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Analysis of the factors predicting clinical response to tocilizumab therapy in patients with severe COVID-19

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Abbreviations: ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ePO_2/FiO_2, estimated arterial oxygen/fraction of inspired oxygen ratio; HCQ, hydroxychloroquine; ICU, intensive care unit; IFN-β, interferon-β; IQR, interquartile range; IL-6, interleukin-6; IMV, invasive mechanical ventilation; LDH, lactate dehydrogenase; LPV/r, lopinavir/ritonavir; NAT, nucleic acid testing; OTR, oxygen therapy requirements; SCI, Significant clinical improvement; RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCZ, tocilizumab.

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ABSTRACT

Background: Controversy remains about the efficacy of tocilizumab (TCZ) for the treatment of severe COVID-19. We aimed to analyze the profile of TCZ-respondent patients.
Methods: We retrospectively analyzed a cohort of patients with severe COVID-19 who received off-label TCZ after recommendation by a local committee and were admitted to the University Hospital "12 de Octubre" until May 2020. The primary end point was a significant clinical improvement (SCI) on day 14 after administration of TCZ. Factors independently related to SCI were analyzed by multivariate logistic regression models.
Results: Of 428 (63.3%) patients treated with TCZ, 271 (63.3%) experienced SCI. After adjustment for factors related to unfavorable outcomes, TCZ administration within the first 48 hours from admission (odds ratio [OR]: 1.98, 95% confidence Interval [95% CI]: 1.1–3.55; $P = 0.02$) and ALT levels >100 UI/L at day 0 (OR: 3.28; 95% CI: 1.3–8.1; $P = 0.01$) were independently related to SCI. The rate of SCI significantly decreased according to the time of TCZ administration: 70.2% in the first 48 hours from admission, 58.5% on days 3-7, and 45.1% after day 7 ($P = 0.03$ and $P = 0.001$, respectively).
Conclusion: TCZ improves the prognosis of patients with COVID-19 the most if treatment starts within the first 48 hours after admission.

Introduction

The deleterious impact of the hyperactive immune response triggered by SARS-CoV-2 has been reported since the start of the pandemic (Giamarellos-Bourboulis et al., 2020, Vabret et al., 2020). Therapeutic immunomodulation emerged as a potentially life-saving option for patients with severe COVID-19 (Luis et al., 2021). Available drugs inhibiting the pleiotropic proinflammatory cytokine interleukin 6 (IL-6) rapidly became of particular interest because elevated IL-6 levels seemed to mediate systemic inflammatory responses associated with SARS-CoV-2 infection and the development of acute respiratory distress syndrome (ARDS) and multiorgan failure (McGonagle et al., 2020). Preliminary case series and cohort studies reported outcomes in patients with severe COVID-19 pneumonia treated off-label with intravenous (IV) or subcutaneous (SC) tocilizumab (TCZ), the humanized monoclonal antibody targeting the IL-6 receptor (IL-6R) most available at that time (Antwi-Amoabeng et al., 2020, Fernandez-Ruiz et al., 2021b, Jordan et al., 2020, Knorr et al., 2020, Toniati et al., 2020), with preliminary data suggesting the safety and potential efficacy of this approach. These early results rapidly prompted the incorporation of this agent in most COVID-19 management protocols pending the results of observational studies and randomized clinical trials (RCTs) investigating the real role of TCZ for this indication.

Contradictory results were first obtained from observational studies. Although most of these studies found benefits in the form of decreased mortality or invasive mechanical ventilation (IMV) requirements among TCZ-treated patients (Deftereos et al., 2020, Mikulska et al., 2020, Rojas-Marte et al., 2020, Rossotti et al., 2020, Roumier et al., 2021, Somers et al., 2020), some others failed to demonstrate significant outcome differences compared with the standard of care (Campochiaro et al., 2020, Della-Torre et al., 2020). Surprisingly, similar variable results are currently being reported from RCTs. Although recent meta-analyses that included all 10 RCTs with available results up to May 2021 (Snow et al., 2021, Tleyjeh et al., 2021) found an overall statistically significant but modest benefit in terms of mortality in patients with the most severe COVID-19 and a trend for lower risk of progression to IMV, the specific results from placebo-controlled RCTs failed to demonstrate a significant prognostic effect (Rosas et al., 2021, Stone et al., 2020). In this regard, there is a need to identify specific factors that would prompt the use of tocilizumab and some experts are currently advocating for the identification of the clinical profile of patients most likely to respond to TCZ therapy to optimize the outcomes of this potentially effective treatment for severe COVID-19 (Fernandez-Ruiz et al., 2021a, Klopfenstein et al., 2021).

This study aimed to analyze the baseline clinical factors related to clinical response in a broad homogeneous cohort of patients who received off-label treatment with TCZ under an institutional protocol throughout the first wave of the COVID-19 pandemic.

Materials and Methods

Study population and design

This retrospective study was conducted at the University Hospital "12 de Octubre" (Spain). The research was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

The study population included all patients aged ≥18 years consecutively admitted at our center from March 16, 2020, to May 16, 2020, who received IV TCZ as immunomodulatory therapy for COVID-19 pneumonia.

We collected the following data from electronic medical records using a standardized case report form: demographics and major comorbidities, symptoms at presentation, vital signs, laboratory values and radiological features at day 0, use of antiviral therapy, the evolution of clinical status at days +1, +3, +5, +7, +10 and +14, treatment-related adverse events, and outcomes. Day 0 was defined as the calendar date on which the first dose of TCZ was administered. Follow-up for all participants was completed at 28 days or death (whichever occurred first).

The primary outcome was a significant clinical improvement (SCI) by day +14 after the first TCZ dose, defined by hospital discharge and/or a decrease of ≥2 points from baseline (day 0) on the 6-point ordinal scale detailed later.

