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Original Article

Real-world experience with Tocilizumab for the treatment of COVID-19: a retrospective series of 314 patients

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Abstract

Background: In December 2019, a novel coronavirus, SARS-CoV-2, caused an outbreak of pneumonia that spread worldwide triggering the worst pandemic in recent history. Some patients with COVID-19 developed a hyperinflammatory syndrome resulting in acute respiratory distress syndrome with high mortality. We report our experience with tocilizumab (TCZ) for the treatment of patients with acute respiratory failure in the context of COVID-19 severe pneumonia. **Methods:** We performed a retrospective study including the patients treated with Tocilizumab from March 11 to April 30 2020 in HM Hospitals in Madrid, Spain. **Results:** We identified 314 patients treated with TCZ in our institution. The mean age was 64.9 ± 12.4 (24.1 - 91.4) and most patients were male (79.1%). One week after TCZ infusion, 75% of patients had improved in terms of oxygen intake and 25.6% did not need further oxygen therapy. Prior to TCZ administration, most patients had elevated levels of CRP, ferritin and D-Dimer. CRP levels rapidly ameliorated after TCZ infusion. Median D-Dimer increased after TCZ, more importantly in non-survivor patients. Median duration of hospitalization was 13.5 days (range 2-96; IQR 10-22). Seventy-two patients (22.9%) died. Sixty-four patients (20.4%) were admitted to the Intensive Care Unit (ICU), twenty-six of which died. **Conclusions:** Tocilizumab seems to be effective decreasing inflammation parameters, improving the respiratory condition and reducing mortality of severe patients. Randomized clinical trials will provide further data to evaluate the effectiveness of this promising therapy.

Introduction

In December 2019, an outbreak of pneumonia caused by a new coronavirus officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China [1]. This novel coronavirus disease (COVID-19) has caused a pandemic with great worldwide health and economic repercussions. The spectrum of COVID-19 ranges from mild, self-limiting disease of the respiratory tract to severe progressive pneumonia, acute respiratory distress syndrome (ARDS), septic shock, multiple organ failure, and death.

COVID-19 pathogenesis remains unclear and the optimal therapeutic approach is still uncertain. An excessive and prolonged cytokine response known as "cytokine storm" has been previously described in others highly pathogenic coronavirus such as SARS or MERS resulting in high morbidity and mortality [2]. Similarly, in severe patients (pts) infected with SARS-CoV-2, high levels of cytokines including IL-6, IL-2, IL-7, IL-10, granulocyte-colony stimulating factor, interferon-γ (IFN-γ)–inducible protein, monocyte chemoattractant protein, macrophage inflammatory protein 1α, and TNF-α have been observed [3]. IL-6 plays a pivotal role in acute inflammation and in cytokine release syndrome (CRS) [4,5]. Therefore, blocking the IL-6 pathway might be a potential key therapeutic strategy in patients with severe or critical COVID-19.

Tocilizumab (TCZ) is a recombinant humanized monoclonal antibody that targets both soluble and membrane-bound IL-6 receptors (IL-6R). It has been used in clinical practice for the treatment of rheumatoid arthritis [6] or in severe cytokine release syndrome induced by T-cell adoptive therapy [7].

This study aims to present our experience with tocilizumab for the treatment of patients with acute respiratory failure in the context of COVID-19 severe pneumonia.

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Methods

Study design and participants

We performed a retrospective study including the patients treated with TCZ from March 11 to April 30 2020 in HM Hospitals in Madrid, Spain. We collected retrospective data from the medical records including demographic data, clinical features, laboratory results, imaging studies, treatments and clinical outcomes. We analyzed respiratory status, inflammatory laboratory parameters and radiological findings before TCZ administration and then at day 3 and 7. This study was approved by the HM Hospitals Ethics Committee. Since medical files were retrospectively obtained and data were anonymously processed, the Ethics Committee approved this study without the need to obtain patient informed consent form signatures.

Statistical analysis

Continuous variables were tested for normality using Shapiro test and presented as mean ± standard deviation if normally distributed, or median (IQR) otherwise. Categorical variables were presented as n (%). We compared survivors versus non-survivors and ICU versus non-ICU patients using the T test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables and X2 test of Fisher's exact test for categorical variables. We used univariate and multivariate logistic regression to explore the risk factors associated with in-hospital death and with ICU entry. Univariate analyses were restricted to variables with p value < 0.2 for differences between group and that were measured before the beginning of Tocilizumab treatment. To avoid overfitting, multivariate analyses were limited to 7 and 6 variables for death and ICU entry models, respectively.

