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Tocilizumab therapy in individuals with COVID -19 infection and hyperinflammatory state

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Introduction

Coronavirus disease 2019 (COVID-19), an illness caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), has spread rapidly worldwide resulting in a global pandemic. A subset of individuals with COVID-19 present with severe pneumonia, evolving in some cases to acute respiratory distress syndrome (ARDS), coupled with clinical and biochemical features of hyperinflammatory syndrome. This in turn may reflect circulating IL-6, possibly a key driver of a dysregulated inflammatory response in COVID-19. Tocilizumab is a humanized monoclonal antibody targeting the IL-6 receptor. Current data on the use of Toculizumab in the COVID-19 setting is scarce. Our aim was to describe our experience of using tocilizumab to treat severe COVID-19 pneumonia with hyperinflammatory syndrome.

Methods

Between March 7 and April 7, 193 COVID-19 positive patients were admitted to St Vincent's University Hospital and enrolled into the All-Ireland Infectious Diseases Cohort Study. Patients were identified for conisderation of toculizumab therapy based on evidence of moderate to severe respiratory disease progression. This was defined by

- a ratio of peripheral capillary oxygen saturation compared to fraction of inspired oxygen (SpO2:FiO2) of ≤315mmHg
- progression of pulmonary infiltrates on chest imaging
- Hyperinflammation with temperature > 38°C in the past 48 h, D-dimer > 1.5 μg/mL and elevated CRP, ferritin, lactate dehydrogenase (LDH) or fibrinogen.

Patients were considered for tocilizumab at a multidisciplinary team (MDT) meeting and selected based on the presence of severe COVID-19 pneumonia and evidence of hyperinflammatory response.

Results

Of 193 cases, 8 (4.1%) were considered for tocilizumab therapy of whom 6 patients were treated with a single dose of intravenous tocilizumab at 8 mg/kg (maximum dose: 800 mg). On admission, 4 had pulmonary infiltrates on imaging, all had systemic inflammatory response, CRP (median: 72.3 mg/L, interquartile range (IQR): 40.1–127.8 mg/L) and ferritin levels (median:1803 mg/L, IQR: 1071–3163 mg/L) and the median SpO2:FiO2 ratio was 322 mm Hg (IQR: 291–421 mmHg).

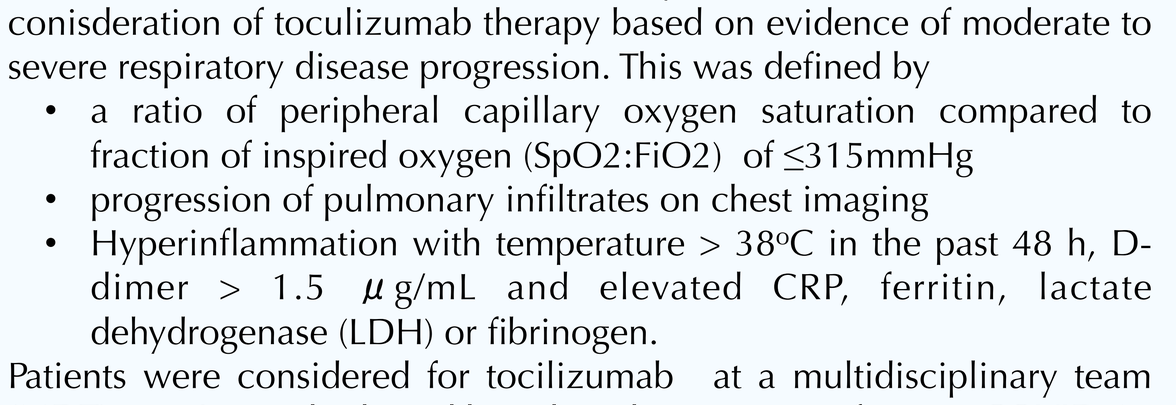

Figure 1: Chest radiographs from a patient taken (A) on admission, (B) pre- Toculizumab and (C) post treatment with Toculizumab

The median duration from symptom onset to MDT discussion was 9.5 days (IQR: 8–11.5 days). All had progression of pulmonary infiltrates on chest radiograph and SpO2:FiO2 ratio had deteriorated (median: 236 mmHg, IQR: 226–247 mm Hg) (Fig.2D,E). All met the criteria for hyper-inflammatory state, CRP (median: 126.6 mg/L, IQR: 103.2–242.2 mg//L), ferritin (median: 3451.5 mg/L, IQR:2950–4138.2 mg/L) and fibrinogen (median: 6.33 g/L,IQR: 5.96–6.93 g/L).

