Original article

Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients

T. Klopfenstein[a],[1],[*], S. Zayet[a],[1],[*], A. Lohse[b], J.-C. Balblanc[b], J. Badie[c], P.-Y. Royer[a], L. Toko[a],
C. Mezher[c], N.J. Kadiane-Oussou[a], M. Bossert[b], A.-M. Bozgan[b], A. Charpentier[b],
M.-F. Roux[d], R. Contreras[d], I. Mazurier[e], P. Dussert[e], V. Gendrin[a], T. Conrozier[b],
For the HNF Hospital Tocilizumab multidisciplinary team

[a] *Infectious Disease Department, Nord Franche-Comté Hospital, 90400 Trévenans, France*
[b] *Rheumatology Department, Nord Franche-Comté Hospital, 90400 Trévenans, France*
[c] *Intensive Care Unit Department, Nord Franche-Comté Hospital, 90400 Trévenans, France*
[d] *Pharmacology Department, Nord Franche-Comté Hospital, 90400 Trévenans, France*
[e] *Biological Department, Nord Franche-Comté Hospital, 90400 Trévenans, France*

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ABSTRACT

Introduction. – No therapy has yet proven effective in COVID-19. Tocilizumab (TCZ) in patients with severe COVID-19 could be an effective treatment.
Method. – We conducted a retrospective case-control study in the Nord Franche-Comté Hospital, France. We compared the outcome of patients treated with TCZ and patients without TCZ considering a combined primary endpoint: death and/or ICU admissions.
Results. – Patients with TCZ ($n = 20$) had a higher Charlson comorbidity index (5.3 [± 2.4] vs 3.4 [± 2.6], $P = 0.014$), presented with more severe forms (higher level of oxygen therapy at 13 L/min vs 6 L/min, $P < 0.001$), and had poorer biological findings (severe lymphopenia: 676/mm^3 vs 914/mm^3, $P = 0.037$ and higher CRP level: 158 mg/L vs 105 mg/L, $P = 0.017$) than patients without TCZ ($n = 25$). However, death and/or ICU admissions were higher in patients without TCZ than in the TCZ group (72% vs 25%, $P = 0.002$).
Conclusion. – Despite the small sample size and retrospective nature of the work, this result strongly suggests that TCZ may reduce the number of ICU admissions and/or mortality in patients with severe SARS-CoV-2 pneumonia.

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1. Introduction

Coronavirus disease 2019 (COVID-19) is now a huge medical issue around the world. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a high mortality rate, for example 28% of 191 hospitalized patients in two hospitals in Wuhan, China [1]. Around the world intensive care unit (ICU) capacities are challenged to face this outbreak [2]. No therapy has yet been proven effective [3]. Data is particularly needed on treatments able to reduce mortality and the number of critical ill patients [4]. Death mainly results from acute respiratory distress syndrome (ARDS) [5]. Markers of inflammation such as C-reactive-protein (CRP),

ferritin, and interleukin-6 are significantly associated with mortality [6,7]. COVID-19-related multiple-organ failure and ARDS are mainly caused by cytokine storm [8]. Post-viral hyperinflammation with onset on the second week of the disease mostly seems to explain disease severity [9]. Tocilizumab (TCZ) is a recombinant humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody used in the treatment of rheumatoid arthritis. Several arguments show that TCZ administered to patients with severe COVID-19 could be an effective treatment to reduce mortality. By neutralizing a key inflammatory factor in the cytokine release syndrome (CRS), this molecule may block the cytokine storm during the systemic hyperinflammation stage and reduce disease severity [10,11]. To our knowledge, there is no evidence of TCZ ability to reduce the number of COVID-19 severe cases and/or mortality. We aimed to compare the outcome, especially ICU admissions and/or mortality, between COVID-19 patients treated with TCZ and without TCZ.

* Corresponding author.
 E-mail addresses: timothee.klopfenstein@hnfc.fr (T. Klopfenstein),
souhail.zayet@gmail.com (S. Zayet).
 [1] The first and second authors (T.K. and S.Z.) made equal contributions.