The National Early Warning Score (NEWS) was calculated at admission. Respiratory function was assessed by the pulse oximetry oxygen saturation/fraction of inspired oxygen (SpO_2/FiO_2) ratio. Dynamic changes in the clinical status were assessed according to the following 6-point ordinal scale: 1.- discharged to home; 2.- admitted to the hospital, not requiring supplemental oxygen; 3.- admitted to the hospital, requiring low-flow supplemental oxygen (FiO_2 <40%); 4.- admitted to the hospital, requiring high-flow supplemental oxygen (FiO_2 ≥40%) or non-invasive mechanical ventilation; 5.- admitted to the hospital, requiring IMV, extracorporeal membrane oxygenation (ECMO), or both; and 6.- death. Comorbidity burden was assessed by means of the age-adjusted Charlson comorbidity index. Immunosuppression was defined by the presence

of solid organ transplantation, HIV infection, or receipt of corticosteroid therapy (prednisone ≥20 mg daily or equivalent dose for more than 1 week), cytostatic agents, or other immunosuppressive drugs within the previous month.

Antiviral and immunomodulatory therapies

According to the clinical guidelines issued by the Spanish Ministry of Health during the study period (Ministerio de Sanidad, 2020), off-label antiviral regimens included co-formulated lopinavir/ritonavir (LPV/r) (200/100 mg twice daily for up to 14 days), hydroxychloroquine (HCQ) (400 mg twice for the first day, followed by 200 mg twice daily for 5-10 days), and subcutaneous (SC) interferon (IFN)-β (250 μg every 48 hours). In addition, some patients received IV remdesivir (200 mg during the first day, followed by 100 mg daily for 5-10 days) in the context of an ongoing RCT. Corticosteroids were administered at different dosing regimens (IV methylprednisolone 0.5-1 mg/Kg daily for ≤5 days or as pulses of 100-250 mg for 3 days). By April 2020, the use of corticosteroids was generalized for patients presenting to the emergency room with COVID-19 pneumonia and SpO2 <92% on room air, regardless of the subsequent administration of TCZ. Most patients received empirical antibiotic therapy (usually with a second- or third-generation cephalosporin), and thromboprophylaxis with low-molecular-weight heparin (SC enoxaparin 40 mg once daily, 60 mg once daily, or 40 mg twice daily if bodyweight <80 kg, 80-100 kg, or >100 kg, respectively, with renal dose adjustment if needed).

Beginning March 18, 2020, a local multidisciplinary committee that included representatives from different clinical specialties and from the Department of Pharmacy was established to standardize decisions regarding immunomodulatory therapies for COVID-19 patients. The committee held daily meetings (except for the weekends) during the first wave of the pandemic. The off-label use of TCZ was considered for patients potentially eligible for intensive care unit (ICU) admission, with bilateral or rapidly progressive infiltrates in chest x-ray or computerized tomography (CT) scan, and fulfilling 1 or more of the following criteria: (a) respiratory rate >30 bpm and/or pulse oximetry oxygen saturation (SpO_2) <92% while breathing room air; (b) C-reactive protein (CRP) level >10 mg/dL; (c) IL-6 level >40 pg/mL; and/or (d) D-dimers >1,500 ng/mL. Exclusion criteria included liver function abnormalities (alanine transaminase [ALT] and/or aspartate transaminase [AST] levels >5 times the upper limit of normal), uncontrolled bacterial or fungal infection, or acute diverticulitis or bowel perforation. An initial IV 400 mg (if bodyweight <75 kg) or 600 mg (if bodyweight ≥75 kg) dose was administered as a 1-hour infusion. Until March 26, 2020, a second 400 mg dose was routinely administered 12 hours later, whereas a third dose could be given after 24 hours from the first infusion for selected patients according to the criteria of the treating physician (Ministerio de Sanidad, 2020). After that date, a single dose was prescribed according to the updated recommendations of the Ministry of Health of Spain.

Statistical analysis

Quantitative data were shown as the mean and SD or the median with interquartile range (IQR), whereas qualitative variables were expressed as absolute and relative frequencies. Categorical variables were compared using the chi-square test. Student's *t* test or Mann-Whitney *U* test was applied for continuous variables, as appropriate. No imputation for missing data was applied.

A multivariate logistic regression model was created to analyze factors independently related to SCI by day +14 on the basis of clinical factors and laboratory values available at baseline (day 0). Those variables with univariate $P \leq 0.1$ were entered into a backward stepwise logistic regression model. Some continuous variables of interest were dichotomized according to the optimal cutoff value, as determined by Youden's index. Goodness-of-fit was assessed by the Hosmer-Lemeshow test. Multicollinearity among explanatory variables was analyzed using the variance inflation factor (VIF), with VIF values <3 being considered acceptable. The most parsimonious model (ie, the highest outcome variability explained with the lowest number of variables) was selected. Results are given as odds ratios (ORs) with 95% confidence intervals (CIs).

All the significance tests were 2-tailed. The threshold for significance was set at a $P < 0.05$. Statistical analysis was performed with SPSS version 20.0 (IBM Corp, Armonk, New York) and graphs were generated with Prism version 6.0 (GraphPad Software Inc., La Jolla, California).

Table 1
Demographics and baseline characteristics of patients included in the cohort.

