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Safety and efficacy of anti-il6-receptor tocilizumab use in severe and critical patients affected by coronavirus disease 2019: A comparative analysis

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**SUMMARY**

**Background:** As the novel SARS-CoV-2 pandemic occurred, no specific treatment was yet available. Inflammatory response secondary to viral infection might be the driver of severe diseases. We report the safety and efficacy (in terms of overall survival and hospital discharge) of the anti-il6 tocilizumab (TCZ) in subjects with COVID-19.

**Methods:** This retrospective, single-center analysis included all the patients consecutively admitted to our Hospital with severe or critical COVID-19 who started TCZ treatment from March 13th to April 03rd, 2020. A 1:2 matching to patients not treated with TCZ was performed according to age, sex, severity of disease, P/F, Charlson Comorbidity Index and length of time between symptoms onset and hospital admittance. Descriptive statistics and non-parametric tests to compare the groups were applied. Kaplan Meier probability curves and Cox regression models for survival, hospital discharge and orotracheal intubation were used.

**Results:** Seventy-four patients treated with TCZ were matched with 148 matched controls. They were mainly males (81.5%), Caucasian (82.0%) and with a median age of 59 years. The majority (69.8%) showed critical stage COVID-19 disease. TCZ use was associated with a better overall survival (HR 0.499 [95% CI 0.262–0.952], \( p = 0.035 \)) compared to controls but with a longer hospital stay (HR 1.658 [95% CI 1.088–2.524], \( p = 0.019 \)) mainly due to biochemical, respiratory and infectious adverse events.

**Discussion:** TCZ use resulted potentially effective on COVID-19 in terms of overall survival. Caution is warranted given the potential occurrence of adverse events.

**Financial support:** Some of the tocilizumab doses used in the subjects included in this analysis were provided by the “Multicenter study on the efficacy and tolerability of tocilizumab in the treatment of patients with COVID-19 pneumonia” (EudraCT Number: 2020-001110-38) supported by the Italian National Agency for Drugs (AIFA). No specific funding support was planned for study design, data collection and analysis and manuscript writing of this paper.

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https://doi.org/10.1016/j.jinf.2020.07.008

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Background

Following the emergence of a novel coronavirus (SARS-Cov-2) in Wuhan, China, in December 2019, a pandemic of COVID-19 (Coro-
navirus Disease 2019) spread globally. According to the ECDC, as of April 18th, SARS-Cov-2 infected 2,114,269 subjects in 180 Coun-
tries and caused 145,144 of deaths.1 So far, Italy – especially the Lombardy Region – showed one of the largest concentration of in-
fection and deceased individuals cases in Europe and worldwide. In the largest published case series including 1099 patients in Wuhan, 173 subjects (15.7%) showed a severe disease, 55 (5.0%) required admission to Intensive Care Unit (ICU) and 15 (1.4%) died.2 Never-
theless, the clinical impact of COVID-19 outside China seems dra-
matically worse with the estimated case fatality rate in Italy well above 10%.1

So far, no established treatment for SARS-CoV-2 has been ap-
proved. Since the clinical severity of COVID-19 appears to be rel-
ated to a cytokines storm with an overproduction of soluble in-
flammatory mediators, several immune-modulatory agents are cur-
cently under investigation.3 Interleukin-6 (IL-6) is a cytokine in-
volved in the physiological inflammatory reaction and immune re-
sponse4 but it has also been recognized also as a major driver in
severe diseases such as chimeric antigen receptor T-cell (CAR-T)-
associated cytokine release syndrome (CRS)5 and KSHV-associated
inflammatory cytokine syndrome (KICS).6 Moreover, plasma IL-6
levels are elevated in ICU patients with COVID-197 and they ap-
pear to be positively correlated with mortality.8 As a consequence of
these evidences, tocilizumab (TCZ), a recombinant humanized
monoclonal antibody acting as IL-6 receptor agonist, has been pro-
posed for the treatment of patients affected by COVID-199. Few
clinical experiences have been published and no randomized cli-
nical trial is currently available. Luo and colleagues recently reported
the treatment of 15 subjects10 showing that single dose of TCZ
failed to improve the disease in critically ill patients, while adding
a second dose provided better outcomes. Of note, clinical improve-
ment was observed only in 1 patient (6.7%), while two worsened
(13.4%) and three died (20.1%).

