Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
The utility of CRP with the use of dexamethasone and Tocilizumab in critically ill patients with COVID-19

Harry Zacharias, Ritwik Mungara, Andrew Peter Wilson, Mervyn Singer, Nishkantha Arulkumaran

A total of 215 patients received dexamethasone alone and a further 45 patients received Tocilizumab in addition to dexamethasone. There were no significant differences in age (p = 0.120), sex (p = 0.233), or APACHE II score (p = 0.253) between patients receiving dexamethasone alone or Tocilizumab in addition to dexamethasone (Supplementary Table 1). Of the 215 who received dexamethasone alone, 105 patients (49%) died. Of the 45 patients who received Tocilizumab in addition to dexamethasone 22 (49%) died (p = 0.999).

Sequential CRP data were available in 174 (81%) patients receiving dexamethasone and in 40 (89%) patients receiving Tocilizumab. Among patients who received dexamethasone, CRP was higher among non-survivors (p = 0.0003). A reduction in CRP was seen in the first three days of treatment among survivors and non-survivors (p < 0.0001), with no difference in the change in CRP over time (p = 0.120). Over the subsequent week, CRP levels increased among non-survivors but not survivors (p = 0.001) (Fig. 1).

Among patients who received Tocilizumab, a reduction in CRP was seen in the first three days of treatment among survivors and non-survivors (p < 0.0001), and CRP was higher among non-survivors (p = 0.023). Over the subsequent week, CRP levels continued to fall among survivors and non-survivors, with no difference between groups (p = 0.295) (Fig. 1).

As CRP was no longer able to differentiate between eventual survivors and non-survivors among patients receiving Tocilizumab, we evaluated other routinely collected clinical biomarkers associated with systemic inflammation. Levels of ferritin, D-dimer, BNP, lymphocytes, and neutrophils in eventual survivors and non-survivors who received Tocilizumab were assessed over a 10-day period (Fig. 2). There were no differences in the change of ferritin (p = 0.361), D-dimer (p = 0.310), BNP (p = 0.970), lymphocytes (p = 0.493) or neutrophils (p = 0.629) over time between eventual survivors and non-survivors who received Tocilizumab.

Nine patients of 45 (20%) who received Tocilizumab developed a positive blood culture. The time to positive blood culture was 19 (17–27) days from receiving Tocilizumab. Levels of inflammatory markers two- days prior to and three days after a positive blood culture showed a significant change in CRP (p = 0.002) but not neutrophils (p = 0.903), lymphocytes (p = 0.997), or temperature (p = 0.064) (Supplementary Fig. 1).

We report a significant reduction in CRP three days following the administration of dexamethasone, which subsequently increased in
non-survivors, but remained low in survivors. In contrast, CRP levels fell and remained low in survivors and non-survivors who received tocilizumab. The suppression of CRP for more than a week in patients with COVID-19 receiving Tocilizumab has been described by others [4]. We therefore sought to investigate the effect of Tocilizumab on CRP and other biomarkers which have been associated with poor outcome among patients with COVID-19, including ferritin, D-dimer, and neutrophil: lymphocyte ratio [5]. None of the biomarkers distinguished between survivors and non-survivors who received tocilizumab.

The concurrent use of dexamethasone and Tocilizumab have been associated with a reduction in mortality among patients with COVID-19 [6]. However, the risk of secondary infections remains a significant concern [7]. Among patients receiving tocilizumab, the time to develop a bloodstream infection (BSI) was between 2 and 3 weeks; as reported by others [4,8]. The investigation and diagnosis of a BSI was triggered by an increase in CRP levels and temperature. We cannot exclude the possibility of occult BSI which was undiagnosed closer to the time of dexamethasone and Tocilizumab administration, as clinical features associated with BSI, including a rising temperature and CRP may have been attenuated [4].

As with all retrospective analyses, we cannot correct for residual confounding, data are associative. Additionally, our sample size was limited. We did not have report data on procalcitonin as this was not collected on a daily basis. There are a number of other biomarkers of

Fig. 1. CRP trajectory of patients receiving dexamethasone alone or dexamethasone with Tocilizumab.

Fig. 2. Trajectory of ferritin, B-type natriuretic peptide (BNP), D-dimer, neutrophils, lymphocytes, and neutrophil: lymphocyte ratio (NLR) among patients receiving dexamethasone with Tocilizumab.
interest including lactate and IL-6 levels which may have prognostic value, which we have not reported. We have chosen to focus on the few inflammatory markers that are routinely available and have been shown to be associated with mortality in COVID-19. While multiple reports describe the trajectory of physiological parameters and laboratory biomarkers among survivors and non-survivors with COVID-19 [5,9], few have described the utility of these biomarkers in response to therapy and the therapeutic and prognostic implications.

The trajectory of CRP distinguished between survivors and non-survivors among patients who received dexamethasone, but not among those who receive tocilizumab in conjunction with dexamethasone. The trajectory of alternative biomarkers including ferritin, D-dimer, BNP, neutrophils and lymphocytes do not distinguish between survivors and non-survivors who receive tocilizumab. However, at the time of a bloodstream infection, occurring on average 18 days following tocilizumab, CRP levels increase. Further research is required to ascertain the optimal biomarker to detect secondary infections closer to the time of tocilizumab administration.

**Funding**

NA receives salary support from UCLH BRC (University College London Biomedical Research Council).

**Ethical approval**

Ethical approval was granted by the London-Westminster Research Ethics Committee, the Health Research Authority and Health and Care Research Wales (HCRW) on 2nd July 2020 (REC reference 20/HRA/2505, IRAS ID 284088).

**Author contributions**

HZ and RM curated data.
APRW curated data and reviewed the manuscript.
MS reviewed the manuscript.
NA designed the study, performed statistics, wrote the manuscript.

**Declaration of Competing Interest**

The authors have no competing interest to declare.

**Acknowledgements**

None.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2022.154053.

**References**

[1] Manson JJ, Crooks C, Naja M, et al. COVID-19-associated hyperinflammation and escalation of patient care: a retrospective longitudinal cohort study. Lancet Rheumatol. 2020;2:e594–602.
[2] Group RC. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397:1637–45.
[3] Group RC, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693–704.
[4] Kooistra EJ, van Berkel M, van Kempen NF, et al. Dexamethasone and tocilizumab treatment considerably reduces the value of C-reactive protein and procalcitonin to detect secondary bacterial infections in COVID-19 patients. Crit Care. 2021;25:281.
[5] Zanella A, Florio G, Antonelli M, et al. Time course of risk factors associated with mortality of 1260 critically ill patients with COVID-19 admitted to 24 Italian intensive care units. Intensive Care Med. 2021;1–14.
[6] Gordon AC, Mouncey PR, et al. REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med. 2021;384(16):1491–502.
[7] Buetti N, Ruckly S, de Montmollin E, et al. COVID-19 increased the risk of ICU-acquired bloodstream infections: a case-cohort study from the multicentric OUTCOMEREA network. Intensive Care Med. 2021;47:180–7.
[8] Abeleña-Alonso G, Rombaats A, Gudiol C, et al. Immunosuppressive therapy, risk factors and outcomes of hospital-acquired bloodstream infection in patients with severe COVID-19 pneumonia: a Spanish case-control matched multicentre study (BACTCOVID). Clin Microbiol Infect. 2021;27(11):1685–92.
[9] Patel BV, Haar S, Handslip R, et al. Natural history, trajectory, and management of mechanically ventilated COVID-19 patients in the United Kingdom. Intensive Care Med. 2021;47:549–65.