Variable	Overall cohort (n = 428)
Age, years [mean ± SD]	55 ± 13.4
Age distribution [n (%)]	
21 to 40 years	57 (13.3)
41 to 60 years	235 (54.9)
61 to 80 years	120 (28)
More than 80 years	16 (3.7)
Male sex [n (%)]	278 (65)
Ethnicity [n (%)][a]	
Caucasian	248 (57.9)
Latino	158 (36.9)
Asian	5 (1.3)
Other	17 (3.9)
Comorbidities [n (%)]	
None	193 (45.1)
Hypertension	136 (31.8)
Dyslipidemia under statin treatment	106 (24.8)
Obesity	74 (17.2)
Diabetes mellitus	72 (16.8)
Atherothrombotic disease	24 (5.6)
Asthma	28 (6.5)
Sleep apnea-hypopnea syndrome	20 (4.7)
Chronic obstructive pulmonary disease	14 (3.3)
Immunosuppression	44 (10.2)
Previous corticosteroid therapy	27 (6.3)
Solid organ transplantation	18 (4.2)
Previous chemotherapy	11 (2.6)
HIV infection	6 (1.4)
Pregnancy	11 (2.6)
Active solid malignancy	17 (4.8)
Active or former smoking	89 (20.7)
Charlson Comorbidity Index [median (IQR)]	1 (0–3)
Previous ACEi/ARB therapy [n (%)]	123 (28.7)
Previous anticoagulant therapy [n (%)]	27 (6.3)
Influenza vaccination in the current (2019/20) season [n (%)]	87 (20.3)

[a] Data on ethnicity not available for 9 patients.ACEi/ARB: angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; IQR: interquartile range.

Results

Clinical characteristics of study groups

After excluding 7 patients with insufficient follow-up data owing to transfer to another institution, a total of 428 patients were included in the analysis. As listed in **Table 1** and **Table 2**, most patients were male, of Caucasian ethnicity, with a mean age of 55 years, more than half with some underlying disease and presented to the emergency department with cough, dyspnea, and diffuse infiltrates on the initial chest x-ray after a median interval of 7 days since symptom onset. Most patients were treated with HCQ, half of them received corticosteroid therapy, and about one-third received LPV/r before or simultaneously with the first dose of TCZ.

Table 2
Clinical characteristics, laboratory values, and radiologic findings at hospital admission.

Variable	Overall cohort (n = 428)
Symptoms at hospital admission [n (%)]	
Cough	317 (74.1)
Dyspnea	309 (72.2)
Fever	209 (48.8)
Myalgia	158 (36.9)
Diarrhea	150 (35)
Vomiting	55 (12.9)
Expectoration	66 (15.4)
Impaired mental status	15 (3.5)
Interval from symptom onset to hospital admission, days [median (IQR)]	7 (5 – 10)
NEWS at hospital admission [median (IQR)][a]	5.5 (3 – 7)
Vital signs at hospital admission	
Axillary temperature, °C [mean ± SD]	37.8 ± 1.1
Respiratory rate, rpm [median (IQR)]	22 (16 – 30)
Heart rate, bpm [mean ± SD]	101.3 ± 17.3
SpO_2 (at room air) [median (IQR]	92 (88 – 95)
Laboratory values at hospital admission	
Leukocytes, × 10^9 cells/L [mean ± SD]	7.8 ± 3.4
Neutrophils, × 10^9 cells/L [mean ± SD]	6.3 ± 3.3
Lymphocytes, × 10^9 cells/L [mean ± SD]	0.92 ± 0.5
Leukocyte-to-lymphocyte ratio [median (IQR)]	8.5 (5.8 – 13.3)
Platelet count, × 10^9 cells/L [mean ± SD]	237.9 ± 100
ALT, U/L [median (IQR)]	39 (25.3 – 63)
AST, U/L [median (IQR)]	46 (32 – 68)
Creatinine, mg/dL [mean ± SD]	1.03 ± 0.56
CRP, mg/dL [mean ± SD]	16.9 ± 9.2
LDH, U/L [median (IQR)]	426 (356 – 536)
Ferritin, ng/mL [median (IQR)][b]	1,526 (779 – 2,264)
Interleukin-6, pg/mL [median (IQR)][c]	44 (20.2 – 144)
Chest imaging at hospital admission [n (%)]	
Diffuse pneumonia	368 (86)
Multiple lobe pneumonia	26 (6.1)
Single lobe pneumonia	18 (4.2)
No pneumonia	14 (3.3)

[a] NEWS hospital admission available for 266 patients
[b] Ferritin levels at hospital admission available for 278 patients
[c] Interleukin-6 levels at hospital admission available for 140 patients.ALT: alanine transaminase; AST: aspartate transaminase; bpm: beats per minute; CRP: C-reactive protein; IQR: interquartile range; LDH: lactate dehydrogenase; NEWS: National Early Warning Score; rpm: respirations per minute; SpO_2: pulse oximetry oxygen saturation.

Empiric antibiotic therapy including second- or third-generation cephalosporins or amoxicillin/clavulanic acid was also common.

Clinical and analytical data of patients at the time of TCZ administration are listed in **Table 3**. According to the clinical criteria for being considered as candidates for TCZ by the multidisciplinary committee, 1 criterion was fulfilled in 13 (3.0%) patients, 2 criteria in 80 (18.7%), 3 in 207 (48.4%), 4 in 116 (27.1%) and 5 in 12 (2.8%). TCZ was administered mainly at a single dose schedule at a median of 2 days from hospital admission.

As listed in **Table 4**, in the entire study cohort, 271 of 428 patients experienced SCI by day +14, accounting for an overall rate of 63.3% (95% CI: 58.6–67.9). Regarding other outcome parameters, ICU admission was required in 98 (22.9%) patients, IMV in 93 (21.7%), and 30-day all-cause mortality was 13.8% (59/428). Reported adverse events after TCZ treatment were bacterial superinfection in 13 (3%) patients and hypertransaminasemia in 30 (7%). No cases of disseminated strongyloidiasis or other opportunistic infections were reported in our cohort.

