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Early use of tocilizumab in patients with severe pneumonia secondary to severe acute respiratory syndrome coronavirus 2 infection and poor prognostic criteria

Impact on mortality rate and intensive care unit admission

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2, keeps spreading globally. Evidence suggests that a subgroup of patients with severe symptomatology might have cytokine storms, which increases mortality. The use of interleukin-6 (IL-6) inhibitors may help in controlling the pathological immune response to the virus. Tocilizumab, a monoclonal antibody against IL-6, stands as an optional treatment for COVID-19 patients presenting this inflammatory hyper-response.

We conducted a retrospective, observational, cohort study including 50 patients affected by COVID-19 with severe pneumonia and poor prognosis criteria, who have also undergone standard treatment; 36 of these patients additionally received tocilizumab in an early stage. The need for intensive care unit (ICU) admission, mortality, recovery of respiratory function, and improvement of biochemical and hematological parameters were compared between cohorts.

Most patients were men, non-smokers and the most frequently reported comorbidities were hypertension and diabetes. Recurrent symptoms were fever, cough, and dyspnoea. 54.8% of patients from the tocilizumab group needed intubation, while in the control group 85.7% needed it. Treatment with tocilizumab significatively increased IL-6 levels, (554.45; CI 95% 186.69, 1032.93; $P < .05$) while C-reactive protein mean levels were reduced (–108.19; CI 95% –140.15, –75.33; $P < .05$), but no significant difference was found between cohorts. In comparison with the controls, tocilizumab reduced mortality (25.0% vs 42.9%, $P = .021$) and the number of ICU admissions (63.9% vs 100.0%, $P = .021$). 44.1% of patients treated with tocilizumab showed favorable radiological evolution, when compared with 15.4% of patients from the control group.

Tocilizumab may improve clinical symptoms and mitigate deterioration observed in severe COVID-19 patients, and could be considered as an effective therapeutic option in subjects experiencing a significant inflammatory response to the disease.

Abbreviations: COVID-19 = coronavirus disease 2019, CoVs = coronaviruses, ICU = intensive care unit, IL-6 = interleukin 6, SARS = severe acute respiratory syndrome, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, TCZ = tocilizumab.

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1. Introduction

Coronaviruses (CoVs) have co-evolved with their hosts, including human beings, for thousands of years. Until 2003, only 2 human CoVs were known to cause mild illness, like the common cold. However, outbreaks of severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) have changed the perception of how destructive and critical a CoV infection can be.[1,2]

A novel coronavirus disease (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China, in December 2019. It rapidly spread across continents and has become a world-wide public health challenge.[3] On January 30, 2020, WHO's International Health Regulations Emergency Committee triggered its highest global emergency alert by declaring COVID-19 a Public Health Emergency of International Concern. At the time, there were fewer than 100 cases and no deaths outside China. On March 11, 2020, WHO recognized it as a global pandemic. In Spain, as of December 15, 2020, there had been a reported total of 1,762,212 confirmed cases of COVID-19 and 48,401 deaths.[4]

Morbidity and mortality associated with COVID-19 are highest in the elderly and among people with comorbidities, which brings a huge burden to healthcare facilities.[5,6] According to a systematic review and meta-analysis, approximately 20% of COVID-19 patients with comorbidities required intensive care unit (ICU) admission and >13% of hospitalized patients had fatal outcomes,[6] with the mortality in critically ill patients reaching as high as 61.5%.[7] Thus, finding therapeutic approaches that could reduce the number of deaths is now of great importance. Like other viral respiratory pathogens, in most cases COVID-19 develops with a rapid progression of fever, cough, and dyspnoea, with leukopenia and the quick progress to acute respiratory distress syndrome (ARDS) being its key defining factors.[6]