Aims of present study are to evaluate the efficacy of TCZ in se-
vere and critical COVID-19 subjects comparing survival and hospi-
tal discharge with controls matched for disease severity. We also
aimed to assess clinical safety, especially in terms of respiratory
and blood biochemical recovery and infectious complications in
treated individuals.

Methods

This retrospective, single center analysis included all the pa-
tients consecutively admitted to our Hospital in Milan, in the Lom-
bardy Region, with a diagnosis of severe or critical COVID-19 and
who started TCZ treatment from March 13th to April 03rd, 2020.
The approved local protocol for an off-label TCZ administration en-
rolled subjects aged 18 years or older with a real-time PCR on
rhino-pharyngeal swab positive for SARS-CoV-2; CT scan findings
of severe, bilateral interstitial pneumonia; presence of an active
inflammatory status alternatively defined by abnormal C reactive
protein (CRP) levels (>1 mg/dL), IL-6 >40 pg/mL, d-dimer >1.5
mcg/mL, or ferritin >500 ng/mL. Only individuals with severe or
critical clinical picture according to the Chinese Guidelines for the
management of COVID-19 were eligible.11 A “severe” case was de-
efined as the presence of respiratory distress (respiratory rate >30
per min), oxygen saturation on room air at rest ≤93% or P/F (or
Horowitz Index, partial pressure of oxygen in arterial blood / frac-
tion of inspired oxygen) <300 mmHg; a “critical” case was de-
fined as the presence of respiratory failure with need of ventila-
tion (either invasive or not), septic shock or any other organ dys-
function requiring ICU monitoring and treatment. Exclusion cri-
eria were as follows: alanine aminotransferase (ALT) value >5 x
ULN; neutrophil cell count <500 cell/mm3; platelet count <50,000
cell/mm3; data suggesting the presence of an active bacterial in-
fecction or a complicated intestinal diverticulitis (including perfor-
ated diverticulitis, as indicated in the TCZ summary of product); a
positive pregnancy test; a positive HBsAg status; any concomitant
disease not defined as “under control”. In analogy with what per-
formed with CAR-T-associated CRS, TCZ dose was 8 mg/kg infused
over 60 min (maximum dose of 800 mg); a second dose would be
administered after 12 h in case of fever persistence. Clinical and
laboratory features were collected at baseline, Day 1, Day 3, Day 5
and Day 7. IL-6 level was measured at baseline, 12 h after the first
dose (just before the possible second dose), then at Day 1, Day 3,
Day 5 and Day 7. Potential infective complications were assessed
over the whole hospital stay.

The local Ethics Committee approved the protocol under the
special conditions indicated by the Italian 648/96 law. All subjects
provided written informed consent.

For survival and hospital discharge analyses, a paired group of
controls was selected. They were matched 2:1 to patients treated
with TCZ according to age, sex, severity of disease, P/F, Charlson
Comorbidity Index (CCI) and length of time between symptoms
onset and hospital admittance. The severity of disease was estab-
lished according to the worst condition observed over the entire
length of hospital stay.

Descriptive statistics (median and interquartile range [IQR] for con-
tinuous variables, absolute and relative [%] values for categori-
ical variables) and non-parametric tests (Mann Whitney U for con-
tinuous and Chi-square for categorical variables) to compare the
groups were applied. ANOVA test for repeated measures was used
to compare laboratory parameters trend after treatment. Mean IL-
6 levels change after TCZ administration were estimated with
AN-
COVA; the relationship between IL-6 and P/F values was calculated
with the Pearson correlation coefficient. Kaplan Meier probability
curves and Cox regression models for survival, hospital discharge
and orotracheal tube (OTT) were used. Two-tailed p-values were
calculated and a value <0.05 was considered statistically signifi-
cant. Data management and analysis were performed using SPSS
version 25.