Factors predicting clinical response by day +14

The preliminary comparative analysis between patients presenting with SCI or without SCI by day +14 is listed in **Table 5**. The mean time to TCZ administration from admission was significantly lower in patients that experienced SCI by day +14 (2.9 days vs 4.9 days; $P = <0.0001$). The area under the receiver operating characteristics curve analyses supported by Youden's index yielded the cutoff of 48 hours from hospital admission as the most predictive with regards to the achievement of SCI by day +14. As depicted in **Figure 1**, the rate of SCI by day +14 was significantly higher in those patients receiving TCZ within the first 48 hours (165/235 [70.2%]), compared with 58.5% (83/142) for those treated between days 3 and 7, and 45.1% (23/51) for those receiving TCZ after day 7 ($P = 0.03$ and $P = 0.001$, respectively). Median serum ALT levels at day 0 were also significantly higher in the group with SCI compared with those without (43 vs 36 IU/L, respectively; $P = 0.001$), and the cutoff of 100 IU/L was selected as the most predictive in terms of combined sensitivity and specificity.

Conversely, increased age, certain comorbidities (hypertension, dyslipidemia, obesity, chronic obstructive pulmonary disease, immunosuppression, and solid malignancy), active or former smoking habit and clinical and analytical data indicative of severe disease at day 0 (low SpO_2/FiO_2 ratio, high leukocyte, and low lymphocyte counts, high leukocyte-to-lymphocyte, high CRP, LDH, and ferritin levels, bilateral alveolar infiltrates, and previous or concomitant corticosteroid therapy) were found to be significantly more frequent in patients not achieving SCI.

Univariate and multivariate analyses of factors related to SCI by day +14 through logistic regression models are listed in **Table 6**. Significant collinearity was observed between the clinical status assessed by the 6-point ordinal scale and the SpO_2/FiO_2 ratio at day 0 (VIF values >6.1). Only the SpO_2/FiO_2 ratio was maintained in the multivariate model because the more objective nature of this variable does not depend on the availability of health care resources (ie, number of ICU beds). In addition, owing to the existence of collinearity between leukocyte and lymphocyte counts and the leukocyte-to-lymphocyte ratio (VIF values >3.5), only the latter parameter was retained.

In the final multivariate model variates inversely related to the probability of achieving SCI included certain comorbidities such as dyslipidemia under statin treatment (odds ratio [OR]: 0.38; 95% CI: 0.19–0.73; $P <0.0001$) or active solid malignancy (OR: 0.19; 95% CI: 0.04–0.94; $P = 0.04$) and analytical parameters at day 0 indicating advanced disease such as higher leukocyte-to-lymphocyte ratio (OR [per unitary increment]: 0.94; 95% CI: 0.91–0.97; $P = 0.001$), higher CRP (OR [per unitary increment]: 0.97; 95% CI: 0.94–1.00; $P = 0.065$) or LDH levels (OR [per unitary increment]: 0.99; 95% CI: 0.99–0.99; $P = 0.013$). After adjustment by these factors related to poorer outcomes, TCZ administration within the first 48 hours from admission was still independently associated with a 2-fold increase in the probability of SCI by day +14 (OR: 1.98; 95% CI: 1.1–3.55; $P = 0.02$). Hepatitis expressed by serum ALT levels >100 IU/L also defined a group of patients with a 3-fold increased odds of having a favorable response to TCZ therapy (OR: 3.28; 95% CI: 1.3–8.1; $P = 0.01$).

Although the groups of patients stratified by the timing of TCZ administration (within the first 48 hours of admission or beyond) were not entirely comparable (**Table S1**), different comorbidity and disease severity variables were also included in the final multivariate model. Early (first 48 hours) initiation of TCZ therapy still retained the statistical significance after such adjustment.

Discussion

A specific analysis of this large series of patients treated with IV TCZ has allowed us to elucidate the factors that may predict a significant clinical response to this immunomodulatory agent in patients with COVID-19. An advantage of this series was the homogeneity in the indications for treatment with TCZ because all patients were selected by a specific committee that applied the

Table 3
Vital signs and laboratory values at day 0, and treatments administered previous to or simultaneously with tocilizumab.

Variable	Overall cohort (n = 428)
Vital signs at day 0	
Axillary temperature, °C [mean ± SD]	37.4 ± 0.9
Respiratory rate, rpm [median (IQR)]	26 (20 – 30)
Heart rate, bpm [mean ± SD]	88.6 ± 16.4
SpO_2/FiO_2 ratio [median (IQR)]	230 (166 – 321)
Laboratory values at day 0	
Leukocytes, × 10^9 cells/L [mean ± SD]	8.7 ± 5.4
Lymphocytes, × 10^9 cells/L [mean ± SD]	1.04 ± 3.1
Leukocyte-to-lymphocyte ratio [median (IQR)]	10.2 (6.5 – 16.3)
ALT, U/L [median (IQR)]	41 (25 – 65)
AST, U/L [median (IQR)]	43 (31 – 60)
CRP, mg/dL [mean ± SD]	16.3 ± 9.2
LDH, U/L [median (IQR)]	426.5 (356 – 536)
Ferritin, ng/mL [median (IQR)][a]	1,526.5 (779 – 2,264)
Interleukin-6, pg/mL [median (IQR)][b]	53 (17 – 136)
Chest imaging at hospital admission [n (%)]	
Bilateral interstitial infiltrates	217 (50.7)
Bilateral alveolar infiltrates	198 (46.3)
Single lobe infiltrates	7 (1.6)
Other	6 (1.4)
Interval from symptom onset to day 0, days [median (IQR)]	10 (8 – 13)
Interval from hospital admission to day 0, days [median (IQR)]	2 (1 – 4)
Administration of more than 1 TCZ dose [n (%)]	68 (15.8)
Clinical status according to the 6-point ordinal scale at day 0 [median (IQR)]	3 (2 – 3)
Clinical status at day 0 [n (%)]	
2. Hospitalized, no supplemental oxygen requirement	24 (5.6)
3. Hospitalized, low-flow supplemental oxygen requirement (FiO_2 <40%)	188 (44.2)
4. Hospitalized, high-flow supplemental oxygen requirement (FiO_2 ≥40%) or NIMV	190 (44.4)
5. Hospitalized, IMV and/or ECMO	25 (5.8)
Previous or simultaneous therapies [n (%)]	
HCQ	382 (89.2)
LPV/r	154 (35.9)
IFN-β	39 (9.1)
Remdesivir	2 (0.4)
Corticosteroids	218 (51)
Interval to day 0, days [median (IQR)][a]	1 (0 – 2)
Azithromycin	222 (51.8)
Other antibiotics	
Second- or third-generation cephalosporin	289 (67.5)
Amoxicillin/clavulanic acid	100 (23.3)
Carbapenem	14 (3.2)
Fluoroquinolones	15 (3.5)
Others	4 (0.9)

