

Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19

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ABSTRACT

Objective. No agent has yet been proven to be effective for the treatment of patients with severe COVID-19.

Methods. We conducted a pilot prospective open, single-arm multicentre study on off-label use of tocilizumab (TCZ) involving 63 hospitalised adult patients (56 males, age 62.6±12.5) with severe COVID-19. Clinical and laboratory parameters were prospectively collected at baseline, day 1, 2, 7 and 14. No moderate-to-severe adverse events attributable to TCZ were recorded.

Results. We observed a significant improvement in the levels of ferritin, C-reactive protein, D-dimer. The ratio of the partial pressure of oxygen (PaO₂) to the fraction of inspired oxygen (FiO₂) improved (mean±SD PaO₂/FiO₂ at admission: 152±53; at day 7: 283.73±115.9, at day 14: 302.2±126, p<0.05). The overall mortality was 11%; D-dimer level at baseline, but not IL-6 levels were predictors of mortality. TCZ administration within 6 days from admission in the hospital was associated with an increased likelihood of survival (HR 2.2 95%CI 1.3–6.7, p<0.05).

Conclusion. In hospitalised adult patients with severe COVID-19, TCZ could be a safe option. An improvement in respiratory and laboratory parameters was observed. Future controlled trials in patients with severe illness are urgently needed to confirm the definite benefit with IL-6 target therapy.

Introduction

No agent has yet been proven to be effective for the treatment of patients with severe COVID-19. Acute respiratory distress syndrome and multiorgan dysfunctions are among the leading causes of death in critically ill patients with COVID-19. The elevated levels of inflammatory cytokines, especially interleukin 6 (IL-6), suggest that a cytokine storm may play a critical role in the progression of the diseases (1). However, the efficacy of corticosteroids, commonly used anti-inflammatory agents, to treat SARS-CoV-2-induced cytokine storm is controversial (2, 3). Recently, TCZ, a humanised anti interleukin-6 (IL-6) receptor antibody of the IgG1 subclass, has emerged as a potential

tool for tapering the cytokine storms in critically ill patients (4).

Methods

We conducted a prospective open, single-arm multicentre study on the off-label use of TCZ in hospitalised adult patients with confirmed severe COVID-19 infection. Inclusion criteria were the following: a) polymerase chain reaction-confirmed COVID-19 infection; b) pulmonary involvement, assessed either by oxygen saturation (SaO₂) of <93% if they were breathing ambient air, or a ratio of the partial pressure of oxygen (Pao₂) to the fraction of inspired oxygen (FiO₂) of less than 300 mm Hg; c) markedly deranged pro-inflammatory and pro-thrombotic profile (at least 3 of the following): C-reactive protein (CRP) > x 10 normal values; ferritin >1000 ng/ml; D-dimer x 10 normal values; LDH x 2 the upper limits. IL-6 levels (Elecys® IL-6; Diagnostics, Roche) were also measured. The four hospitals of the ASL Città di Torino were included in this study.

Study design was multidisciplinary developed and the drug administration approved by the local ethics committee and the Off-Label Commission.

Patients received either TCZ i.v. (8 mg/kg) or s.c. (324 mg); a second administration within 24 h was given in 52 out of 63 patients. The route of administration was not pre-determined but disposed according to the drug availability. The primary end-point was the safety of the medication. Secondary end-points were the improvement of respiratory and laboratory parameters. Clinical and laboratory parameters were collected at baseline, day 1, 2, 7 and 14.

For comparison of variables at baseline and follow-up, Student's *t*-test was used for normally distributed parameters and the non-parametric Mann-Whitney test for non-normally distributed parameters. Correlations were calculated and significance determined by Fisher's test. Multivariable logistic regression analysis was used to identify any independent predictors of poor prognosis (death and/or no improvement of PaO₂/FiO₂): age >70 years, time lapse between symptoms onset and TCZ treatment; baseline laborato-

Table I. Clinical characteristics at baseline.

