Interleukin-6 receptor blockade with subcutaneous tocilizumab in severe COVID-19 pneumonia and hyperinflammation: a case–control study

Many patients with severe COVID-19 rapidly progress to critical disease with refractory hypoxemia requiring invasive mechanical ventilation (IMV).[1] Elevated levels of C reactive protein (CRP) and interleukin-6 (IL-6), reflecting an hyperinflammatory response, identify patients at risk of progression to refractory hypoxemia and death.[2] Recent evidences suggested that high-dose intravenous tocilizumab (TCZ), a humanised anti-IL-6 receptor antibody, may rapidly reduce fever and inflammatory markers, and improve oxygenation in severe to critical COVID-19.[3–5] Data on the safety and efficacy of subcutaneous TCZ, already approved for the treatment of rheumatoid arthritis, are limited. The aim of this study was to compare the clinical course and outcomes of patients treated with subcutaneous TCZ on top of standard of care (SOC) with those of patients receiving SOC only.

In this retrospective case–control study, we treated with TCZ 324 mg, given as two concomitant subcutaneous injections, all consecutive patients at Pescara General Hospital, Italy between 28 March and 21 April 2020, with laboratory-confirmed COVID-19 pneumonia (involving ≥20% of lung parenchyma on chest CT), hyperinflammation (CRP ≥20 mg/dL), hypoxemia (oxygen saturation <90% on room air) requiring supplemental oxygen through nasal cannulas or mask, who had no contraindications to treatment such as bacterial or fungal infection, neutropenia or liver injury. Patients signed an informed consent for the off-label use of TCZ. We reviewed all patients hospitalised for COVID-19 pneumonia when TCZ was not available in our centre and identified those matching the same treatment criteria: 40 subjects matched for sex and age were selected as SOC group (online supplementary table 1).

Clinical data were available for all patients until discharge or death, and for those discharged prior to day 35, additional clinical information was obtained by phone contact. Data are presented as median and IQR. Within-group changes were compared using the Wilcoxon test for paired analysis, and between-groups differences were analysed using the Mann-Whitney U test for unpaired test. Log-rank (Mantel-Cox) analysis was used to compare event-free survival between the two groups.

Treatment with TCZ was well tolerated, with no serious or clinically relevant adverse events. None of the patients experienced neutropenia (absolute neutrophil count <1000/mm^3), one (2.5%) developed bacterial pneumonia while on IMV, as compared with three (7.5%) in the SOC group, and one (2.5%) had transient moderate liver injury (elevation in alanine aminotransferase five times above the upper limit of normal value), as compared with none in the SOC group (online supplementary table 2).

Treatment with TCZ resulted in an improvement of oxygenation, as assessed by the ratio of partial pressure of oxygen to fraction of inspired oxygen (P/F), which increased at day 1 (+8%, IQR −9 to +25; p=0.005 for within-group and p<0.006 for between-group comparisons) and day 3 (+25%, IQR +10 to +52; p<0.001 for within-group and p<0.001 for between-group comparisons), whereas it continued to worsen in the SOC group (p<0.001, online supplementary figure S1).

When compared with SOC-treated patients, fewer TCZ-treated patients had disease progression, defined as requirement of IMV or death (2 (5%) vs 12 (30%), p=0.003), or died (2 (5%) vs 11 (27.5%), p=0.006) (figure 1). Online supplementary table 3 shows the WHO Ordinal Scale for Improvement for the two groups.

TCZ was associated with a reduction in CRP at day 1 (−32%, IQR −18 to −60) and day 3 (−83%, IQR −63 to −83; p<0.001 for within-group changes), whereas it increased in the SOC group (p<0.001 for between-group comparisons at both time points; online supplementary figure 2).

Our findings suggest that IL-6 receptor blockade with subcutaneous TCZ may reduce the risk of progression from severe to critical COVID-19 and mortality when administered on top of SOC. Infection from SARS-CoV viruses results in an inflammasome-mediated response characterised by elevated levels of interleukin-1β,[6] which trigger IL-6 release, promoting lung injury. TCZ is often provided intravenously on a compassionate-use basis to patients with COVID-19 with refractory hypoxemia on IMV. Randomised controlled trials are under way with IL-6 blockers. Nevertheless, many patients with COVID-19 are hospitalised with hypoxemia not requiring IMV. Hyperinflammation may promote disease progression as indicated by higher levels of inflammatory biomarkers being associated with

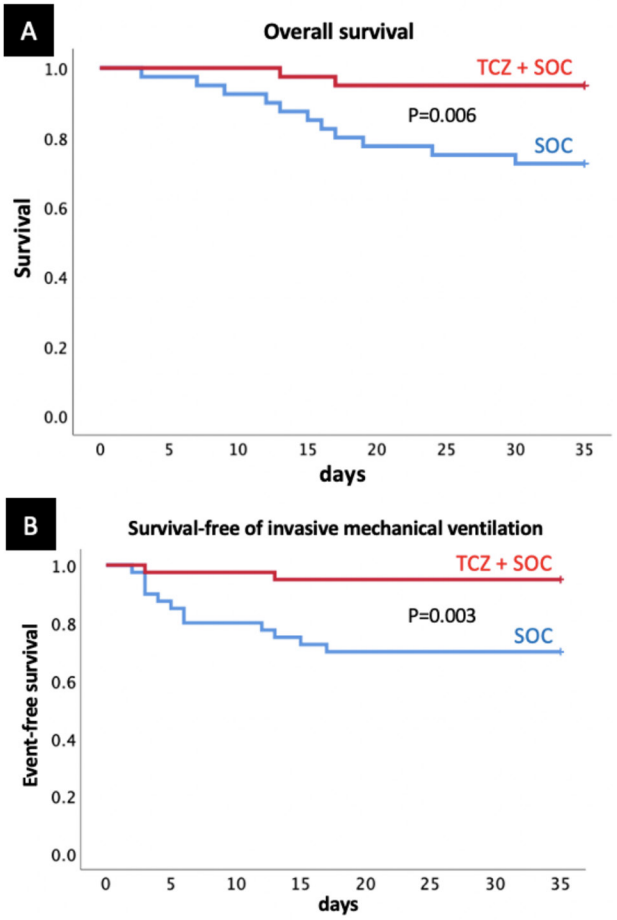

Figure 1 Survival and survival-free of invasive mechanical ventilation. Patients receiving tocilizumab (TCZ) on top of standard of care (SOC) were significantly less likely to die (A), or need invasive mechanical ventilation or die (B) than patients treated with SOC only matched for sex, age and severity of illness (log-rank Mantel-Cox χ^2 7.418, p=0.006 and χ^2 8.605, p=0.003 for panels A and B, respectively).

increased risk for dire outcomes.[2] We herein report on the innovative use of early subcutaneous TCZ in a subgroup of patients with severe COVID-19 pneumonia who are at risk for progression to IMV and death. While limited by the small number of patients included and the non-random nature of the comparisons, data appear reassuring in terms of safety, and encouraging when compared with those of patients treated with SOC in our centre or other published cohorts.[1 3–5]

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