[a] Ferritin levels at day 0 available 203 patients.
[b] Interleukin-6 levels at day 0 available for 128 patients.[c]Time interval from the initiation of the corresponding therapy to the administration of the first dose of tocilizumab (day 0).ALT: alanine transaminase; AST: aspartate transaminase; bpm: beats per minute; CRP: C-reactive protein; ECMO: extracorporeal membrane oxygenation; HCQ: hydroxychloroquine; IFN-β: interferon-β; IQR: interquartile range; IMV: invasive mechanical ventilation; LDH: lactate dehydrogenase; LPV/r: lopinavir/ritonavir; NIMV: non-invasive mechanical ventilation; rpm: respirations per minute; SpO_2/FiO_2: SpO_2/FiO_2: pulse oximetry oxygen saturation/fraction of inspired oxygen; TCZ: tocilizumab.

Table 4
Vital signs, laboratory values, and clinical status at day 0, 3, 7 and 14 from the initiation of TCZ therapy.

Clinical data	Day 0	Day 3	Day 7	Day 14
Main vital signs				
Axillary temperature, °C [mean ± SD]	37.4 ± 0.9	36.8 ± 0.8	36.8 ± 0.6	36.9 ± 0.5
SpO_2/FiO_2 ratio [median (IQR)]	230 (166 – 321)	268 (170-343)	322 (187-438)	337 (252-448)
Main laboratory values				
Lymphocytes, x 10^9 cells/L [mean ± SD]	1.04 ± 3.1	1.4 ± 3.8	1.5 ± 2.9	1.6 ± 2.2
CRP, mg/dL [mean ± SD]	16.3 ± 9.2	4.2 ± 1.7	1.1 ± 2.9	1.3 ± 3.1
LDH, U/L [median (IQR)]	426.5 (356 – 536)	427 (338 – 566)	394 (306 – 532)	337(252 – 448)
Clinical status [n (%)]				
1. Discharged to home	0	11 (2.6)	143 (33.4)	256 (59.8)
2. Hospitalized, no supplemental oxygen requirement	24 (5.6)	48 (11.2)	36 (8.4)	21 (4.9)
3. Hospitalized, low-flow supplemental oxygen requirement (FiO_2 <40%)	188 (44.2)	144 (33.6)	71 (16.6)	40 (9.3)
4. Hospitalized, high-flow supplemental oxygen requirement (FiO_2 ≥40%) or NIMV	190 (44.4)	137 (32)	73 (17.1)	32 (7.5)
5. Hospitalized, IMV and/or ECMO	25 (5.8)	69 (16.1)	72 (16.8)	33 (7.7)
6. Death	0	19 (4.4)	33 (7.7)	46 (10.7)
Improvement in clinical status (at least 1 scale degree) [n (%)]	-	79 (18.5)	207 (48.4)	306 (71.5)
Improvement in clinical status (at least 2 scale degrees) [n (%)]	-	10 (2.3)	145 (33.9)	271 (63.3)

CRP: C-reactive protein; ECMO: extracorporeal membrane oxygenation; IQR: interquartile range; IMV: invasive mechanical ventilation; LDH: lactate dehydrogenase; NIMV: non-invasive mechanical ventilation; SpO_2/FiO_2: SpO_2/FiO_2: pulse oximetry oxygen saturation/fraction of inspired oxygen.

Table 5
Comparative analysis of factors at the time of the initiation of TCZ therapy (day 0) among patients with or without significant clinical improvement by day +14[a].