Men:	56 (88%)
Mean age:	62.6 ± 12.5
<i>Underlying diseases</i>	
Hypertension	24 (38.0%)
Diabetes mellitus	6 (9.5%)
Heart disease	5 (7.0%)
Chronic Obstructive Pulmonary Disease	3 (4.7%)
<i>Concomitant treatment</i>	
Antivirals	63/63 (100%)
Lopinavir/ritonavir in 45/63 patients	(71.4%)
Darunavir/cobicistat in 18/63	(28.6%)
<i>Disease severity</i>	
Bilateral pulmonary infiltrates	60 (95.2%)
Invasive mechanical ventilation	5 (7.9%)

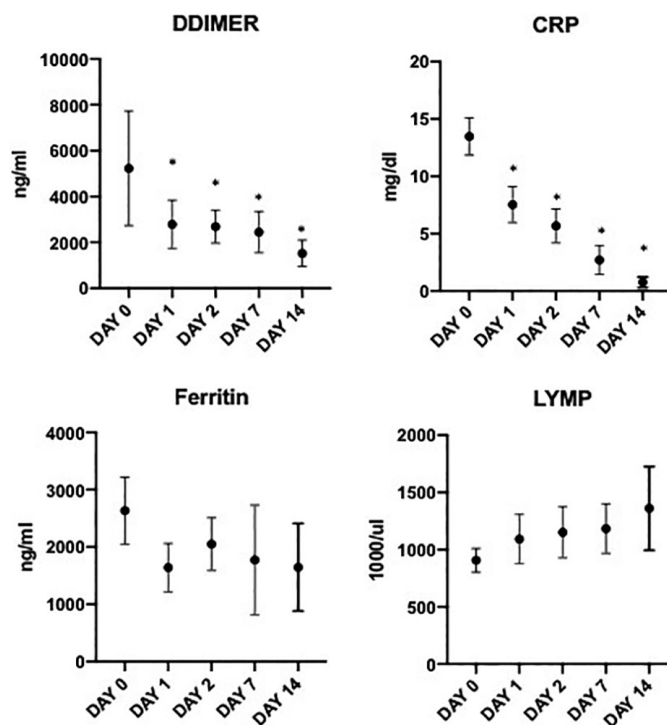
ry profile to include IL-6 levels, CRP, ferritin, D-dimer. Kaplan-Meier hazard plots were constructed for survival. For these analyses, the Prism (GraphPad Software, CA, USA) and SPSS (IBM Corporation, NY, USA) software programmes were used; $p < 0.05$ was considered significant.

Results

A total of 63 patients (56 males, age 62.6±12.5) with laboratory-confirmed COVID-19 infection, were prospectively followed for at least 14 days after admission. Thirty-four patients received TCZ i.v. (8 mg/kg). Thirty-one of them (91%) received a second dose [25 (73.5%) i.v., 6 cases (17.5%) 162 mg s.c.]. Twenty-nine patients received TCZ s.c. (324 mg), with a second administration of 162 mg s.c. in 21 cases (72%, all s.c.). Table I describes the main clinical characteristics at baseline. Overall, mortality at 14 days was 11% (7/63 patients). We observed no differences between the route of administration in terms of mortality, as rates were 12.9% (4/31) and 10.3% (3/29) in the TCZ i.v. and s.c. groups, respectively (difference, -2.6 percentage points; OR 1.16, 95% CI: 0.24-5.65, $p=0.858143$). All patients with fatal outcome received a second dose of TCZ and death was observed within the first week after the first TCZ dose (mean 5±1.5 days). No patients reported severe-to-moderate adverse events directly related to TCZ infusions.

