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


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ABSTRACT

Introduction

No agent has yet been proven to be effective for the treatment of severe patients with COVID-19. Acute respiratory distress syndrome and multi-organ 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 tampering 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 <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 <93% if they were breathing ambient air; and 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 (Elexys® IL-6; Diagnostics, Roche) were also measured. The four hospitals of the ASL Città di Torino were included in this study. Study design was multidisciplinarily developed and the drug administration approved by the local ethical 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. 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.

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).

Conclusions

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.

No agent has yet been proven to be effective for the treatment of severe patients with COVID-19. Acute respiratory distress syndrome and multi-organ 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 tampering the cytokine storms in critically ill patients (4).
ment of PaO2/FiO2): age >70 years, time lapse between symptoms onset and TCZ treatment; baseline laboratory 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 programs 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°C, that resolved in all but one patient within 24h after 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).

Table I. Clinical characteristics at baseline.

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

Fig. 1. Laboratory parameters at baseline and after treatment with tocilizumab (results are shown as mean and SEM, *p<0.05).
phases of the COVID-19 outbreak, when available evidence and therapeutic strategies were very limited. Similarly, background therapies, including antiviral agents, were not protocollled, 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 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, \( p<0.05 \)), an observation that, if confirmed, has the potential to provide direct guidance in the management of severe 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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