Variable	Clinical improvement (n = 271)	No clinical improvement (n = 157)	*P* value
Age, years [mean ± SD]	52.5 ± 13.1	60.9 ± 12.2	<0.0001
Aged 55 yrs. old or less [n (%)]	271 (64.6)	157 (44.6)	0.0001
Male gender [n (%)]	176 (64.9)	102 (65)	0.661
Non-Caucasian ethnicity [n (%)]	127 (46.8)	53 (33.7)	0.01
Hypertension [n (%)]	71 (26.2)	65 (41.4)	0.001
Dyslipidemia under statin treatment [n (%)]	48 (17.7)	58 (36.9)	<0.0001
Obesity [n (%)]	39 (14.4)	35 (22.3)	0.05
Diabetes mellitus [n (%)]	38 (14)	34 (21.7)	0.05
Atherothrombotic disease [n (%)]	12 (4.4)	12 (7.6)	0.24
Asthma [n (%)]	20 (7.4)	8 (5.1)	0.46
COPD and/or SAHS [n (%)]	13 (4.8)	19 (12.1)	0.01
Immunosuppression [n (%)]	20 (7.4)	24 (15.3)	0.01
Pregnancy [n (%)]	9 (3.3)	2 (1.3)	0.356
Active solid malignancy [n (%)]	4 (1.5)	13 (8.3)	0.001
Active or former smoking [n (%)]	43 (15.9)	46 (29.3)	0.001
Cough at admission [n (%)]	205 (75.6)	112 (71.3)	0.388
Dyspnea at admission [n (%)]	195 (72)	73 (69.5)	0.387
Fever at admission [n (%)]	139 (51.9)	70 (44.6)	0.175
Myalgia at admission [n (%)]	111 (41)	47 (29.9)	0.02
Diarrhea at admission [n (%)]	109 (40.2)	41 (26.1)	0.004
Myalgia and/or diarrhea at admission [n (%)]	172 (63.5)	72 (45.9)	0.0006
Impaired mental status at admission [n (%)]	7 (2.6)	8 (5.1)	0.344
NEWS at admission [median (IQR)]	5 (3–7)	6 (4–7)	0.144
Diffuse pneumonia at admission [n (%)]	233 (86)	135 (86)	0.854
Axillary temperature at day 0, °C [mean ± SD]	37.5 ± 1.0	37.5 ± 1.0	0.989
Respiratory rate at day 0, rpm [median (IQR)]	26 (20–30)	26 (22–30)	0.771
Heart rate at day 0, bpm [mean ± SD]	88.0 ± 17.9	88.2 ± 15.3	0.929
SpO_2/FiO_2 ratio at day 0 [median (IQR)]	288 (181–339)	175 (101– 258)	<0.0001
Leukocytes at day 0, x 10^9 cells/L [median (IQR)]	7.3 (5.4–10)	7.9 (6.2–12.2)	0.007
Lymphocytes at day 0, x 10^9 cells/L [median (IQR)]	0.8 (0.6–1.1)	0.6 (0.4–0.87)	0.344
Leukocyte-to-lymphocyte ratio at day 0 [median (IQR)]	9.2 (5.8–13.3)	12.4 (8.7–21.4)	<0.0001
ALT at day 0, IU/L [median (IQR)]	43 (28–71)	36 (23–58)	0.001
ALT at day 0,>100 IU/L [n (%)]	42 (15.5)	11 (7)	0.008
AST at day 0, IU/L [median (IQR)]	43 (30.5–59.5)	44 (31–60)	0.888
CRP at day 0, mg/dL [mean ± SD]	15.3 ± 8.9	18 ± 9.45	0.003
LDH at day 0, IU/L [median (IQR)]	409 (327–482)	481 (403–636.5)	<0.0001
Ferritin at day 0, ng/mL [median (IQR)]	1,479 (808–2,115)	1,662 (741–2,958)	0.062
Interleukin-6 at day 0, pg/mL [median (IQR)]	53 (16.7–116)	55 (18.7–251)	0.883
Bilateral alveolar infiltrates at day 0 [n (%)]	112 (41.3)	86 (54.8)	0.009
Interval from symptom onset to day 0, days [mean ± SD]	10.8 (4.6)	11.6 (6.1)	0.13
Interval from admission to day 0, days [mean ± SD]	2.9 (2.6)	4.9 (6)	<0.0001
Tocilizumab in the first 2 days of admission	271 (60.9)	157 (44.6)	0.001
Clinical status 4 or 5 at day 0 [n (%)]	97 (35.8)	118 (75.2)	<0.0001
Previous or concomitant therapy with remdesivir [n (%)]	8 (3)	8 (5.1)	0.4
Previous or concomitant therapy with HCQ [n (%)]	266 (98.2)	151 (96.2)	0.342
Previous or concomitant therapy with LPV/r [n (%)]	102 (37.6)	73 (46.5)	0.08
Previous or concomitant therapy with IFN-β [n (%)]	16 (9.5)	10 (9.5)	0.988
Previous or concomitant therapy with azithromycin [n (%)]	116 (57.2)	84 (53.5)	0.52
Previous or concomitant corticosteroid therapy [n (%)]	124 (45.8)	94 (59.9)	0.006

[a] Defined by hospital discharge and/or a decrease of ≥2 points from baseline (day 0) on the 6-point ordinal scale.ALT: alanine transaminase; AST: aspartate transaminase; bpm: beats per minute; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; HCQ: hydroxychloroquine; IFN-β: interferon-β; IQR: interquartile range; LDH: lactate dehydrogenase; LPV/r: lopinavir/ritonavir; NEWS: National Early Warning Score; rpm: respirations per minute; OR: odds ratio; SAHS: sleep apnea-hypopnea syndrome; SpO_2/FiO_2: SpO_2/FiO_2: pulse oximetry oxygen saturation/fraction of inspired oxygen.

pre-established criteria. All the patients presented bilateral infiltrates on chest x-ray or CT scan, elevated serum CRP levels, and respiratory deterioration, overall suggesting the hyperinflammatory phase of the disease. Aligned with most of the latest published RCTs (Rosas et al., 2021, Soin et al., 2021, Stone et al., 2020) we chose the clinical response defined as a reduction of at least 2 scale degrees on clinical status at day 14 after TCZ administration as the primary outcome, as it was deemed to be better explicative of the potential effect of TCZ and less biased than other frequently used variables such as all-cause mortality.

