16%) survivors and 44(45.83%) non-survivors. The older age group among non survivors was shown to be statistically significant when compared to survivors (62.78±12.86 vs 51.65±11.68, p=0.003). Non-survivors had a higher body mass index (p=0.006). Hypertension was the most prevalent co-morbid disease, followed by diabetes (35.42% and 29.17%, respectively). Diabetes, asthma, COPD, and cancer patients died at a considerably greater rate (P=0.01, 0.006, 0.004, and 0.001, respectively). Lactate dehydrogenase (LDH) did not differ substantially across groups (p=0.09), however other inflammatory markers such as C-reactive protein (CRP), D. Dimer (D.D), serum ferritin, procalcitonin (PCT), and interlukin-6 (IL-6) were revealed to be significant predictors of death (p=0.0001, 0.05, 0.001, 0.004, respectively). These markers were significantly different between the two groups (Tables 1-2).

Table 1: Comparison of demographic variables and co morbid conditions

Variables	Survivors (n=52)	Non-survivors (n=44)	p-value
Age	51.65±11.68	62.78±12.86	0.003
Gender			
Male	29	25	0.12
Females	22	20	0.09
Body mass index (kg/m^2)	27.56±5.68	29.58±4.21	0.006
Co morbid conditions			
Hypertensive	16	18	0.08
Diabetics	11	17	0.01
Ischemic heart disease	5	6	0.81
Asthmatic	4	10	0.006
COPD	8	14	0.004
Renal Dysfunction	2	4	0.17
Gastrointestinal issues	5	7	0.47
Psychiatric illness	2	3	0.28
Malignancies	2	6	0.001

Table 2 Comparison of biochemical variables of prognostic importance

Variables	Survivors (IQR)	Non-survivors (IQR)	p-value
CRP (mg/L)	43.98 (1.9–349.62)	122.25 (4.6–406.85)	<0.001
D. Dimer (ug/ml)	0.3 (0.1-1.5)	1.8 (0.6-4.5)	0.05
Serum Ferritin (ng/ml)	467 (20.56-3427)	826 (72.5–5314)	0.001
Procalcitonin (ng/ml)	0.10 (0.02-16.6)	0.48 (0.04-39.22)	0.001
IL-6 (pg/ml)	30.42 (12.6-968)	55.51 (11.2-733.42)	0.004
LDH (U/L)	265.54 (25.5-410.22)	302.56 (26.5-422.68)	0.09

DISCUSSION

SARS-CoV-2 hypercytokinemia is associated with hypersensitivity, immunosuppression, and hyperinflammation, which emerges as a cytokine storm during the second week of COVID-19.[12] Increased cytokine levels may be to blame for COVID-19's disastrous consequences, which have been linked to a higher death rate. This study provides information on the demographics of Asians who may or may not benefit from tocilizumab-induced IL-6 inhibition[13]. A variety of demographic and clinical variables were found to be more frequent in the death group. it was found that the ratio of death was greater in older age as compared to the younger age groups. Similar results were noted in the earlier studies.

Due to age-related changes, older people's capability to respond properly to infections through an efficient immune response may have been compromised.[14] Between the ages of 40 and 50, the creation of new naive T-cells decreases rapidly, reducing the elderly's ability to combat emerging viruses like SARS-CoV-2. Diabetes and hypertension are two instances of co-morbidities that are becoming more frequent as individuals age[15,16].

The most common comorbidity in this study was high blood pressure, while diabetes mellitus (DM) was shown to be substantially more prevalent in the non-survival group (p=0.01).

Another study indicated that tocilizumab administration did not lower the risk of severe outcomes like death and irreversible changes in hyperglycaemic individuals compared to those with normoglycemia (p=0.009).[17] Heart disease, bone disease, and cancer are a few more co-morbid conditions that may be connected to the bad outcomes with SARS-CoV-2 infections. To fully understand the mechanisms underlying COVID-19 infections, more study is required. Additionally, higher LDH levels were associated with death, but this association lacked statistical significance (p=0.09). Similar findings have been made in other studies, where it was discovered that tocilizumab-treated patients who died from COVID-19 infection had greater levels of LDH than survivors. Despite the fact that several studies indicated that these outcomes lacked statistical significance.

Patients with greater D. Dimer levels died at a considerably higher rate (p=0.05), according to our findings. Lippi et al[18] reported in their research that COVID-19 patients with greater D-dimer levels have a higher mortality rate. This study supports the use of tocilizumab in those who are diagnosed early and have lower D-dimer levels than people who have higher D-dimer levels. This evidence supports the use of anticoagulants in COVID-19 patients on tocilizumab. The pharmacokinetic mechanism is most likely responsible for the initial spike in IL-6 levels, which was followed by a steady decrease.

Hyperferritinemia, which is caused by infection-related inflammation, is linked to hospitalisation and high mortality and should be utilised to identify high-risk patients and guide therapy action to reduce inflammation. Serum ferritin, a sign of hemophagocytic lympho-histiocytosis, a known result of viral infection, has been associated to poor recovery in COVID-19 patients, with ferritin levels being greater in those with a damaged lung lesion. These studies, however, had a limited sample size and/or were done in a single location.[19] Ferritin's pro-inflammatory involvement in an unchecked cytokine storm and its capacity to foretell unfavourable outcomes in COVID-19 patients should be further established.[20] In the course of our research, we found that the non-survivor group had statistically significantly higher ferritin levels than the survivors. We discovered contrasting findings in the literature. Ferritin has been shown in some research to be a poor predictor of death, whereas in other studies it has been shown to be a useful indicator of disease progression in covid-19 infection. The findings of COVID-19 illness investigations on CRP, procalcitonin, and ferritin, as well as interesting biochemical findings, were published in the research by Guan et al[21], who presented data from several areas in China; C-reactive protein (CRP) was increased in approximately sixty percent of patients. Procalcitonin levels are elevated in 5.5% of patients, and an elevation in lactate dehydrogenase (LDH) was seen, which might indicate a subsequent bacterial infection. This secondary infection exacerbated COVID-19's clinical development. When compared to non-severe instances, the severity of the cases rose significantly (81.5% vs 56.4% for CRP, 13.7% vs 3.7% for procalcitonin, and 58.1% vs 37.2% for LDH). Serum ferritin, D-dimers, CRP, and interlines were all shown to be significantly associated with an increased risk of mortality in the study. Our research has a few drawbacks as well. Because this is single-centric research with a small number of individuals A vast number of multicentric trials are required to have a better knowledge of the effect of tocilizumab.