Results

A total of 222 subjects were selected: 74 patients treated with
TCZ and 148 matched controls treated with standard of care
(SOC, represented by hydroxychloroquine plus lopinavir/ritonavir
or remdesivir according to regional recommendations, drug avail-
ability in the Lombardy Region during the study period and remde-
sivir compassionate use program). They were mainly males (81.5%),
Caucasian (82.0%) and with a median age of 59 (IQR, 51–70) years.
The respiratory function was heavily impaired as described by a
median P/F value of 180 mmHg (IQR 96–259). The majority (69.8%)
exhibited a critical clinical picture as defined according to the Chi-
nese recommendations. Table 1 shows baseline demographic and
clinical features of treated and matched controls: they did not
show any statistically significant difference.

In the overall survival analysis TCZ administration showed an
advantage over SOC (Fig. 1A) with a Hazard Ratio (HR) of 0.499
(95% CI 0.262–0.952, p = 0.035) according to Cox regression model.
In subjects with severe disease TCZ did not seem to have any ben-
eficial effect, while it exerted an evident improvement in criti-
 cal patients (Fig. 1B). The number of doses of TCZ did not ap-
pear to have an impact on survival (HR 0.748, 95% CI 0.201–2.783,
p = 0.665) as well as baseline IL-6 value (HR 0.448, 95% CI 0.100–
2.386, p = 0.376).


Table 1
Baseline features of study population.

|                          | Tocilizumab (N = 74) | Standard of care (N = 148) | p     |
|--------------------------|----------------------|-----------------------------|-------|
| Age (years), median [IQR]| 59 [51–71]          | 59 [52–70]                  | 0.865 |
| Male sex,%               | 82.4                 | 81.1                        | 0.807 |
| Ethnicity,%              |                      |                             |       |
| Caucasian                | 78.4                 | 84.5                        | 0.267 |
| MENA Region              | 9.5                  | 3.4                         |       |
| South American           | 10.8                 | 7.4                         |       |
| Asian                    | 1.3                  | 3.4                         |       |
| Black African            | –                    | 1.3                         |       |
| Critical disease,%       | 79.7                 | 69.6                        | 0.109 |
| P/F (mmHg), median [IQR] |                      |                             |       |
| Severe disease           | 229 [183–276]        | 295 [222–375]               | 0.009 |
| Critical disease         | 136 [93–197]         | 159 [93–246]                | 0.459 |
| Charlson Comorbidity Index, median [IQR] |            |                             |       |
| Time from symptoms onset to hospital admittance (days), median [IQR] | 7 [5–10] | 6 [4–8] | 0.080 |
| Antiviral treatment,%    |                      |                             |       |
| LPV/rtv                  | 75.7                 | 85.1                        | 0.084 |
| Hydroxychloroquine       | 90.5                 | 89.9                        | 0.644 |
| Remdesivir               | 9.5                  | 8.1                         | 0.689 |

IQR: interquartile range; MENA: Middle East and North Africa; P/F: Horowitz Index, defined as the ratio of partial arterial oxygen pressure and fraction of oxygen in the inhaled air; LPV/rtv: lopinavir co-formulated with ritonavir.

On the contrary, TCZ administration was associated with a longer hospital stay (Fig. 2) with a HR of 1.658 (95% CI 1.088–2.524, p = 0.019).

Fig. 3 shows blood cell count and biochemistry trends over the first 7 days from TCZ administration. As expected, CRP values decreased significantly while total leukocytes, lymphocytes, and platelets increased. D-dimer showed a dramatic rise by Day 5, then it decreased but without returning to baseline values. Moreover, a significant ALT increase was observed passing from a baseline value of 37 IU/L to 110 IU/L by Day 7.

Respiratory function displayed a complex trend after TCZ administration. In patients who underwent OTT immediately after admission TCZ had a beneficial effect (Fig. 4A). On the contrary, subjects who received TCZ outside the ICU showed a sudden need of OTT after the administration (Log Rank 12.659 with p<0.001, Fig. 4B).

Fig. 5 summarizes the trajectories of oxygen and ventilation requirements within 7 days from anti-IL6 receptor administration: a large number of patients became critical after TCZ with a rapid need of assisted ventilation (either invasive or not).

Respiratory deterioration seemed generally temporary with a return to baseline P/F values by Day 3 and an improvement by Day 5 and 7. At the end of the follow up period, one third of the 74 treated individuals (35.1%) showed a worsening of clinical conditions (in terms of ventilation requirements or death), while the majority (64.9%) had a stable or improved state. Comparing IL-6 trends in these two subgroups, both displayed an increased 12 h after TCZ administration, but later on the curves diverged significantly: those with a worsening condition continued to increase their IL-6 values, while the others showed a less steep increase. When calculating the Pearson correlation coefficient between IL-6 and P/F, an inverse correlation with a R=-0.2472 was observed (p = 0.002) (Fig. 6).

