JIM Letter to the Editor

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Tocilizumab shortens time on mechanical ventilation and length of hospital stay in patients with severe COVID-19: a retrospective cohort study

Dear Editor,

Amongst patients with COVID-19 who require treatment in intensive care for acute respiratory distress syndrome (ARDS), mortality rates have been reported between 16 and 78% [1]. In patients who are discharged alive, an increased risk of sequelae from COVID-19 is anticipated [2]. The hyperinflammatory response induced by SARS-CoV-2 is pivotal in the pathogenesis of COVID-19 and is accompanied by an upregulated expression of interleukin 6 (IL-6) that correlates with disease severity [3]. Tocilizumab, a monoclonal antibody against the IL-6 receptor originally licensed for the use in rheumatoid arthritis, is also approved for treatment of chimeric antigen receptor T cell–related cytokine release syndromes and secondary hemophagocytic syndromes that share important features with the hyperinflammatory phase in COVID-19. Several small studies from China and Europe have reported promising results of the treatment with tocilizumab in patients with COVID-19, preventing the need for admission to an intensive care unit and improving clinical outcomes [4,5]. We aimed to evaluate the impact of treatment with tocilizumab compared to routine care on important clinical outcomes in critically ill patients admitted to an intensive care unit with ARDS due to COVID-19.

Methods

We conducted a retrospective cohort study at Karolinska University Hospital Huddinge between 11 March and 15 April 2020 (regional ethical approval: Drn 2020-3139). Patients over 18 years with confirmed SARS-CoV-2 infection were eligible when admitted to the intensive care unit (ICU) for severe ARDS and were followed for 30 days from admission to ICU until discharge from hospital or until death, whichever occurred first.

All patients who received tocilizumab before admission to or on ICU during the study period were included. Consideration of treatment with a single dose of tocilizumab at 8 mg/kg was at the discretion of the attending physician and required consultation of at least two members of an expert panel of infectious disease specialists as well as the fulfilment of specific criteria based on respiratory and inflammatory parameters. The control group consisted of consecutively admitted patients to the same ICU receiving routine care only (see supplement for details). The primary outcome was 30-day all-cause mortality after admission to ICU (= day 0). Secondary outcomes were time to freedom from mechanical ventilation, number of ventilator-free days in survivors, length of stay in ICU and length of stay in hospital. Clinical end-points were assessed in the native cohort and in a sub-cohort of patients matched by a propensity score (see supplement for detailed methodology).

Results

Of 87 patients in the cohort, 29 received tocilizumab and 58 patients received routine care only (control group). Twenty-two patients (n = 22) from each group were matched within a propensity score-matched sub-cohort. Notable differences between groups in the native cohort included a higher proportion of male patients in the tocilizumab group and a lower body mass index. Respiratory parameters were comparable upon admission to the hospital and upon admission to ICU. In accordance with the prespecified treatment criteria, inflammatory biomarkers were higher in the tocilizumab group upon admission to ICU. Baseline comparability was improved in the propensity score-matched sub-cohort (Table S1). As to the outcomes, the difference in all-cause mortality at 30 days was not statistically significant (HR = 0.52, 95% CI 0.19–1.39, P = 0.19) (Figure 1). However, patients receiving tocilizumab had significantly more ventilator-free days (Table S2). Freedom from mechanical ventilation was achieved earlier and in a higher proportion of patients (HR 2.83, 95% CI = 1.48–5.40, P = 0.002) (Figure 1). Length of stay in ICU and length of stay in hospital were both significantly shorter in patients treated with tocilizumab (Figure 1). The