For the analysis of the evolution over time of variables with repeated measures we used the sign test and p values were adjusted for multiple comparison using the Benjamini & Hochberg method.

A two-sided α less than 0.05 was considered statistically significant. All statistical analyses were done using R (version 4.0.0).

Results

Demographic and clinical characteristics

From March 11 to April 30 2020 we identified 314 patients treated with TCZ in our institution. The characteristics of patients are summarized in Table 1. The mean age was 64.9 ± 12.4 (24.1 - 91.4) and most patients were male (79.1%). Among comorbidities, hypertension was the most frequent (38%), followed by diabetes (12%) and cardiovascular disease (7.6%).

The most common symptom was fever (262, 83.4%) followed by dyspnea (230, 73.2%) and cough (213 pts, 67.8%). Real time-PCR on nasopharyngeal swab was performed in 215 patients (68.2%). SARS-CoV-2 infection was confirmed in 175 patients (55.7%). The rest of the patients were treated without a RT-PCR confirmation as they had a clinical presentation highly suggestive of COVID-19 and the tests were unavailable (99 pts, 31.5%) or considered false negative by the clinician (40 pts, 12.8%).

Treatment

All patients received Tocilizumab. Median time between hospital admission and TCZ administration was 3 days (range 0-35). Most patients received a single dose of TCZ (191, 60.1%)

Table 1. Patients demographic characteristics, clinical presentation and treatments

Patients (n=314)		**n(%)**
Demographic characteristics		
Age (years)	Mean ± sd	64.9 ± 12.4 [24.1, 91.4]
Gender	Male	239 (76.1%)
	Female	75 (23.9%)
Cancer	Yes	16 (5.1%)
	No	298 (94.9%)
Diabetes Mellitus	Yes	38 (12.1%)
	No	276 (87.9%)
Hypertension	Yes	119 (37.9%)
	No	195 (62.1%)
Asthma	Yes	12 (3.8%)
	No	302 (96.2%)
Cardiovascular comorbidities	Yes	24 (7.6%)
	No	290 (92.4%)
IECA/ARAII previous treatment	Yes	81 (25.8%)
	No	233 (74.2%)
Chronic steroids treatment	Yes	4 (1.3%)
	No	310 (98.7%)
Symptoms		
Dyspnea	Yes	230 (73.2%)
	No	84 (26.8%)
Cough	Yes	213 (67.8%)
	No	101 (32.2%)
Fever	Yes	262 (83.4%)
	No	52 (16.6%)
Nausea	Yes	16 (5.1%)
	No	298 (94.9%)
Diarrhea	Yes	26 (8.3%)
	No	288 (91.7%)
COVID-19 treatment		
Tocilizumab	Yes	314 (100%)
Anticoagulation	Prophylactic dose	155 (51.2%)
	Therapeutic dose	148 (48.8%)
	N/A	11 (3.5%)
Antiretrovirals	Yes	230 (73.2%)
	No	84 (26.8%)
Hydroxychloroquine	Yes	311 (99%)
	No	3 (1%)
Antibiotics	Yes	305 (97.1%)
	No	9 (2.9%)
Interferon	Yes	42 (13.4%)
	No	272 (86.6%)
Corticosteroids	Yes	288 (91.7%)
	No	26 (8.3%)

*N/A= not available data.

Table 2. Predictive factors for death and for ICU admission at univariate and multivariate analysis.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Predictive factors for death				
Age	1.11 (1.07 - 1.14)	< 0.0001	1.09 (1.05 - 1.13)	< 0.0001
Female gender	0.57 (0.27 - 1.09)	0.10	0.31 (0.11 - 0.80)	0.021
Hypertension	2.76 (1.62 - 4.77)	0.0002	2.48 (1.20 - 5.26)	0.016
Asthma	2.49 (0.72 - 8.07)	0.13	4.25 (0.80 - 22.1)	0.082
High Oxygen need (> 5L) before TCZ	15.98 (4.81 - 99.09)	0.0002	6.84 (1.85 - 44.5)	0.013
CRP levels > 140 mg/L before TCZ	3.40 (1.87 - 6.47)	< 0.0001	2.91 (1.36 - 6.56)	0.0074
Predictive factors for ICU admission				
ACEI/ARB treatment before CO-VID-19	2.89 (1.61 - 5.16)	0.0003	3.20 (1.61 - 6.44)	0.00096
High Oxygen need (> 5L) before TCZ	13.8 (4.18 - 85.80)	0.00033	7.38 (2.11 - 46.80)	0.0078
D-Dimer levels > 1000 ng/mL before TCZ	2.87 (1.54 - 5.55)	0.0012	1.97 (0.98 - 4.06)	0.06
CRP levels > 140 mg/L before TCZ	2.23 (1.23 - 4.18)	0.0095	2.00 (0.97 - 4.29)	0.067