Twenty-seven infectious complications in 24 patients (32.4%) were observed. The majority of them (21 out of 27) was recorded in ICU patients. Of note, 11 severe events (14.9%) were registered: 6 sepsis cases due to gram-negative bacteria; 2 sepsis cases due to gram-positive bacteria; 1 candidemia; 1 lung abscess and 1 epidural abscess, both requiring surgical drainage. Among these subjects, one death from septic shock after ICU discharge was observed.
**A. Hospital discharge in Overall Study Population**

| Factor       | HR     | 95% CI  | p    |
|--------------|--------|---------|------|
| TCZ          | 0.598  | 0.367   | 0.007|

Log Rank 8.030  
*p* = 0.005

**B. Hospital discharge Stratified according to Disease Severity**

| Factor       | HR     | 95% CI  | p    |
|--------------|--------|---------|------|
| Severe Disease | 4.831  | 3.203   | 7.604| -0.001|
| Age ≥85 years | 1.715  | 1.122   | 2.622| 0.013|

Log Rank 93.989  
*p* = 0.001

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**Fig. 2.** Kaplan-Meier probability curves and Cox regression models for hospital discharge in the overall population (A) and stratified according to disease severity (B).

**Fig. 3.** Trends of hematologic and biochemical parameters (median values with interquartile ranges) after tocilizumab administration (ANOVA test for repeated measures).

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**Discussion**

Overproduction of soluble inflammatory mediators leading to CRS seems to have a pivotal role in the pathogenesis of COVID-19, so several interleukin antagonists or cytokine signaling inhibitors are currently under investigation. For example, anakinra, an anti-interleukin-1 receptor, proved to be effective in preliminary studies in critical patients. Additionally, also Janus kinase (JAK)1/JAK2 inhibitors, such as baricitinib, have been speculated to be active against COVID-19 and small clinical experiences have been published. We used TCZ in severely and critically ill patients infected by SARS-CoV-2 with a significant improvement in terms of overall survival. To date, few data are available about TCZ efficacy in COVID-19. To date, there are only some case reports in special population (oncologic, onco-hematologic and rheumatologic subjects, or other small case series). The mentioned paper by Luo and colleagues is a small case series and provides unsatisfactory and conflicting results. One paper recently published by Guaraldi and colleagues evaluated a large group (*n* = 179) of unselected patients treated with TCZ but the comparison was performed with 222 individuals with significantly less severe baseline features of disease. Nevertheless, the improvement in terms of mortality was similar to what we observed. Our data suggest that TCZ may be beneficial in critically ill patients, while its effect in severe cases does not appear to affect survival, even though it may prevent diseases progression requiring mechanical ventilation.

Unexpectedly, TCZ use was associated with a longer hospital stay. This finding might be the result of several biochemical, respiratory and infectious complications. In Phase III and IV trials conducted with TCZ in rheumatologic subjects, a decrease in total leukocytes was recorded: these studies describe a common and reversible neutropenia, usually mild (grade 1–2), while more severe decreases in neutrophils (grade 3–4) occur less frequently (largely...
Fig. 4. Kaplan Meier probability curves and Cox regression models for orotracheal intubation requirement. (A): extubation achievement in subjects directly hospitalised in ICU because of the baseline critical respiratory failure. (B): intubation requirement during hospital stay for those who were admitted in general medical wards with no need of invasive mechanical ventilation at admittance.