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Results (cont.)

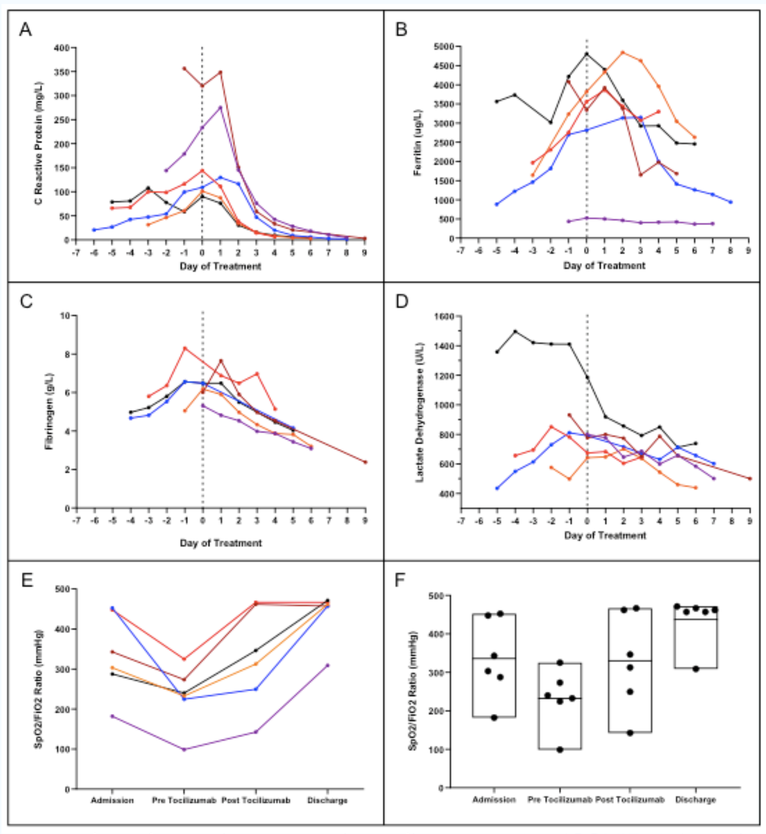

Figure 2. Laboratory data from six coronavirus disease 2019 (COVID-19) patients treated with tocilizumab. Day 0 (dashed line) is the day on which tocilizumab treatment was administered and data are presented prior to this and following drug administration for C-reactive protein (mg/L) (A), ferritin (μg/L) (B), Fibrinogen (g/L) (C) and lactate dehydrogenase (U/L) (D). (E) SpO2:FiO2(ratio of peripheral capillary oxy-gen saturation (SpO2) compared to fraction of inspired oxygen (FiO2)) per patient at four time points. (F) SpO2:FiO2ratio range for all six patients on admission, immediately before tocilizumab administration (pre tocilizumab), 3–4 days after administration (post tocilizumab) and at the time of discharge from hospital (range: 6–8 days).

Following tocilizumab, we observed a rapid decline in inflammatory markers and decreased oxygen requirements in all patients. All patients were discharged home at a median of 7 days (IQR: 7–8 days) post tocilizumab. One patient was readmitted to the hospital 2 days after discharge.

Discussion

We describe the clinical outcomes of 6 patients with COVID-19 pneumonia and a hyper-inflammatory response treated with tocilizumab in the pre-ICU setting. We see a marked reduction in the levels of CRP, ferritin and fibrinogen. The reduction in CRP levels is likely a direct effect of tocilizumab, the other markers may be more representative of a change in inflammatory state. All patients had elevated body mass index (BMI). IL-6 levels correlate with BMI and enhanced IL-6 signalling drives inflammation in obesity. A limitation of this study is that serum IL-6 levels were not measured, as this was not a routinely available clinical biomarker. However, CRP and ferritin are both acute phase proteins that are released in response to IL-6 stimulation, and can be used as surrogates. In summary, tocilizumab was well tolerated and effective in this cohort and associated with a positive outcome. Randomized, controlled trials are needed to determine the true efficacy and safety of tocilizumab in COVID-19.

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