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Tocilizumab and COVID-19: timing of administration assessment

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Introduction

Infection by SARS-CoV-2 can lead to acute respiratory distress syndrome (ARDS) associated with an elevated level of acute phase reactants and pro-inflammatory cytokines [1]. To fight against this hyperinflammatory state, immunomodulatory therapies were suggested. Among them, tocilizumab (TCZ), an inhibitor of the interleukin-6 pathway, was promising. After controversial results, a recent large randomized trial reported a reduction in mortality at day 28 in the group of patients treated with TCZ [2]. Interestingly, a greater benefit was observed in the oxygen-dependent subgroup of patients only but not in those who received high-flow or invasive mechanical ventilation. The efficacy of TCZ was also statistically significant only when patients presented with symptoms that had progressed for less than 7 days. Thus, these results underline the interest of an early administration of TCZ. However, the ideal timing of TCZ injection in the subgroup of oxygen-dependent patients remains unclear.

The aim of this study was to explore whether the timing of TCZ injection had an impact on mortality in patients with moderate to severe COVID-19.

Patients and methods

We retrospectively collected multicentric data from moderate to severe COVID-19 patients – according to the WHO clinical progression scores 5 to 6 [3] – compassionately treated with TCZ, before the start of the French randomized clinical trial CORIMUNO-TOCI. At this time, TCZ was only used in patients with oxygen level ≥4 L/min associated with increased acute-phase reactants (C-reactive protein [CRP] >50 mg/L). Exclusion criteria were contraindication to TCZ (active bacterial infection, history of allergy to tocilizumab, history of sigmoiditis or diverticulosis, hepatic cytolysis >5 upper limit of normal), hospitalization in an intensive care unit (ICU) before or during the 24 hours following TCZ administration,

pregnancy, patients with a do-not-resuscitate order at admission, opposition to data collection by the patient or legal representative.

The inclusion period was from March 17 to April 12, 2020, corresponding to the first epidemic peak in France.

TCZ (Roche, France) was administered intravenously, 8 mg/kg with a maximum of 800 mg per dose, and combined with usual care. Usual care included various combinations of ceftriaxone (1 g per day), azithromycin (500 mg on day 1, then 250 mg per day on days 2 to 5), hydroxychloroquine (600 mg per day), lopinavir/ritonavir (200 mg twice daily), or corticosteroids, in the absence of contraindication. All patients were treated with low-molecular-weight heparin. Concomitant treatments were recorded if administered for at least 48 hours.

The day of TCZ infusion was considered as day 0 (D0). The timing of TCZ infusion was defined from symptom onset (SO) to D0. Oxygen level on D0 and CRP level on D0 were considered as indirect markers of TCZ infusion timing, considering that COVID-19 seems to follow a relatively linear course, as reported by Huang *et al* [1]. The oxygen support target was SpO2 ≥95% except in patients with chronic obstructive pulmonary disease where the oxygen support target was SpO2 ≥92%.

Multivariate logistic and Cox models were built using AIC-based forward and backward selections. Candidate factors were all variables with p <0.30 in univariate analysis among age, sex, obesity, comorbidities, SO to D0 period, baseline oxygen level, severity of CT scan, CRP level on D0, and combined steroid therapy.

Survival analysis was performed using the day of hospitalization as the start of follow-up, and conditional adjusted survival curves were built using a Cox model.

Results

Between March 17 and April 12, 2020, 97 patients received TCZ for moderate to severe COVID-19 pneumonia in eight French hospitals. Baseline characteristics and outcomes for all TCZ-treated patients are shown in Table 1. TCZ was injected 9 ± 4.6 days after symptom onset. The mortality rate was 24.7%. Relevant baseline characteristics of TCZ-treated COVID-19 patients according to deceased or alive status are shown in Table 2. There was no statistically significant difference between the "deceased" or "alive" groups regarding symptom duration before TCZ injection (9.7 versus 10.3 days, respectively, p=0.30) and the oxygen level on D0 (10.9 and 9.2 L/min, respectively, p=0.08). However, the "deceased" group had a significantly larger lung involvement on computerized tomography scan (p=0.02).

