

Compassionate Use of Tocilizumab in Patients with Coronavirus Disease 2019 in a Low-resource Country, Pakistan: A Pilot Study

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Abstract

Background: We herein report our experience of optimized utilization of tocilizumab for patients with coronavirus disease 2019 (COVID-19) in a limited-resource tertiary care hospital.

Methods: This single-center, single-arm, open-label, interventional study was conducted to determine the effect of tocilizumab on the mortality of patients with COVID-19.

Results: Fifty-nine patients were administered tocilizumab. Patients who received invasive respiratory support were identified to have a higher risk of mortality than those who received oxygen support.

Conclusion: Our study showed that the maximum benefit of tocilizumab was observed as a prophylactic treatment of cytokine syndrome in patients with COVID-19, particularly those with moderate to severe symptoms who are not receiving invasive respiratory support.

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Keywords

Tocilizumab (interleukin 6 inhibitor), Pakistan, COVID-19 management, recovery trial, mortality, pharmacist.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), the causative agent of coronavirus disease 2019 (COVID-19), has been a major reason for global concern since December 2019 [1]. Mortality rate among patients with mild to moderate symptoms remained low; however, a significant number of patients progresses to a severe stage requiring hospitalization. These severe to critical patients are at high risk of mortality [2]. It was later identified that the severity of the disease was linked with cytokine release syndrome (CRS) due to elevated interleukin 6 (IL-6) [3]. Thus, it was strongly proposed that halting the progression of CRS or its treatment may contribute to a lower mortality rate in such patients [4].

Tocilizumab, an IL-6 inhibitor, is approved for life-threatening CRS induced by chimeric antigen receptor T-cell therapy. It was postulated that suppression of cytokine release shock may lead to a better outcome in patients with SARS-COV-2;

hence, the use of tocilizumab was considered [5]. Initial observational studies showed the drug's beneficial effects of on the outcome; thus, it was approved by many counties for compassionate use [6, 7]. As with other countries, the Drug Regulatory Authority of Pakistan authorized the use of tocilizumab for COVID-19.

Because of the high cost of the drug as well as its accessibility and unknown effects, a pilot pragmatic study was conducted to observe the effect of tocilizumab on in-hospital mortality in patients with COVID-19.

Methods

Study design

This single-center, single-arm, open-label, interventional study was conducted to determine the effect of tocilizumab on the in-hospital mortality of patients with COVID-19.

Site of study

Lady Reading Hospital-MTI (LRH) Peshawar, a 1770-bed, tertiary care, government hospital, was responsible for providing services for moderately, severely, and critically ill patients with COVID-19. Approximately 250 beds in high-dependency units provided care to moderately to severely ill patients requiring high-intensity oxygen therapy, and 25 beds in the intensive critical units were assigned for critically ill patients requiring invasive respiratory support or cardiac support [8].

Intervention

A single intravenous dose of 400 mg tocilizumab in 100 mL 0.9% NaCl was administered in 60 minutes. To standardize the administration and reduce the chances of error, tocilizumab was administered at 10 am. Because of the high cost of the medication and the lack of availability as well as to reduce wastage, a standard dose of 400 mg was used during the study.

Prescribing protocol

A multidisciplinary team involving a pulmonologist, a pharmacist, and an internal medicine physician were responsible for prescribing tocilizumab based on patient condition and inflammatory markers such as C-reactive protein, ferritin, D-dimer, and lactate dehydrogenase. Other investigational treatments such as hydroxychloroquine, azithromycin, steroids, and antiviral drugs were not given to the patients during the study. Anticoagulants, antibiotics, and gastroprotective agents were part of the treatment protocol. Verbal approvals were obtained from patients or their relative.

Statistical analysis

With rate of ventilator use as high as 50% and $\alpha=0.05$ (two-tailed), a sample size of at least 47 patients was required to give an estimate at a width of $\pm 7.5\%$ and with a 95% confidence interval.

Categorical variables in demographic data are presented as frequencies and percentages. Chi-square test were carried out to mortality with different variables. All analyses were carried out using Statistical Packages for Social Sciences version 21 (IBM Corp., Armonk, NY, USA). Statistical significance was indicated by $p<0.05$.

Results

A total of 59 patients received tocilizumab from 16 April to 15 August 2020. Of these patients, 89% were PCR-positive and 11% were clinically suspected; 29 of the patients were critically ill and required invasive respiratory support, whereas 30 of the patients were classified as being

moderately to severely ill and required high-intensity oxygen therapy (Table 1).