Fig. 5. Trajectories of oxygen and ventilation requirements within 7 days from tocilizumab administration (Chi-square test). Soon after drug start oxygen requirement increased significantly with 28.4% of subjects worsening their respiratory condition and only 8.1% improving by Day 3. At Day 7, 30.0% worsened while 38.3% improved baseline clinical status.
Fig. 6. P/F (A) and IL-6 (B) trend during the first seven days from tocilizumab administration (ANOVA for repeated measures and ANCOVA tests). P/F slightly decreased by Day 1, while it improved significantly by Day 5 and 7. IL-6 values exhibited a different trend between those who improved and those who worsened baseline clinical condition. The relationship between IL-6 and P/F values (C) showed a statistically significant inverse correlation (Pearson correlation coefficient).

below 5%). This outcome is the result of repeated administrations of TCZ over a longer follow up (generally of 24 weeks). We observed a transient decrease in total leukocytes in the first days, but later on they increased mainly as a result of the rise in lymphocytes. The different administration schedule and the shorter follow up could explain this apparent contradiction with existing literature. Indeed, we observed a significant rise in platelets and lymphocytes, which may reflect an improvement of the inflammatory status. On the contrary, d-dimer showed a significant increase despite the improvement in other inflammatory markers, an observation which may suggest a persistent alteration of the coagulation. The perturbation of coagulative homeostasis has already been related to death in COVID-19 patients. Our data indicate that the risk of thrombotic complications after treatment might not be completely reduced. Additionally, liver enzyme elevation is widely described in previous rheumatologic literature where it is generally recorded in about 30% of treated subjects, while in our population an increase in ALT values appeared with higher frequency and greater severity than what hitherto reported: an additive effect of drug and viral toxicity could be hypothesized.

The consequences of TCZ on lung function were complex. Soon after the drug administration, a severe worsening of P/F with a large need of OTT was observed. Such worsening appeared transitory but could hamper the clinical advantages of this treatment. Although the majority of patients improved their respiratory conditions by Day 7, in the first hours after TCZ administration an urgent need of non-invasive and mechanical ventilation emerged. From a practical point of view, clinicians should be aware that soon after TCZ administration respiratory failure could progress to a critical state. Thus, a continuous monitoring of respiratory parameters after TCZ seems warranted.

The reasons for this evolution are not clear. Previous published data indicate that critical patients have higher levels of IL-6 leading to an augmented risk of death. We observed a steep increase in IL-6 levels in subjects with a worse outcome compared to those with a stable or improving clinical condition. Moreover, IL-6 increase seems to be inversely correlated with the P/F value. In animal models, IL-6 values are associated with a reduced lung function affecting several functional parameters (residual capacity, lung compliance, inspiratory capacity, and so on). Additionally, this cytokine could induce a significant, dose-dependent increase in the respiratory system resistance mechanisms. Thus, IL-6 seems to play a role by itself in the pathogenesis of lung diseases. A sudden rise in IL-6 level over the first hours after drug infusion is expected: it might be speculated that, in some conditions, this trigger leads to a worse inflammatory state that TCZ is not able to completely contain. A worse cytokine storm compartmentalized in the lung may result in the observed decrease in P/F. For this reason, a co-administration of TCZ with steroids might be taken into account.

In the above-mentioned studies performed in rheumatological setting, the overall rate of infective complications is high (around 70%), but the proportion of severe events is relatively low (3%). Indeed, we observed a rate of severe infections well above 10%, showing that these complications are probably the main drawback of TCZ, especially in the ICU where the majority of infectious events occurred. Compared to historical data, the characteristics of observed infections were similar, but our rate of septic complications seems higher. Since the effect of TCZ on fever and inflammatory markers might delay the diagnosis of an underlying infection leading to severe manifestations, exclusion of active bacterial infection is mandatory before treatment and microbiological monitoring in absence of clear symptoms should be taken into account.

The main limitations of our study are common to all case-control analyses compared to randomized controlled trials: although the choice of matched controls seems effective, selection biases could not be completely ruled out. Additionally, the retrospective nature of the study could hamper the strength of the observations. Finally, any inference should be assessed prudently be-
cause the small sample size in a single center did not allow to draw strong conclusions.

This study confirms the potentially effectiveness of TCZ on COVID-19 — especially in critically ill patients — with a reliable comparison group that allows to weigh the potential clinical impact of this treatment. Nevertheless, we suggest using it cautiously due to drug-related adverse events, remarkably transitory respiratory worsening and bacterial infections. Several trials are currently registered on ClinicalTrials.gov and many are still enrolling patients: study designs, drug combinations and target population are very different and could provide in the forthcoming months a detailed overview of TCZ use in the COVID-19 setting.

Declaration of Competing Interest

None.

Acknowledgments

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