Overall survival of patients who received TCZ with an SO to D0 period <7 days was not significantly different from those who received TCZ with an SO to D0 period of 8 to 10 days or >11 days using Fisher's exact test (p=0.30) and multivariate logistic analysis. Likewise, survival times were not associated with SO to D0 period (Figure 1A). In both logistic and Cox model selections, SO to D0 period was eliminated in the process because of too large AIC.

Regarding indirect markers of administration timing, we found that oxygen level on D0 >12 L/min compared to 4-8 L/min (OR 9.73, 95% CI [2.10-45.12]; HR 5.20, 95% CI [1.62-16.67], Figure 1B) was significantly associated with death in TCZ-treated patients, whereas CRP on D0 was not.

We analyzed other risk factors for death in TCZ patients, and we found that older age (OR 1.09, 95% CI [1.02-1.18]; HR 1.08, 95% CI [1.02-1.15]) was significantly associated with death.

Discussion

In this retrospective multicenter observational cohort study reporting the real-life compassionate use of TCZ in French patients with moderate to severe COVID-19 hospitalized in non-ICU wards, timing of the injection after symptom onset was not associated with the efficacy of TCZ. While TCZ was associated with a statistically significant reduction of mortality only in patients who presented with symptoms for less than 7 days in the RECOVERY study, here, we found no evidence that the timing of administration of TCZ infusion had an impact on patient survival. However, our limited cohort (97 patients) is certainly not statistically powerful enough for detecting this difference.

In a secondary exploratory analysis, we showed that oxygen level at the time of TCZ injection, could be an important factor of TCZ efficacy. Indeed, the injection of TCZ when patients presented with an oxygen level >11 L/min was statistically associated with death compared to an injection when the oxygen level was between 4 and 8 L/min. Thus, our study could suggest that TCZ could be less effective when oxygen requirement is >11 L/min and we hypothesize that earlier administration could be associated with better outcome.

This result is consistent with the RECOVERY study which also supports early injection of TCZ, before the need for high-flow oxygen therapy or invasive mechanical ventilation. Likewise, this result is also consistent with the study by Roja-Marte *et al*. in which TCZ was shown to be more effective in non-intubated rather than intubated patients, and with the study by Gupta *et al*., in which TCZ was more effective among patients receiving invasive mechanical ventilation who had a duration of symptoms <3 days compared to those whose symptoms lasted for >3 days [4,5]. Thus, oxygen level at TCZ injection could be an important data to collect in COVID-19 clinical trials; yet none but one of the randomized clinical trials on TCZ in COVID-19 patients reported the detailed oxygen level of patients at the time of TCZ injection [6].

However, survival is possibly linked to the severity of lung involvement and the subsequent O2 requirement, more than the proper timing of TCZ administration. Nevertheless, in our study, the oxygen level on D0 was not identified as a risk factor for death by univariate analysis as shown in Table 2. However, severity of lung involvement was considered a risk factor for death. Thus, controlled clinical trials are still required to confirm the hypothesis of a potentially increased benefice of early TCZ injection.

Interestingly, Biran *et al.* and Martinez-Sanz *et al.* reported that TCZ was only effective when patients had CRP level >150 mg/L. Here we reported a cohort of patients with a mean CRP level of 157.5 mg/L ± 77.8 showing that patients with WHO scores 5 or 6 already had a sufficient increase in acute phase reactants for TCZ to be effective [7,8].

Finally, as our results showed an odds ratio of mortality of nearly 10 for patients with different oxygen flow rates but yet all classified in the same WHO ordinal scale score 5, we suggest optimizing this score by creating subgroups of increasing severity (1-3 L/min, 4-8 L/min, 9-11 L/min, 12-15 L/min). Moreover, this heterogeneous WHO score 5 might conceal a potential effect of TCZ if the change in score is used as an outcome.

Our study also has other limitations. First, we reported a retrospective and uncontrolled cohort. Second, we reported a cohort of COVID-19 patients from the first epidemic peak, who were not systematically treated with glucocorticoids. However, this does not prevent result extrapolation, as evidenced by the recent COVACTA study in which only 19% of patients received glucocorticoids. In addition, using data from patients not treated with corticosteroids highlights the actual effect of TCZ in COVID-19 patients rather than the combination of TCZ and glucocorticoids which could have a synergistic effect.