The first interesting finding of the current study was the identification of the early initiation of TCZ therapy as an independent predictor of better clinical response after adjustment by other variables potentially related to the prognosis of severe COVID-19. Patients beginning TCZ therapy within the first 48 hours of admission—as performed in more than half of our cohort—had a 2-fold increased probability of presenting an SCI by day +14, after adjustment by other prognostic factors in a multivariate model. Moreover, we observed a gradient in the rates of clinical response according to the time interval between admission and initiation of TCZ (**Figure 1**).

Since the beginning of the pandemic, early initiation of TCZ in patients with bilateral pneumonia has generally been advised and specifically recommended in most compassionate off-label protocols (Mikulska et al., 2020, Moreno Diaz et al., 2021) owing to the characteristics of the drug and the specific features of COVID-19 (McGonagle et al., 2020). Although a maximum interval of 48 hours from admission was considered as inclusion

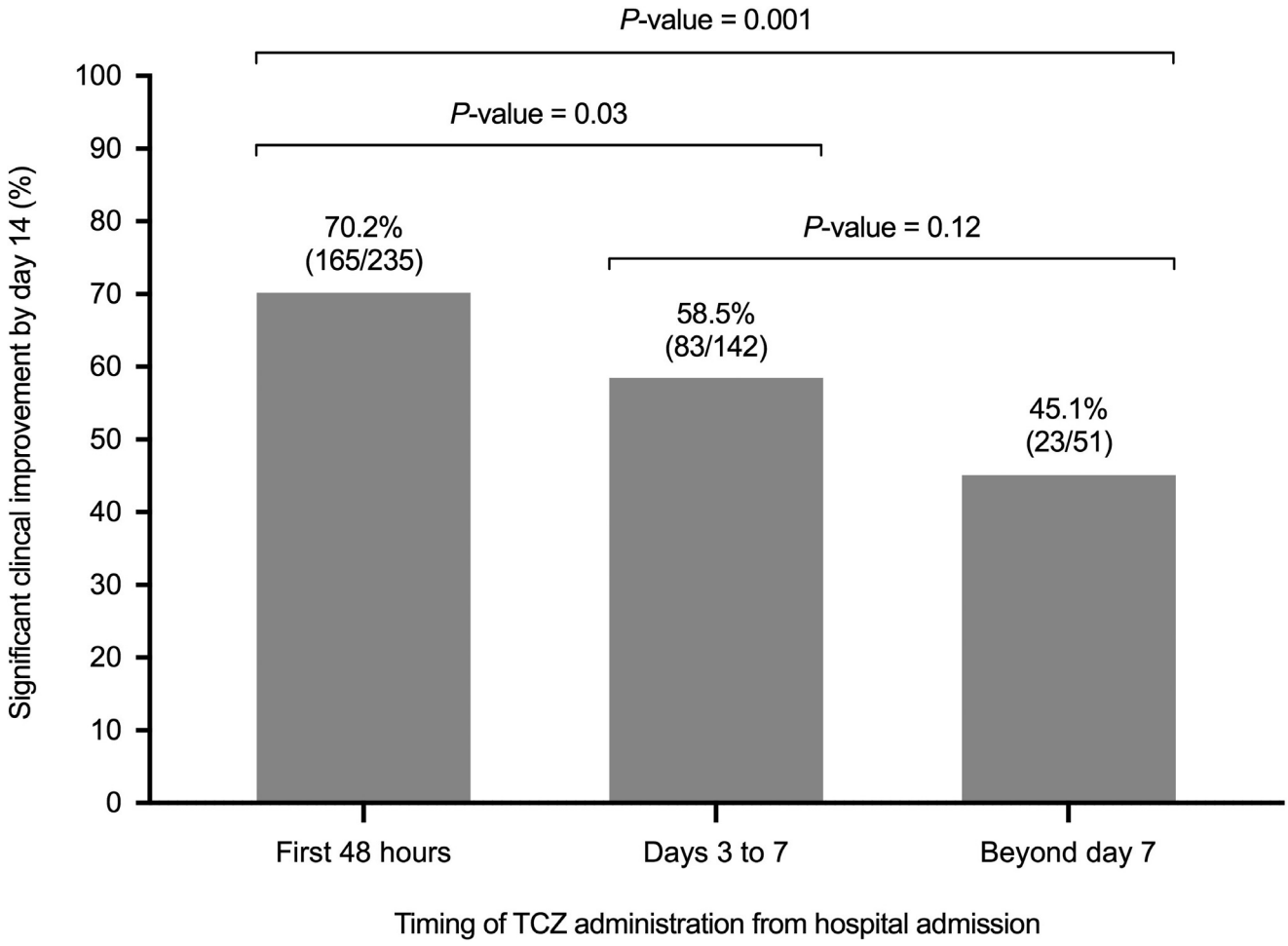

Figure 1. Rates of significant clinical improvement by day +14 according to the timing of TCZ administration.

Table 6
Univariate and multivariate analysis of factors related to significant clinical improvement by day +14 from the initiation of TZM therapy.

