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LETTER TO THE EDITOR

Insights from compassionate use of tocilizumab for COVID-19 to inform appropriate design of randomised controlled trials

A proportion of patients with progressive COVID-19 display a cytokine release syndrome (CRS)-like pattern of hyperinflammation and immune dysregulation in association with respiratory failure. CRS is a form of systemic inflammatory response syndrome characterised by fever, systemic inflammation, multi-organ failure, and high mortality. In severe COVID-19,[1,2] there appears to be a unique pattern of hyperinflammatory responses and immune dysregulation, driven by overproduction of pro-inflammatory cytokines.[3] In particular, very high levels of interleukin-6 (IL-6) production are associated with low HLA-DR expression and profound lymphopenia.[3] This has fuelled intense interest in the role of IL-6 and other cytokine receptor blockade in COVID-19, using immunomodulatory treatments licensed for conditions such as rheumatoid arthritis and cytokine release syndrome (CRS).

Xu reported a case series of 21 patients treated with intravenous tocilizumab 4–8 mg/kg with lopinavir/ritonavir, interferon-α and/or glucocorticoids.[4] There was a rapid clinical improvement, and all patients were eventually discharged at an average of 15.1 days after tocilizumab. Although only two of 21 patients were mechanically ventilated, this series triggered initiation of clinical trials to test IL-6 receptor blockade in severe and critical COVID-19. Preliminary results from trials of tocilizumab and sarilumab (press release)[5,6] are conflicting. In a phase 2 trial of sarilumab 200 mg, 400 mg, or placebo in 457 patients, a positive trend for clinical improvement was seen only in patients classed as critical (requiring high flow oxygen, non-invasive or mechanical ventilation) with a negative trend in patients with milder disease and no overall treatment benefit in a pooled analysis.[5] In contrast, in a French open-label study of 129 non-ICU patients with moderate to severe pneumonia, tocilizumab 8 mg/kg reduced need for ventilation and death by day 14.[6] We note that inclusion criteria for both trials did not include markers of hyperinflammation and outcome measures selected were inconsistent.

In March 2020, we considered the compassionate use of tocilizumab in selected patients, recognising the high COVID-19 mortality[7] and that clinical trials take time to set up and may not report in time to save patients' lives. Treatment criteria were established, which on the basis of the current literature and multidisciplinary discussion, we felt predicted the best outcomes and adhered to WHO guidelines.[8] Criteria for hyperinflammation were based on emerging data in COVID-19[1,9,10] and an extrapolation of the CRS treatment indications in CAR-T therapy.[11] Patients needed at least three of D-dimer above upper limit of normal (ULN), rising CRP, ferritin >1000 ng/ml, lactate dehydrogenase (LDH) > ULN, in addition to confirmed SARS-CoV-2, radiographic evidence of pneumonia and increasing oxygen requirement. Patients intubated and ventilated for more than 24 h (or 48 h for external referrals) were excluded as we considered that the treatment indication might have passed. Standard tocilizumab contraindications applied[12] in addition to evidence of multi-organ failure, bacterial sepsis, and intubation for reasons other than COVID-19. Oral consent for off label prescription of tocilizumab was obtained from patients or representative, whenever possible.

Seventeen patients were considered for treatment, and 11 patients (seven ventilated and four receiving high flow oxygen) received 1–2 doses of tocilizumab 8 mg/kg 11.7 ± 4.3 days after first symptoms and 2.8 ± 2.3 days after hospital admission. Over 48 h after first dose, CRP (half-life 19 h)[13] fell from 311 (138–332) (median, IQR mg/L) to 110 (58–184) P = 0.001 (Figure 1A) and temperatures normalised (Figure 1B). Other hyperinflammation markers are as follows: ferritin (long half-life)[14] fell by 44% of baseline over 7 days, LDH was unresponsive to tocilizumab, and D-dimers increased. For the whole group, oxygen requirements fell by 60 ± 32% [95% CI 38 to 81] over 1 week, P < 0.001. Individual parameters are shown in Figure 1C, D. The clinical course of patients from day 1 to discharge or death is shown in Figure 1E. Nine of the 11 patients were discharged at 14 ± 6 days after treatment. Four patients (A, F, J, and L in Figure 1) were given the second dose as they were judged not to have responded. Two of these intensive care patients (F and J) died from multiorgan failure, ventilator-associated pneumonia (*Klebsiella aerogenes* in sputum), and refractory respiratory failure.

The good clinical response in this small series suggests that patients might best be selected for IL-6 blockade on the basis of the clinical manifestation of a specific pathophysiology, namely, hyperinflammation, rather than by respiratory parameters. Our cohort had higher baseline CRP values compared to those reported by Xu et al.[4] (mean 311 versus 65 mg/L) and more patients requiring ventilation (64% versus 10%), yet had similarly good outcomes. Similarly, the French study did not include any patients who required ventilation at baseline. The responders (82%) in our series may have been in a phase of the disease driven mainly by IL-6-mediated inflammation before the development of a more complex, multi-cytokine dysregulated state due to advanced COVID-19 and/or complicating bacterial sepsis. We did not measure IL-6 levels as this was an urgent compassionate access programme rather than an exploratory clinical trial, but we recognise the potential future use of this in patient selection.