Conclusion

We reported that the timing of TCZ injection does not seem to be crucial for TCZ efficacy and our study suggests that TCZ could be less effective when oxygen requirement is >11 L/min. Thus, we hypothesized that an early injection ─ when patients still have a lower oxygen requirement ─ could be associated with better outcome. However, the ideal timing for TCZ injection remains to be determined by administration timing-related randomized clinical trials.

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Figure 1. Probability of death depending on (A) period from symptom onset to TCZ injection, or (B) oxygen level requirement on the day of TCZ injection, as of day of admission

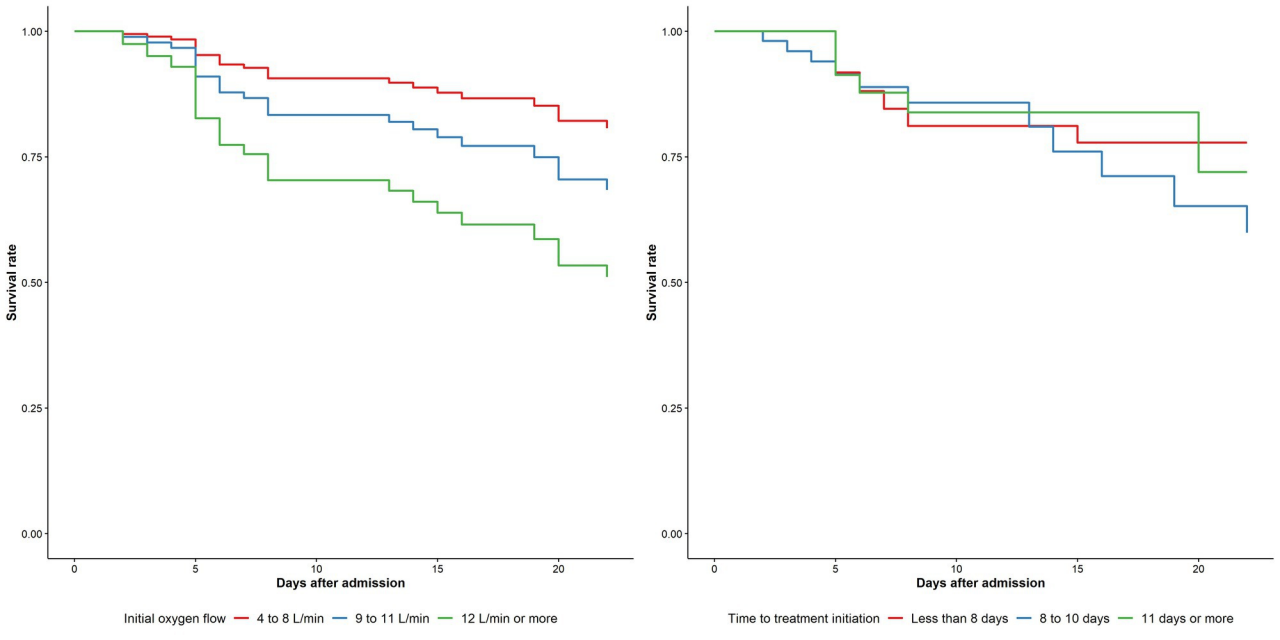
1.00
0.75
0.50
0.25
0.00
Survival rate
0
5
10
15
20
Days after admission
Initial oxygen flow
4 to 8 L/min
9 to 11 L/min
12 L/min or more
1.00
0.75
0.50
0.25
0.00
Survival rate
0
5
10
15
20
Days after admission
Time to treatment initiation
Less than 8 days
8 to 10 days
11 days or more

Table 1. Baseline characteristics and outcomes of all TCZ-treated COVID-19 patients