2. Method

We conducted a retrospective case-control study in NFC (Nord Franche-Comté) Hospital. On March 1, a first case of COVID-19 was confirmed in our hospital. "Standard treatment" was offered to patients requiring oxygen therapy: hydroxychloroquine or lopinavir-ritonavir therapy and antibiotics, and less commonly corticosteroids. On April 1, in relation with the increasing medical literature data, the NFC hospital scientific medical committee including infectious disease specialists, ICU specialists, rheumatologists, biologists, and pharmacists, approved the off-label use of TCZ in patients with general status deterioration despite well-conducted standard care. Daily "tocilizumab multidisciplinary team meetings" were organized to discuss patients' eligibility to receive TCZ. Based on the medical literature, we checked several criteria before starting TCZ treatment: no contraindication to TCZ, confirmed COVID-19 with SARS-CoV-2 RT-PCR, failure of standard treatment, time to symptom onset □ 7 days, oxygen therapy ≥ 5 liters/min, > 25% of lung damages on chest computed tomography (CT) scan, and ≥ 2 parameters of inflammation or biological markers of mortality (with a high level) such as ferritin, CRP, D-dimers, lymphopenia, and lactate dehydrogenase. As false-negative SARS-CoV-2 RT-PCR results may be observed during the second week, we suggested treating high suspicion of COVID-19 with obvious clinical, biological, and imaging (chest CT-scan) data and without differential diagnosis despite a negative SARS-CoV-2 RT-PCR result after multidisciplinary discussion.

The present work compares two groups of patients.

The "tocilizumab group" (TCZ group) included all patients who received standard treatment and tocilizumab (1 or 2 doses). Between April 1 and April 13, 2020, we enrolled all adult patients who received TCZ for confirmed COVID-19 by SARS-CoV-2 RT-PCR or diagnosis confirmed during the tocilizumab multidisciplinary team meeting. All patients receiving tocilizumab were informed that this prescription was used outside of its marketing authorization indications, and that their anonymized medical data would be used for a retrospective medical study. Patients were also informed that they could deny study participation.

The standard treatment group (ST group) included patients receiving standard treatment but without tocilizumab. This group included all hospitalized adult patients with confirmed COVID-19 by SARS-CoV-2 RT-PCR between March 1 and March 18, 2020. Because patients from the TCZ group were all critically ill patients and for comparable population purposes in the two groups, we excluded from the control group patients with moderate disease (i.e. those hospitalized for less than 48 hours and/or who did not receive the standard treatment and/or oxygen therapy). We also excluded patients with treatment not routinely administered in our hospital such as remdesivir and immunoglobulins.

In all patients, diagnosis of COVID-19 was confirmed by real-time RT-PCR on respiratory samples. Briefly, viral RNA was extracted using the NucleoSpin® RNA Virus kit (Macherey-Nagel) according to the manufacturer's instructions, and amplified by RT-PCR protocols developed by the Charité (E gene) [12] and the Institut Pasteur (RdRp gene) [13] on LightCycler 480 (Roche).

We collected the following data from the medical files of patients in both groups: demographic characteristics, comorbidities, clinical and paraclinical characteristics of the infection, and outcome.

To increase statistical power, we chose a combined primary endpoint (death and/or ICU admission) to compare the two groups. Continuous variables were expressed as mean and standard deviation (SD) and compared with ANOVA test. Categorical variables were expressed as number (%) and compared by χ^2 test or Fisher's exact test between the two groups. A P-value < 0.05 was considered significant. We used the SPSS v24.0 software (IBM, Armonk, NY, USA).

3. Results

We included 20 patients in the TCZ group. Twenty-one patients were treated with TCZ between April 1 and April 13, 2020. One patient was excluded because he received a non-standard treatment (IV immunoglobulins). We included 25 patients in the ST group. Fifty-nine patients with confirmed COVID-19 were hospitalized between March 1 and March 18, 2020. Thirty-four patients hospitalized for less than 48 hours or without standard treatment were excluded (11 and 23, respectively).

No statistical differences were observed between the two groups (TCZ and ST) with regard to age, sex, and comorbidities (Table 1). However, TCZ patients had a higher Charlson comorbidity index than non-TCZ patients (5.3 [±2.4] vs 3.4 [±2.6]; P = 0.014), and patients aged above 70 years were more frequent in the TCZ group than in the ST group (75% vs 44%, P = 0.036).

No statistically significant between-group difference was observed in terms of clinical features on admission. However, during hospitalization, oxygen requirement (flow and duration) was higher in the TCZ group than in the ST group (respectively, 13L/min vs 6L/min, P < 0.001 and 12 days vs 4 days, P = 0.009). Biological findings on admission were statistically more severe in the TCZ group than in the ST group for lymphopenia (676/mm^3 vs 914/mm^3, P = 0.037) and CRP level (158 mg/L vs 105 mg/L, P = 0.017). However, lung involvement on CT scan at admission did not seem different, but we noticed that only 2/8 patients in the ST group had > 50% lung involvement on CT scan (17/25 patients in the ST group did not have a CT scan performed at admission).