The overall survival rate in patients receiving tocilizumab was 32% (Table 1). However, further analysis showed that the in-hospital mortality rate was 86.2% in critical patients who received invasive respiratory support and 50% in non-critical patients who received high oxygen therapy. Thus, tocilizumab was found to be more beneficial in patients receiving oxygen support than in patients on invasive respiratory support (86% vs. 50%; $p<0.05$) (Table 2).

Discussion

During the early phase of the COVID-19 pandemic, there was no standard treatment was available; hence, irrational use of the investigational drug was observed [9]. Many early treatment strategies depended on small, low-quality, observational studies showing positive results [10]. Medications such as azithromycin, hydroxychloroquine, oseltamivir, ivermectin, and others were frequently prescribed [11]. Like other medications, tocilizumab was also considered in patients with COVID-19 based on a few favorable observation studies. At the time, many trials were in process to evaluate its benefits in patients with COVID-19, thus could not enable us to establish a standardized protocol for its use.

The result of our study showed a moderate impact (32%) of tocilizumab on in-hospital patients with COVID-19. Our study also showed that the maximum benefit of tocilizumab was found as a prophylactic treatment of cytokine syndrome in patients with COVID-19 particularly in moderately to severely ill patients not receiving invasive respiratory support. A similar study was conducted in Pakistan evaluating tocilizumab effectiveness in 40 patients with COVID-19. Unlike our study, it reported an overall survival rate of approximately 72% in the tocilizumab group. However, like our study, it had a high in-hospital mortality rate in patients receiving invasive respiratory support (11 patients;

Table 1 Data of Patients who Received Tocilizumab (n = 59)

Sex	
Male	45 (76.3)
Female	14 (29.5)
Age	
<25 years	1 (1.7)
25–35 years	5 (8.5)
35–45 years	8 (13.6)
45–55 years	12 (20.3)
55–65 years	29 (49.2)
>65 years	4 (6.8)
COVID-19 status	
PCR-positive	53 (89.8)
Clinically suspected, PCR-negative	6 (8.5)
Patient status	
Critical	29 (32.2)
Non-critical	30 (67.8)

Values are presented as n (%).

Table 2 In-house Mortality

	Survived	Died	p-Value
Critical patients on invasive respiratory support	4 (13.8)	25 (86.2)	<0.05
Moderately to severely ill patients on high oxygen therapy	15 (50)	15 (50)	
Overall mortality	19 (32.20)	40 (67.80)	

Values are presented as n (%).

mortality rate, 54%) and a high survival rate in other patients (29 patients; mortality rate, 72%) [12].

Based on our study, a drug-use protocol was developed that established the use of tocilizumab in moderate to severe COVID patients with high inflammatory markers. The study did not aim to identify the rationale for the low effectiveness of tocilizumab in patients receiving invasive respiratory support; however, it was suggested that invasive respiratory support might interfere with the pharmacokinetic properties of the drug, which may reduce its effectiveness. More research is required in this regard.

Later, a number of literature on the use of tocilizumab for the COVID-19 treatment were published. Many of these studies directed the early use of tocilizumab [13–15]. Nonetheless, a randomized clinical trial was required to confirm these findings. The results of the RECOVERY trial regarding the effectiveness of tocilizumab in patients with COVID-19 requiring oxygen and evidence of high inflammatory marker have been released. The trial has shown an absolute difference of 4% in mortality inpatient receiving tocilizumab [16], thus endorsing our practices.

In Pakistan, which is a low- to middle-income country, the role of the pharmacist is still evolving, and very few studies have been evaluated the pharmacists' role in the country [17]. Our study has shown that the use of a multidisciplinary approach especially utilizing pharmacists during such limitations has proved to be highly beneficial for judicious use of expensive medication. Standardization of treatment and regular drug utilization review helped in developing an optimized protocol that was used in the second and third waves of COVID-19 in Pakistan.

A strength of this study is the sole use of tocilizumab, and other therapeutic modalities such as azithromycin, ivermectin, etc. were not used. However, the study has some

limitation. The absence of a control group is a major limitation. As we aimed to evaluate the impact of the new protocol in order to observe its benefits, comparison with a control group is necessary.

Contributors

M.A. developed the idea, performed the experiment, and wrote the manuscript. Z.I., S.A., and S.Z. provided clinical support. A.G. was responsible for reviewing the manuscript.