*TCZ: tocilizumab/ ACEI: angiotensin-converting enzyme inhibitor/ ARB: angiotensin receptor blocker

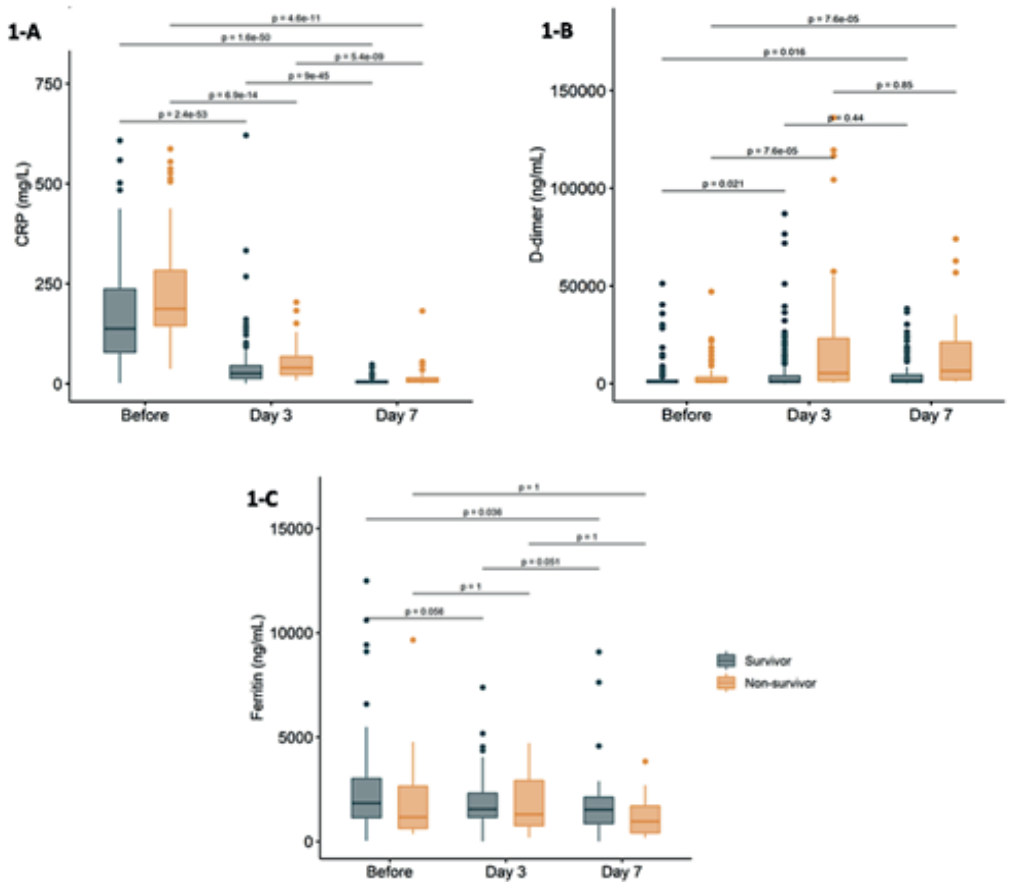

Figure 1. Laboratory parameters evolution before TCZ and at day 3 and 7 after TCZ in survivor and non-survivor subgroups. 1-A: CRP; 1-B: D-dimer; 1-C: ferritin.

whereas 96 patients (30.6%) received 2 doses and 19 patients (6.1%), 3 or more doses. Median administered dose was 600 mg (range 400-2400). 288 patients received concomitant corticosteroids (91.7%), 255 of them at high doses (≥1mg/kg). No significant difference in survival was observed in patients in whom corticosteroids were not administered (p=0.09). Other treatments are summarized in Table 1.

Respiratory and radiological evolution

Before TCZ administration, all patients had pneumonia with acute respiratory failure. Most patients had high requirements of oxygen defined as more than 5L supplemental oxygen (204 pts, 65%) and 25 patients (8%) were under mechanical ventilation.

At 48-72 hours after TCZ, 44.9% of patients showed clinical and respiratory improvement, 25.5% stabilized and 29.6% worsened. At seventh day, 75% of patients had improved in terms of oxygen intake and 25.6% did not need further oxygen therapy.

Radiological improvement was observed in 39.8% and 44% of patients at the third and seventh days, respectively.