Characteristics of patients	(n=97) (n;%)
Demographics	
Age, years, mean±SD	67.9 ± 13.8
Sex, male	77 (79.4)
Comorbidities :	
- **None**	22 (23)
- **One**	34 (35)
- **More than one**	41 (42)
Baseline features on D0	
Duration of symptoms, days, mean±SD	9 ± 4.6
Oxygen level, L/min, mean±SD	9.6 ± 4.0
Respiratory rate, per min, mean±SD	30.4 ± 7.9
WHO scale, median with quartiles	5 [5-6]
WHO scale 5 /6	91 (93.8) /6 (6.2)
C-reactive protein, mg/L, mean±SD	157.5 ± 77.8
Lymphocyte count, per mm^3, mean±SD	872.0 ± 946.5
CT scan performed	86 (88.7)
Lung involvement on CT scan, median with quartiles	25-50 % [<10%- >75%]
Lung involvement on CT-scan >50%	39 (45)
Treatments	
lopinavir/ritonavir	37 (38.4)
azithromycin	42 (43.8)
hydroxychloroquine	27 (27.8)
glucocorticoids	34 (35.4)
Clinical and paraclinical features on D10	
Oxygen level, L/min, mean±SD	4.6 ± 4.4
WHO scale, median with interquartiles	5 [2-10]
WHO scale: 2 or 3	26 (26.8)
WHO scale: 4 or 5	44 (45.4)
WHO scale: 6	3 (3.1)
WHO scale: 7, 8 or 9	7 (7.2)
WHO scale: 10	17 (17.5)
C-reactive protein, mg/L, mean±SD	3.6 ± 5.0
Lymphocyte count, per mm^3, mean±SD	1,444 ± 652
Outcomes at the end of follow-up	
ICU admission	13 (13.4)
Invasive mechanical ventilation	9 (9.3)
Death	24 (24.7)
For survivors, time from D0 to withdrawal of oxygen, days, mean±SD	15 ± 12.1
For survivors, hospitalization duration, days, mean±SD	16.3 ± 13.1

Comorbidities among cardiovascular disease, arterial hypertension, heart failure, diabetes, obesity (BMI >30 kg/m^2), chronic respiratory insufficiency, chronic kidney disease, cirrhosis, immunosuppression.

WHO: World Health Organization; CT scan: computed tomography scan; ICU: intensive care unit; D0: Day of tocilizumab injection; D10: Day 10 after tocilizumab injection

Table 2. Relevant baseline characteristics of TCZ-treated COVID-19 patients according to the deceased or alive status

A. Qualitative variables

	Deceased (n=24)		Alive (n=73)		P value (Fischer test)
	n	%	n	%	
Sex					
Male	20	83%	57	78%	0.77
Female	4	17%	16	22%	
Comorbidities					
None	1	4%	21	29%	0.47
One	10	42%	24	33%	
More than one	13	54%	28	38%	
Glucocorticoids					
Yes	14	58%	20	28%	0.01
No	10	42%	52	72%	
BMI, kg/m^2					
<30	20	91%	47	68%	0.05
≥30	2	9%	22	32%	
Lung involvement on CT scan, %					
<10%	1	5%	1	1%	0.02
10-25%	1	5%	11	16%	
25-50%	3	16%	30	45%	
50-75%	6	32%	14	21%	
>75%	8	42%	11	16%	
Oxygen level, L/min					
4-8L	7	29%	35	49%	0.18
9-11L	5	21%	14	20%	
>11L	12	50%	22	31%	

B. Quantitative variables

	Deceased (n=24)			Alive (n=73)			P value (Mann-Whitney-Wilcoxon test)
	Min	Mean	Max	Min	Mean	Max	
Age, years, mean	55	77.8	92	34	64.7	91	<0.0001
Body Mass Index, kg/m^2, mean	16	25.1	31	15	27.5	50	0.24
Duration of symptoms before injection, days, mean	5	9.7	28	2	10.3	26	0.30

Oxygen level, L/min, mean	4	10.9	15	4	9.2	15	0.08
C-reactive protein, mg/L, mean	48	184.7	362	25	148.6	373	0.13

Comorbidities among cardiovascular disease, arterial hypertension, heart failure, diabetes, obesity (BMI >30kg/m^2), chronic respiratory insufficiency, chronic kidney disease, cirrhosis, immunosuppression.

CT scan: computed tomography scan