Our combined primary endpoint (death and/or ICU admission) was higher in the ST group than in the TCZ group (72% vs 25%, P = 0.002) (Fig. 1). Similarly, patients in the ST group more often required invasive mechanical ventilation than patients in the TCZ group (32% vs 0%, P = 0.006). No statistical difference was observed between the two groups in terms of mortality, unlike ICU admissions; however, death clearly tended to be more frequent in the ST group than in the TCZ group (48% vs 25%, P = 0.066).

4. Discussion

Despite the small sample size and the retrospective nature of the work, the latter strongly suggests that TCZ may reduce the number of ICU admissions and/or mortality in patients with severe SARS-CoV-2 pneumonia.

Our population seems to be older, with more comorbidities, and a higher level of mortality than other studies with COVID-19 patients [1,7]. This may be explained by our methodology (exclusion of patients without hospitalization criteria and without standard treatment) to select critically ill patients and have a comparable population with the TCZ group (which were critically ill patients).

Tocilizumab was administered on average 13 days after COVID-19 symptom onset, after failure of standard treatment, after a mean 7 days from admission, in patients with many comorbidities and critically ill (oxygen therapy flow average at 10 L/min). However, compared with the ST group (which included fewer comorbid and critically ill patients), the occurrence of death and/or ICU admissions are clearly lower (25% versus 72%) with high statistical significance (P = 0.002) despite the low numbers of patients. None of our 20 TCZ-treated patients was hospitalized in the ICU. Finding enough ICU beds is highly challenging during the present COVID-19 pandemic [2]; TCZ could be key in the treatment of COVID-19 cases to reduce ICU admissions. It could also have a huge public health

Table 1
Comparison of demographic, clinical, paraclinical findings and outcome of both groups.

Characteristics	TCZ group (n = 20)	ST group (n = 25)	*P*-value
Demographic characteristics			
Age (y) (mean, range, SD)	76.8 [52–93] ± 11	70.7 [33–96] ± 15	0.141
[18–50]	0	2 (8%)	0.303
[51–70]	6 (30%)	12 (48%)	0.221
[71–80]	5 (25%)	5 (20%)	0.688
> 80	9 (45%)	6 (24%)	0.138
Male (Number, %)			
Current smoking (Number, %)	2 (10%)	0	0.192
Charlson comorbidity index (mean, range, SD)	5.3 [1–10] ± 2.4	3.4 [0–9] ± 2.6	**0.014**
Comorbidities (Number, %)			
No comorbidity	4 (20%)	6 (24%)	1
BMI (kg/m^2)	26.1 [17–32] ± 4.3	27.2 [22–32] ± 3	0.503
Hypertension	11 (55%)	11 (44%)	0.463
Cardiovascular diseases[a]	14 (70%)	17 (68%)	0.885
Diabetes mellitus	5 (25%)	8 (32%)	0.607
COPD[b]	4 (20%)	1 (4%)	0.155
Immunosuppression[c]	0	0	1
Malignancy	7 (35%)	2 (8%)	0.057
Clinical features at admission			
q-SOFA	0.25 [0–1] ± 0.44	0.44 [0–2] ± 0.58	0.235
Blood pressure < 100 mmHg	0	1 (5%)	1
Confusion or Glasgow scale < 15	1 (5%)	3 (12%)	0.617
Respiratory rate > 22 (Number, (%))	4 (20%)	6 (24%)	1
Sat O$_2$ (%) (mean, range, SD)	90 [62–98] ± 9	91 [78–100] ± 5	0.773
Paraclinical findings at admission			
≥ 50% lung involvement on CT scan	12 (60%)	2 (25%)	0.208
Lymphocytes (/mm^3)	676 [210–1730] ± 357	914 [450–1620] ± 345	**0.037**
C-reactive protein (mg/L)	158 [61–309] ± 70	105 [13–271] ± 66	**0.017**
Characteristics during hospitalization			
Positive PCR for SARS-CoV2 (respiratory samples)	19 (95%)	25 (100%)	0.444
Highest level of oxygen therapy ≥ 24 h (L/min)	13 [5–15] ± 4	6 [1–15] ± 4	**<0.001**
Duration of oxygen therapy (days)	12 [4–25] ± 6	4 [1–10] ± 4	**0.009**
Oxygen therapy flow at TCZ initiation (L/min)	10 [5–15]	NA	NA
Time from symptom onset to TCZ initiation (days)	13 [4–21]	NA	NA
Time from admission to TCZ initiation (days)	7 [2–22]	NA	NA
Outcome			
Death and/or ICU admission	5 (25%)	18 (72%)	**0.002**
Death	5 (25%)	12 (48%)	0.066
ICU admission	0	11 (44%)	**<0.001**
Invasive mechanical ventilation (IMV)	0	8 (32%)	**0.006**
Patients still hospitalized[d]	3 (15%)	2 (8%)	0.642
Discharge	11 (55%)	11 (44%)	0.463
Duration of hospitalization (days)	13 [4–32] ± 7	17 [5–41] ± 12	0.324