CONCLUSION

Despite the fact that tocilizumab is associated with a larger percentage of survivors compared to non-survivors, age, diabetes, asthma, COPD, and malignancies are still identified to be contributing factors in the increased death rate. Similar to this, D. dimer, procalcitonin, CRP, and interleukin-6 are biochemical factors that contribute to a bad prognosis in covid-19 infection.

Conflict of interest: Nil

REFERENCES

1. Suri JS, Agarwal S, Gupta SK, Puvvula A, Biswas M, Saba L, et al. A narrative review on characterization of acute respiratory distress syndrome in COVID-19-infected lungs using artificial intelligence. Computers Biol Med 2021; 130:104210.
2. Badraoui R, Alrashedi MM, El-May MV, Bardakci F. Acute respiratory distress syndrome: a life threatening associated complication of SARS-CoV-2 infection inducing COVID-19. J Biomolecular Structure Dynamics 2021; 39(17): 6842-51.
3. Radbel J, Narayanan N, Bhatt PJ. Use of tocilizumab for COVID-19-induced cytokine release syndrome: a cautionary case report. Chest 2020;158(1):e15-e9.
4. Ortiz-Martínez Y. Tocilizumab: a new opportunity in the possible therapeutic arsenal against COVID-19. Travel Med Infec Dis 2020; 37:101678.
5. Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Therapeutic advances Resp Dis 2020;14: 1753466620937175.
6. Stasi A, Franzin R, Fiorentino M, Squiccimarro E, Castellano G, Gesualdo L. Multifaced roles of HDL in sepsis and SARS-CoV-2 infection: renal implications. Int J Molecular Sci 2021; 22(11): 5980.
7. Wu T-C, Chiang C-Y, Chan J-S, Lee C-Y, Leu H-B, Huang P-H, et al. Tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor, inhibits high glucose-induced vascular smooth muscle cell migration through mitogen-activated protein kinase signaling pathways. J Interferon Cytokine Res 2018;38(11):510-6.
8. Rana M, Hashmi M, Pervaiz R, Qayyum A, Saif M, Munir M, et al. Beneficial effects of treatment with tocilizumab in moderate to critically ill COVID-19 patients. Pak J Intensive Care Med 2021; 2021(1).
9. Belletti A, Campochiaro C, Marmiere M, Likhvantsev V, Yavorovskiy A, Dagna L, et al. Efficacy and safety of IL-6 inhibitors in patients with COVID-19 pneumonia: a systematic review and meta-analysis of multicentre, randomized trials. Ann Intensive Care 2021;11(1):1-14.
10. Rana MA, Qayyum A, Hashmi M, Saif MMU, Munir MF, Pervaiz R, et al. Mortality & COVID-19: A Snapshot of a Tertiary Care Facility in Pakistan. medRxiv. 2020.
11. McKeigue P, Shah B, Marmot M. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. Lancet 1991;337(8738):382-6.
12. Pourgholaminejad A, Pahlavanneshan S, Basiri M. COVID-19 immunopathology with emphasis on Th17 response and cell-based immunomodulation therapy: Potential targets and challenges. Scandinavian J Immunol 2022; 95(2):e13131.
13. Banerjee D, Kosagisharaf JR, Rao TS. 'The dual pandemic'of suicide and COVID-19: a biopsychosocial narrative of risks and prevention. Psychiatr Res 2021;295:113577.
14. Boe D, Boule L, Kovacs E. Innate immune responses in the ageing lung. Clin Experimental Immunol 2017;187(1):16-25.
15. Mazucanti CH, Egan JM. SARS-CoV-2 disease severity and diabetes: why the connection and what is to be done? Immunity Ageing 2020; 17(1):1-11.
16. Rana M, Arif B, Siddiqui M, Raza S, Hashmi M, Hafeez M. Strategies to allow family visits to acute care units during the covid-19 pandemic. Pak J Intensive Care Med 2021;2021(1).
17. Desai HD, Sharma K, Parikh A, Patel K, Trivedi J, Desai R, et al. Predictors of mortality amongst tocilizumab administered COVID-19 Asian Indians: a predictive study from a tertiary care centre. Cureus 2021;13(2).
18. Henry BM, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M, et al. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis. Am J Emerg Med 2020;38(9):1722-6.
19. Kumar R, Harilal S, Al-Sehemi AG, Mathew GE, Carradori S, Mathew B. The chronicle of COVID-19 and possible strategies to curb the pandemic. Curr Med Chem 2021;28(15):2852-86.
20. Rabaan AA, Al-Ahmed SH, Muhammad J, Khan A, Sule AA, Tirupathi R, et al. Role of inflammatory cytokines in COVID-19 patients: a review on molecular mechanisms, immune functions, immunopathology and immunomodulatory drugs to counter cytokine storm. Vaccines 2021;9(5):436.
21. Chen R, Sang L, Jiang M, Yang Z, Jia N, Fu W, et al. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. J Allergy Clin Immunol 2020;146(1):89-100.