Variable	Univariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age, years	0.95[a]	0.93–0.97	<0.0001			
Non-caucasian ethnicity	1.73	1.15–2.6	0.008			
Hypertension	0.5	0.33–0.76	0.01			
Dyslipidemia under statin treatment	0.37	0.23–0.57	<0.0001	0.38	0.19–0.73	<0.0001
Obesity	0.58	0.35– 0.97	0.039			
Diabetes mellitus	0.59	0.35– 0.98	0.043			
COPD and/or SAHS	0.37	0.17– 0.76	0.007			
Immunosuppression	0.44	0.23–0.83	0.011			
Active solid malignancy	0.17	0.05–0.51	0.002	0.19	0.04–0.94	0.04
Active or former smoking	0.45	0.28–0.73	0.001			
Myalgia and/or diarrhea at admission	2.05	1.37–3.06	<0.0001			
SpO_2/FiO_2 ratio at day 0	1.01[a]	1.00–1.01	<0.0001	1.01[a]	1.00–1.00	<0.0001
Leukocyte-to-lymphocyte ratio at day 0	0.94[a]	0.91–0.96	<0.0001	0.94[a]	0.91–0.97	0.001
ALT at day 0 >100 IU/L	2.4	1.2–4.9	0.012	3.28	1.3–8.1	0.01
CRP at day 0, mg/dL	0.96[a]	0.94–0.99	0.004	0.97[a]	0.94–1.00	0.065
LDH at day 0, IU/L	0.99[a]	0.99–0.99	<0.0001	0.99[a]	0.99–0.99	0.013
Bilateral alveolar infiltrates at day 0	0.58	0.39–0.86	0.007			
Initiation of TCZ therapy within the first 48 hours from admission	1.93	1.3–2.9	0.001	1.98	1.1–3.55	0.02
Previous or concomitant corticosteroid therapy	0.56	0.38–0.84	0.005			

[a] Odds ratio per unitary increment.ALT: alanine transaminase; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; LDH: lactate dehydrogenase; OR: odds ratio; SAHS: sleep apnea-hypopnea syndrome; SpO_2/FiO_2: SpO_2/FiO_2: pulse oximetry oxygen saturation/fraction of inspired oxygen.

criteria in 1 particular RCT (Salama et al., 2021), no details on the recruitment windows were reported in most published trials (Snow et al., 2021). The impact of the timing of TCZ administration in the clinical response rates had not been accurately analyzed to date. In 2 previous reports, the potential prognostic benefit of early treatment with TCZ was suggested, although the limited sample included in these studies precluded from performing multivariate analyses to adequately confirm this finding (Martinez-Urbistondo et al., 2021; Moreno Diaz et al., 2021). A rational conclusion owing to the findings of the current study is that patients who reach criteria soon after hospital admission and are in the inflammatory phase may benefit more from TCZ administration. Therefore, we recommend a practical approach work-up including the early detection of patients with COVID-19 bilateral pneumonia fulfilling criteria of the hyperinflammatory stage of the disease at the emergency room with daily reevaluation to begin TCZ treatment before development of severe ARDS.

Unexpectedly, the finding of hypertransaminasemia (serum ALT levels >100 IU/L) at the time of treatment initiation was also found to act as an independent marker of subsequent response to TCZ. The explanation of this finding is not clear. The efficacy of TCZ is assumed to be more probable when administered in the hyperinflammatory state of COVID-19 (Rodriguez-Bano et al., 2021), and some experts consider liver inflammation as a complication owing to immune damage rather than direct viral cytopathic effect (Wu et al., 2021). We postulate that high ALT levels could potentially identify patients at the hyperinflammatory state of the disease. Previous use of statins was related to nearly a 3-fold risk of TCZ failure, which could be explained—in line to what has been shown in a particular study (Mitacchione et al., 2021)—by the potential role of this variable as a subrogate marker of underlying cardiovascular disease, conferring a higher risk of more severe COVID-19 disease.

The profile of patients with a favorable response to TCZ therapy in our study was also defined by the absence of major underlying diseases potentially related to a worse outcome, such as active malignancy or the presence of advanced disease with severe respiratory deterioration (as indicated by higher values of CRP or LDH and lower SpO2/FiO2 ratios) (**Table 6**). Such factors have been previously related to poor outcomes (Richardson et al., 2020; Wu et al., 2020; Zhou et al., 2020) and the efficacy of TCZ is lower in advanced stages of SARS-CoV-2-related ARDS (Moiseev et al., 2020). Age was not an independent risk factor for clinical failure in our cohort probably owing to the relatively young population included (only one-third were aged over 60 years).

Limitations

Some limitations of the current study deserve specific consideration. This is a single-center study including patients from the first wave of the COVID-19 pandemic in Madrid, which overwhelmed health resources and limited access to potentially effective therapeutic alternatives such as remdesivir that could have influenced the delayed access to hospital care. Therefore, extrapolation to other centers in different stages of the pandemic should be done with caution. In contrast to the timing from admission, the time interval between symptom onset and TZC administration was not found to have a significant influence on clinical response. A possible explanation of this apparent discrepancy could be the lower accuracy of the patient's precise self-reported calendar date for the initiation of symptoms compared with the more objective date of hospital admission. However, we believe that the beginning of the inflammatory phase of infection is more closely related to the time of worsening symptoms represented by the date of hospital admission. Because stringent criteria were applied to select candidates to receive TCZ therapy, the current cohort may not be representative of the entire COVID-19 population, particularly patients of older age who were underrepresented in the current cohort. Finally, although the large sample allowed us to perform a robust multivariate model to adequately adjust the main prognostic factors, we cannot rule out the impact of unmeasured confounding factors owing to the retrospective nature of the study and the absence of a control group precludes from addressing the potential effect of other administered treatments. In this regard, other limitations of the study include the heterogeneity in the doses and duration of patients receiving co-administration of corticosteroids that could influence therapeutic outcomes (Khiali and Entezari-Maleki, 2021), the changes in the treatment guidelines during the study period, and the effects of other therapies alongside corticosteroids in each group.

Conclusions

The results of this study support the early start of TCZ therapy in patients with severe COVID-19 and suggest incorporating a recruitment window of 48 hours from admission in future RCTs to optimize the efficacy of this therapy.

Appendix

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Conflicts of interest

All the authors declare no potential conflict of interest regarding this study.

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Ethical approval

The Clinical Research Ethics Committee approved the study protocol (CEIm no. 20/117) and granted a waiver of informed consent owing to the observational design.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.01.040.

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