For clinical trials of new treatments to have the best chance of demonstrating a significant effect, selection of appropriate population

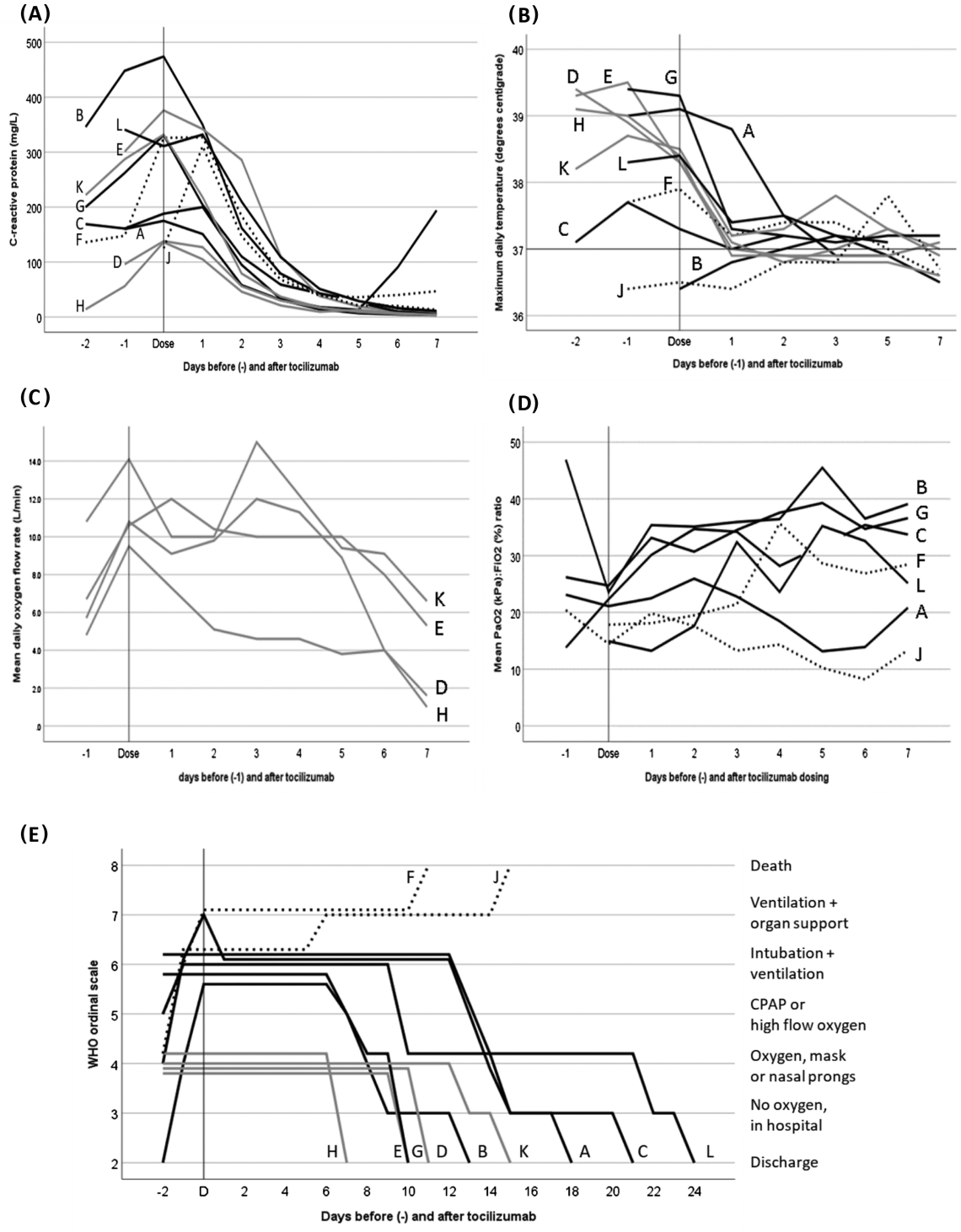

FIGURE 1 Lines represent values for individual patients before and after tocilizumab dosing. Grey lines, ward-based patients; black lines, intensive care patients; solid lines, survivors; dotted, patients who died. Letters identify individual patients for comparison across panels. Values are shown for (A) C-reactive protein; (B) maximum daily temperature; (C) mean daily oxygen flow rate for ward patients; (D) mean daily PaO_2 (kPa):FiO_2 (%) ratio for ICU patients; and (E) WHO ordinal scale for clinical improvement on days before and after the first dose of tocilizumab. Plasma C-reactive protein was 311 (138–332) mg/L on the day leading up to tocilizumab treatment and fell to 218 (151–332) mg/L and 110 (58–184) mg/L, respectively, on the first and second days after treatment ($P = 0.001$; Friedman test). Over 1 week, mean PaO_2:FiO_2 ratios improved in intensive care patients by 41% [95% CI 11 to 70] and mean oxygen flow rates fell in ward patients by 69% [95% CI 36 to 102]

and outcome markers is crucial. We propose that evidence of hyperinflammation should define the population for IL-6 receptor blockade. Our careful description identifies temperature and CRP at 48 h, oxygen requirements at seven days, and WHO ordinal scale at 15 days as useful markers of response and can help estimate effect size. Compassionate use case series such as ours, if carefully conducted and reported, can contribute to the overall evidence base and support the design of randomised controlled trials.

COMPETING INTERESTS

D.F. is acting as a principle investigator for a Roche sponsored trial. S.L. has consulted for Roche without remuneration. The other authors have no conflicts of interest to declare.

CONTRIBUTORS

All authors contributed to the design of this treatment programme, to review of the data and to writing of the manuscript.

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