Ethics

This study was approved by the Ethical Review Board of Lady Reading Hospital-MTI (Ref: 443-1/LRH/MTI).

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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References

- [1] Guan W, Ni Z, Hu Y, Liang W, Ou C, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708-20. [DOI: 10.1056/NEJMoa2002032]
- [2] López-Medrano F, Pérez-Jacoiste Asín MA, Fernández-Ruiz M, Carretero O, Lalueza A, et al. Combination therapy with tocilizumab and corticosteroids for aged patients with severe COVID-19 pneumonia: a single-center retrospective study. *Int J Infect Dis* 2021;105:487-94. [PMID: 33647515 DOI: 10.1016/j.ijid.2021.02.099]
- [3] Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, et al. Tocilizumab in hospitalized patients with severe covid-19 pneumonia. *N Engl J Med* 2021;384:1503-16. [DOI: 10.1056/NEJMoa2028700]
- [4] Wei Q, Lin H, Wei RG, Chen N, He F, et al. Tocilizumab treatment for COVID-19 patients: a systematic review and meta-analysis. *Infect Dis Poverty* 2021;10:71. [PMID: 34001244 DOI: 10.1186/s40249-021-00857-w]
- [5] Chen C, Zhang XR, Ju ZY, He WF. Advances in the research of mechanism and related immunotherapy on the cytokine storm induced by coronavirus disease 2019. *Zhonghua Shao Shang Za Zhi* 2020;36:471-5. [PMID: 32114747 DOI: 10.3760/cma.j.cn501120-20200224-00088]
- [6] Radbel J, Narayanan N, Bhatt PJ. Use of tocilizumab for COVID-19-induced cytokine release syndrome. *Chest* 2020;158:e15-9. [PMID: 32343968 DOI: 10.1016/j.chest.2020.04.024]
- [7] Sciascia S, Aprà F, Baffa A, Baldovino S, Boaro D, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. *Clin Exp Rheumatol* 2020;38:529-32. [PMID: 32359035]

- [8] Ali H, Amir M, Ghafoor A. COVID-19 pandemic helped develop positive impact of pharmacists in a tertiary care Government Hospital in Pakistan. *ACCP Int Clin Pharm* 2020;10:1-2.
- [9] Voice Series COVID-19 Special Collection Part 1: Interview with clinicians: COVID-19 mutation and current breakthrough in vaccine development. *Bio Integration*. Available from: <https://bio-integration.org/10-15212-bioi-2021-0008/>. [Last accessed on 4 Nov 2021]
- [10] Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ*. Published online July 30, 2020;370:m2980. [PMID: 32732190 DOI: 10.1136/bmj.m2980]
- [11] Peyko V. Cytokine release syndrome in COVID-19 should we rethink our approach? *Infectious Disease Special Edition*. Available from: <https://www.idse.net/Covid-19/Article/08-20/Cytokine-Release-Syndrome-in-COVID-19/59218>. [Published 4 Aug 2020]
- [12] Zain Mushtaq M, Bin Zafar Mahmood S, Jamil B, Aziz A, Ali SA. Outcome of COVID-19 patients with use of tocilizumab: a single center experience. *Int Immunopharmacol* 2020;88:106926. [PMID: 32889236 DOI: 10.1016/j.intimp.2020.106926]
- [13] Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol* 2020;2:e474-84. [PMID: 32835257 DOI: 10.1016/S2665-9913(20)30173-9]
- [14] Klopfenstein T, Zayet S, Lohse A, Balblanc JC, Badie J, et al. Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. *Méd Mal Infect* 2020;50:397-400. [PMID: 32387320 DOI: 10.1016/j.medmal.2020.05.001]
- [15] Keske Ş, Tekin S, Sait B, İrkören P, Kapmaz M, et al. Appropriate use of tocilizumab in COVID-19 infection. *Int J Infect Dis* 2020;99:338-43. [PMID: 32726724 DOI: 10.1016/j.ijid.2020.07.036]
- [16] RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021;397:1637-45. [PMID: 33933206 DOI: 10.1016/S0140-6736(21)00676-0]
- [17] Amir M, Feroz Z, Beg AE, Rickles N. Using a pharmacist-led mHealth to improve patient's adherence of antidepressants: patients' experiences in low resourceful country. *BMJ Innov* 2021;7:75-80. [DOI: 10.1136/bmjinnov-2020-000422]