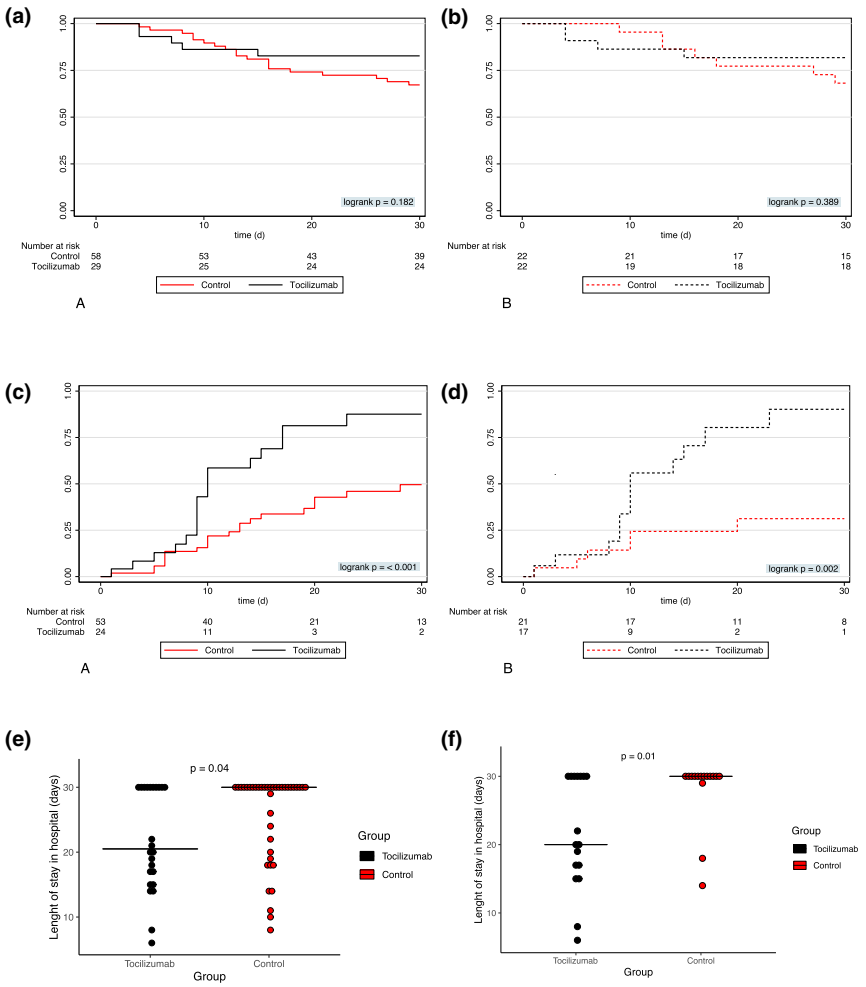

Fig. 1 *Upper panel: Cumulative 30-day survival rate depicted as Kaplan–Meier plots in the native (a) and propensity score matched cohort (b). Central panel: Cumulative rate of freedom from mechanical ventilation amongst invasively ventilated patients depicted as Kaplan–Meier plots in the native (c) and propensity score matched cohort (d). Lower panel: Total length of hospital stay, calculated from admission to the hospital until discharged alive or alive at 30 days in the (e) native cohort and (f) propensity score-matched cohort. [Correction added on 19 October 2020, after first online publication: Figure 1 caption has been corrected in this current version.]*

rate of serious secondary bacterial infections upon treatment with tocilizumab was comparable to controls. No serious adverse events attributable to the intervention were recorded. Analysis of the matched sub-cohort revealed consistent results across all outcomes (Fig. 1, Table S2).

Discussion

In this retrospective cohort study, the administration of tocilizumab did not reduce all-cause mortality but was associated with a shorter time on mechanical ventilation and a shorter length of stay in hospital and in ICU in critically ill patients with ARDS due to COVID-19. The treatment was well tolerated and not associated with an increased rate of serious adverse events during the study period. Results were confirmed in a propensity score-matched sub-cohort.

Mortality in our study was low compared with previous reports [1]. This may be explained by a comparatively low prevalence of comorbidities and a low median age of 56 years [IQR 49–64]. Four out of five (4/5, 80%) patients who died in ICU following treatment with tocilizumab died within nine

days from admission to the hospital from multiple organ failure. Deaths occurred earlier than in the control group (median 8 vs. 14 days). All of these individuals presented with significant comorbidities. We hypothesize that the early deaths amongst patients in the intervention group represent a proportion of patients with a poor baseline prognosis and a potentially irreversible hyperinflammatory syndrome. Patients receiving tocilizumab had significantly more ventilator-free days compared with controls and achieved freedom from mechanical ventilation earlier. A pronounced divergence in respiratory recovery between groups was observed after day 10 (Fig. 1). This may represent a lag time of clinical improvement following the rapid onset of action of tocilizumab. Generally, time on the ventilator correlates with subsequent complications such as infections, cognitive impairment and critical illness neuromyopathy [6]. Thus, our findings suggest a potential role of tocilizumab in the prevention of post-ICU sequelae from severe COVID-19. If confirmed in a prospective randomized trial, the substantial reduction in length of stay in ICU observed in our cohort would most likely render the intervention highly cost-efficient, with a single dose of tocilizumab (8mg/kg, adult patient of 75 kg) being priced around 3035.93 $ in the United States according to recently published model [7].

We acknowledge several limitations. Our study was designed as a retrospective cohort study at a single academic medical centre with inherent limitations to generalizability of findings and potential biases. Furthermore, the limited number of patients treated with tocilizumab restricted the power to detect a significant 30-day mortality difference. A strength of the study is the 30-day follow-up exceeding previous reports on immunomodulatory treatment of COVID-19 and adding further evidence to the course of disease in critically ill patients with COVID-19. In addition to that, the analysis after propensity score-based matching did not significantly alter the results, thus reducing the likelihood of measured confounders being the sole explanation of the differences in outcomes.

In summary, our findings indicate that treatment with tocilizumab of critically ill patients with severe ARDS due to COVID-19 may reduce time on mechanical ventilation and overall length of stay in ICU and in hospital. Treatment appears to be safe. Data from randomized controlled trials are needed to confirm the results and establish causality.

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Conflicts of interest

All authors: No reported conflicts of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Baseline characteristics, clinical and laboratory parameters.

Table S2. Outcomes.