At admission, 25/63 (39.7%) patients had fever with $T > 38^{\circ}\text{C}$, that resolved in all but one patient within 24h after

Fig. 1. Laboratory parameters at baseline and after treatment with tocilizumab (results are shown as mean and SEM, $*p < 0.05$).



the infusion of TCZ. We observed an improvement in the levels of ferritin, C-reactive protein, D-dimer and lymphocytes count, as shown in Figure 1. Conversely, no significant changes in LDH level were found. Respiratory parameters as assessed by PaO₂/FiO₂ improved, albeit a degree of heterogeneity was observed during the follow-up (mean±SD PaO₂/FiO₂ at admission: 152±53; at day 7: 283.73±115.9, at day 14: 302.2±126, $p < 0.05$) (Fig. 2). At admission, 5 patients required mechanical ventilation, one of whom died on day 6. At day 14, mechanical ventilation was still required in 2 patients. D-dimer levels at baseline (HR 5.01; 95%CI 1.04–29.17), but not baseline IL-6 levels, were predictors of death. Kaplan-Meier hazard plots (Fig. 3) showed survival rates according to D-dimer levels. As expected, due to the anti-receptor effect of TCZ, we observed an increase in IL-6 levels, most evident after 14 days of follow-up (Fig. 4). The use of TCZ within 6 days from admission in the hospital was associated with an increased likelihood of survival (HR 2.2 95%CI 1.3–6.7, $p < 0.05$).

Discussion

Taken together, our observations highlight the safety profile of TCZ in the

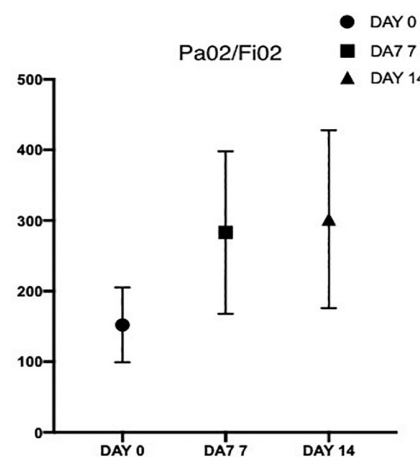


Fig. 2. Respiratory parameters at baseline and after treatment with tocilizumab (results are shown as mean and SEM, $p < 0.05$).

treatment of COVID-19. Besides, as previously postulated (5, 6), our data suggest a promising role of TCZ in terms of efficacy (to be properly investigated in control trials). Notably, the effects on inflammatory markers could be observed even after a short time from the first dose and are in line with previous reports (7). Similarly, a rapid improvement of respiratory parameters and resolution of fever were observed following TCZ administration.

While the overall data seem to be promising, several considerations are worth mentioning. First of all, prop-

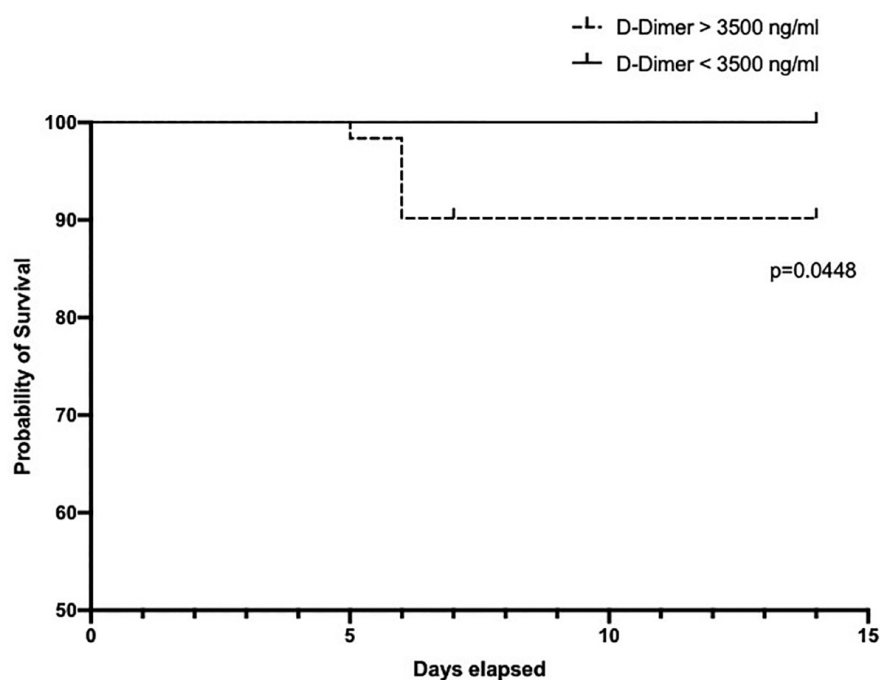


Fig. 3. Kaplan-Meier analysis of survival in patients with COVID-19 according to elevated and non-elevated D-dimer (cut-off level, 3500 ng/mL, representing the 75th percentile of the total study population).