TCZ: tociluzimab; ST: standard treatment

[a] Defined by: cardiac failure, cardiac arrhythmia, coronary heart disease, stroke, peripheral arterial obstructive disease and thromboembolic disease.
[b] COPD: chronic obstructive pulmonary disease.
[c] Defined by: transplantation, cirrhosis, long-term steroids therapy, immunomodulators treatments and human immunodeficiency virus (HIV).
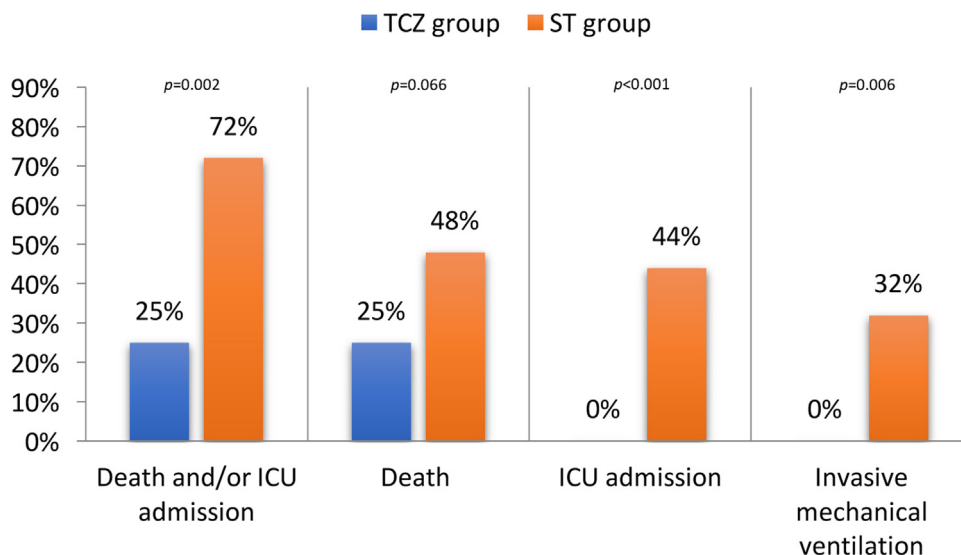[d] For both group we collected outcome data's until April 24th 2020.

Fig. 1. Outcome in the tocilizumab (TCZ) group and in the standard treatment (ST) group.

T. Klopfenstein et al. / Médecine et maladies infectieuses 50 (2020) 397–400

impact as well as an impact on reducing the human and economic cost of the outbreak. The low number of patients included in our work probably explains that the difference in mortality is not significant because of a lack of statistical power, but we can notice a clear trend for fewer deaths in the TCZ group.

Only a few cases and series reported that repeated doses of TCZ may improve the condition of critically ill patients [14–17]. A small clinical trial conducted in China including 21 severe COVID-19 patients treated by TCZ showed that clinical outcome was favorable in more than three quarters of patients. Laboratory findings such as lymphocytes and CRP levels returned to normal and the CT scan showed that the lung lesions of 19 patients resolved [18]. Only recently, Roumier et al. showed that treatment with TCZ significantly reduced the risk of subsequent ICU admission in 30 patients after weighted analysis [19], as in our study.

Our study is retrospective with a low number of patients in each group. Larger prospective randomized trials are required to confirm these findings.

5. Conclusion

We showed that TCZ added to the "standard treatment" reduced intensive care unit admissions and/or mortality in COVID-19 patients. TCZ could be key in the treatment of severe COVID-19 patients. All hospitals should consider these findings.

Contributors

T.K., S.Z., and N.J.K.O. collected the epidemiological and clinical data. T.K. and S.Z. drafted the manuscript. V.G. and T.C. revised the final manuscript. A.L., J.C.B., J.B., P.Y.R., L.T., C.M., M.B., A.M.B., A.C., M.F.R., R.C. I.M., P.D. are all member of the "HNF Hospital Tocilizumab multidisciplinary team".

Disclosure of interest

The authors declare that they have no competing interest.

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