Laboratory findings

Prior to TCZ administration, most patients had elevated levels of CRP, ferritin and D-Dimer. Median CRP levels were 157 mg/L (IQR 85 - 251) at baseline and rapidly ameliorated after Tocilizumab infusion, achieving almost all patients normal CRP levels at day seven (median 4, IQR 2 - 8) (Figure 1-A). Before TCZ, median D-Dimer level was 1030 ng/mL (IQR 600 - 1891) and increased at day 3 (median 1331, IQR 674 - 5244) and 7 (median 1709, IQR 862 - 5902). D-Dimer increased more strikingly in non-survivor patients (Figure 2-B). Median ferritin level was 1633 ng/mL (IQR 959 - 2894) at baseline and did not experienced significant changes after TCZ infusion (Figure 1-C), although ferritin data was missing in more than 70% of patients. Finally, IL-6 analysis was performed in 40 patients, being its median level 71 pg/mL (IQR 22 - 172) before TCZ and raising to 217 pg/mL (IQR 94 - 499) in the 6 patients in whom the test was repeated after 48-72 h.

Clinical outcomes

Median duration of hospitalization was 13.5 days (range 2-96; IQR 10-22). Seventy-two patients (22.9%) died. At multivariate analysis, older age, high oxygen requirement (more than 5L) before TCZ infusion and higher CRP levels before TCZ were identified as independent predictive factors for death. Female gender was a protective factor (Table 2).

Sixty-four patients (20.4%) were admitted to the Intensive Care Unit (ICU), twenty-six (40.6%) of which died. Previous treatment with some antihypertensives (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) and high oxygen requirement (more than 5L) before TCZ infusion were found to be independent risk factors for ICU admission at multivariate analysis (Table 2).

Discussion

In this study, we retrospectively present the experience of our institution after "off-label" use of tocilizumab in 314 patients with pneumonia and acute respiratory failure due to COVID-19.

Pneumonia and respiratory failure represent the main cause of death in SARS-CoV-2 infection and "cytokine storm" seems to play an important role in lung damage. Patients with increased plasma levels of IL-6 have also been reported at higher risk of death [8]. Therefore, IL-6R inhibitor tocilizumab aims to block this pathway decreasing hyperinflammatory syndrome, thus reducing severe and critical COVID-19 patients' mortality [9]. Our findings support the effectiveness of TCZ in this context.

Consistently with other studies [3,10,11], CRP levels were very increased in all patients before the start of TCZ and present a striking decline after treatment. There is no evidence of correlation between CRP decrease and clinical evolution. It is important to be cautious since the lack of CRP production could be a potential problem in the diagnose of concurrent infections [12]. In contrast to CRP, D-Dimer levels experienced an increase after TCZ infusion especially in patients with worse clinical evolution. This suggests that TCZ can act on the inflammatory cascade but has minimal effect on coagulopathy state. It has been described that after cytokine storm some patients experience severe endothelial dysfunction inducing thromboembolic complications or microangiopathy despite heparin prophylaxis which is associated with poor outcome [13]. IL-6 serum values were not available in most patients but we observed an increase after the TCZ infusion. Other studies have shown a trend to further spike and then decrease after starting the treatment because of the IL-6R blockade which led to IL-6 accumulation in serum [10].

In our series, most patients experienced a clinical improvement after TCZ treatment, with a rapid decrease in oxygen requirements in three-quarters of the patients. Fewer patients showed radiological improvement in the first week after TCZ. This could be explained because the lung damage needs some time to repair, which results in a delay in imaging recovery. Finally, our mortality rate was 22.9%. In previous studies, a mortality of 61.5% was reported for critical cases14 or 64.7% for patients who developed ARDS.15 Nevertheless, our population is more heterogeneous since we included patients in earlier stages of the disease. We have recently known preliminary results of COVACTA phase 3 randomized trial, which did not meet its primary endpoint of improved clinical status in patients with COVID-19 associated pneumonia, or the key secondary endpoint of reduced patient mortality.16 The final results of this trial are still pending. We hypothesize that an earlier treatment might be essential to better control clinical deterioration, as previously described.17, 18 We await the results of another randomized trial (NCT04356937) with an earlier administration of TCZ since patients under mechanical ventilation were excluded, in contrast to COVACTA trial.

In conclusion, in our series tocilizumab was associated with a decrease in inflammation parameters and clinical improvement in most patients. However, our results have several limitations since they stem from an uncontrolled retrospective study and significant bias could have existed. Ongoing randomized clinical trials will provide further data to evaluate the effectiveness of this promising therapy.

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