Tocilizumab in COVID-19 management: addressing time of starting treatment

Identifying effective and safe therapies for the management of patients with coronavirus disease 2019 (COVID-19) is crucial in the control of the pandemic. The critical role of immune system dysregulation in the pathophysiology of multisystem organ dysfunction following COVID-19 is well recognised. Several attempts have been made to investigate multiple anti-inflammatory drugs with beneficial effects in the management of COVID-19. Recently, the US Food and Drug Administration issued an emergency use authorisation (EUA) for the use of tocilizumab in combination with corticosteroids in hospitalised patients with COVID-19 aged ≥2 years who require non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation. However, there are uncertainties regarding the time, dose and duration of administration. Some efforts have been made to answer these questions.[1 2]

Diaz et al., in an observational study, evaluated the optimal time of tocilizumab administration in 112 hospitalised patients with COVID-19.[3] The treatment was given within and after 10 days of symptom onset in 47 and 65 patients, respectively. They reported that 90-day mortality was significantly higher in the first group (18.6% vs 5.0%, p=0.048). However, it seems that their findings could be derived by misleading data interpretation. First, the current evidence shows that there is a considerable link between the level of inflammatory biomarkers and the clinical response of patients with COVID-19 to tocilizumab. For example, Mariette et al. recently reported a significant correlation between the serum level of C-reactive protein (CRP) and the mortality rate in patients with COVID-19 who received tocilizumab.[4] Data analysis of patients with moderate-to-severe COVID-19 indicated that tocilizumab could decrease the risk of 90-day mortality in the subgroup of patients with elevated CRP levels (>15.0 mg/dL) (9% vs 35%; HR 0.18 (95% CI 0.04 to 0.89)). In the study by Diaz et al., among the reported inflammatory parameters (lactate dehydrogenase, CRP, D-dimer and total lymphocyte count), the serum level of CRP at the time of tocilizumab administration was significantly higher in the first group than in the second group (208.7 (118.0–270.0) mg/dL vs 153.0 (61.2–238.1) mg/dL, p=0.035). Given the key role of CRP—the surrogate marker for interleukin-6 (IL-6) bioactivity—in the pharmacodynamics of IL-6 blockers, the reported significant difference between the groups is presumably because of the different baseline serum levels of CRP. Besides, the higher mortality rate among patients with elevated CRP levels (208.7 (118.0–270.0) mg/dL) may highlight the importance of tocilizumab administration before progression of the disease to the late inflammatory stages. Second, the genetic characteristics of individuals can influence the disease progression rate. Recently, Pairo-Castineira et al. studied the DNA of 2700 patients with severe COVID-19 and found that five genes—including IFNAR2, TYK2, OAS1, DPP9 and CCR2—are associated with progression to the severe forms of the disease.[5] Consequently, the decision on the administration of tocilizumab based on time to onset of symptoms does not seem to be rational.

Taken together, in contrast to the conclusions of Diaz et al., the level of inflammatory biomarkers, especially CRP, plays a key role in the starting of tocilizumab treatment.

Sajad Khiali , **Taher Entezari-Maleki**

Tabriz University of Medical Sciences, Tabriz, Iran

Correspondence to Dr Taher Entezari-Maleki, Tabriz University of Medical Sciences, Tabriz 5166614766, Iran; tentezari@gmail.com

Contributors All authors have contributed equally to the development of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Khiali S, Entezari-Maleki T. *Eur J Hosp Pharm* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/ejhpharm-2021-003149

Eur J Hosp Pharm 2022;**0**:1. doi:10.1136/ejhpharm-2021-003149

ORCID iD

Sajad Khiali http://orcid.org/0000-0002-2476-4430

REFERENCES

1 Giamarellos-Bourboulis EJ, Netea MG, Rovina N, *et al*. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microbe* 2020;27:992–1000.
2 US Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes drug for treatment of COVID-19, 2021. Available: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-treatment-covid-19 [Accessed 5 Nov 2021].
3 Moreno Diaz R, Amor García MA, Teigell Muñoz FJ, *et al*. Does timing matter on tocilizumab administration? Clinical, analytical and radiological outcomes in COVID-19. *Eur J Hosp Pharm* 2021:ejhpharm-2020-002669.
4 Mariette X, Hermine O, Tharaux P-L, *et al*. Effectiveness of tocilizumab in patients hospitalized with COVID-19: a follow-up of the CORIMUNO-TOCI-1 randomized clinical trial. *JAMA Intern Med* 2021;181:1241–3.
5 Pairo-Castineira E, Clohisey S, Klaric L, *et al*. Genetic mechanisms of critical illness in COVID-19. *Nature* 2021;591:92–8.