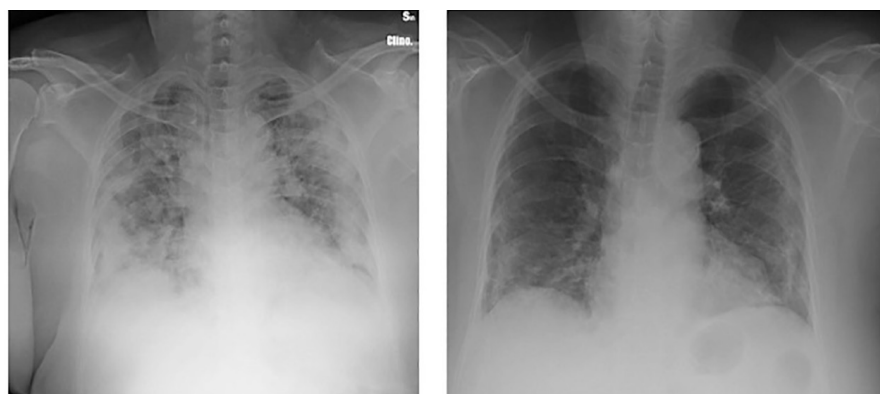


Fig. 5. Chest x-ray of a critically-ill admitted patients at baseline and on day 14.

erly designed controlled trials are urgently needed to confirm or exclude the possibility of a treatment benefit with IL-6 target therapy. Secondly, the route of TCZ administration in our study was heterogeneous and based on drug availability. Similarly, the dose for TCZ s.c. was based on previously reported pharmacokinetic and pharmacodynamic analysis in patients with rheumatoid arthritis (8, 9). While not conventional, this choice was forced by the rapid spreading of the pandemic in Northern Italy, one of most affected areas worldwide, especially in the early phases of the COVID-19 outbreak, when available evidence and therapeutic strategies were very limited. Simi-

larly, background therapies, including antiviral agents, were not protocolled, but their use reflected the rapid evolving scenario related to the knowledge of this condition. While a role for TCZ can be considered, regardless of the concomitant antiviral therapy, our observations need to be confirmed in controlled trials.

Finally, selecting the best candidates to undergo TCZ therapy and the best timing for anti-IL-6 treatment, have still to be addressed. However, albeit preliminary, the present data suggest that early TCZ administration in patients with elevated inflammatory parameters is associated with a two-fold increased survival (HR 2.2 95%CI 1.3–6.7, $p < 0.05$),

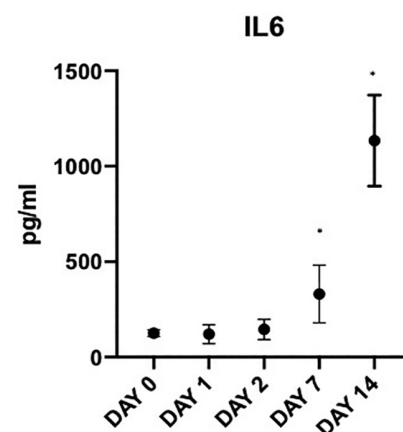


Fig. 4. IL-6 levels at baseline and after treatment with tocilizumab (results are shown as mean and SEM, * $p < 0.05$).

an observation which, if confirmed, has the potential to provide direct guidance in the management of seriously ill patients with COVID-19.

In conclusion, in hospitalised adult patients with severe COVID-19, TCZ might be considered a safe option. An improvement in respiratory and laboratory parameters was also observed. Future controlled trials in patients with severe illness are urgently needed to confirm or exclude the possibility of a treatment benefit with IL-6 target therapy.

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