From what we know so far, SARS-CoV-2 is seemingly less pathogenic but more transmissible than SARS-CoV and MERS-CoV. Most patients with COVID-19 remain asymptomatic or develop mild symptoms, which might contribute to its rapid transmission around the world,[1] but around 15% to 20% of those affected developed severe respiratory distress syndrome or septic shock.[5] These patients often need oxygen therapy and even assisted ventilation in the ICU. This novel virus spreads mainly through respiratory droplets and close contact. As the disease progresses, a number of complications tend to develop, especially in critically ill patients. Although there is no definitive data yet, advances are being made in the study of this disease, and data, both clinical and radiological, is gradually becoming available to identify patients of particular severity. The pathological findings obtained showed representative characteristics of ARDS and the involvement of multiple organs.[2]

As research moves forward, more data on the physiopathogenesis of COVID-19 is increasingly coming to light. Thus, we know of the existence of a first viral and respiratory phase, and of a second stage that is characterized by an inflammatory hyper-response, which is responsible for the poor evolution of patients in many cases. In fact, severe cases of COVID-19 are caused by an inter-inflammatory response that can lead to multiple organ failure and, in many cases, death.[8]

In this regard, cytokine storms mediated by the overproduction of pro-inflammatory cytokines have been observed in a large population of critically ill patients infected with COVID-19.[3,5] On a physiological and pathological level, cytokine release syndrome (CRS) is related to the activation of large numbers of immune cells and the massive release of inflammation mediators. Patients who suffer from CRS progress quickly to cardiovascular collapse, multiple organ dysfunction, and death.[9] Therefore, early identification, treatment, and prevention of cytokine storms are of crucial importance for the prognosis of these patients.

Among the excessive cytokines produced by activated macrophages, interleukin-6 (IL-6) is known as one of the key cytokines. Elevated levels of IL-6 in patients with COVID-19 were reported in several studies and were also correlated with a worse prognosis of the condition,[10–13] which means it could be used as a predictive biomarker of disease severity.[14] A large retrospective cohort study found that IL-6 levels correlated with mortality in patients with COVID-19.[15] Biologically, IL-6 is essential for the generation of T helper 17 (Th17) cells in the dendritic interaction between T cells,[16] therefore, excess of IL-6 may explain the over-activated Th17 cells observed in patients with COVID-19.[17] Taking all this into account, IL-6 may be an effective target for COVID-19 induced CRS. This clinical data could permit early action after the viral phase, helping to adopt measures aimed at controlling the cytokine storm in those patients in whom it is expected, and, thus, being able to prevent or control the unfavorable evolution of the disease.

Blocking the function of IL-6 with a monoclonal antibody against its receptor, for example, by using tocilizumab (TCZ), would help prevent the damaging inflammatory response in some cases of SARS-CoV-2 induced pneumonia.[5] This can prove to be useful in the initial treatment of patients with a risk of cytokine storms,[18] as it would block the IL-6 signal transduction pathway and could become a reliable alternative for the treatment of severe patients.[3,9,18–24]

As for the clinical criteria of poor prognosis, there is already a certain criteria that allows us to identify those serious patients who are most likely to need admission to ICUs. Since admission to ICU implies a high rate of mortality,[25] there is a major necessity to design treatment strategies or guidelines that favor a reduction in the percentage of hospitalized patients requiring to be treated in the ICU.

While current data regarding the effect of TCZ on the inflammatory activity of COVID-19 patients is very preliminary, it shows an improvement in clinical symptoms and a limitation of patients' deterioration,[3] and therefore warrants further studies in order to confirm its effectiveness.

In this context, the present study aims to determine the efficacy of TCZ as an early treatment of severe SARS-CoV-2-driven pneumonia in patients with poor prognosis, after the viral replication phase and prior to their admission to an ICU.

2. Methods

2.1. Study design

This is a multicentre, retrospective, observational, cohort study. One of the cohorts is made up of patients affected by COVID-19 with severe pneumonia and poor prognosis criteria who were treated using standard treatment (hydroxychloroquine, antivirals, and antibiotherapy). The other group included patients affected by COVID-19 with severe pneumonia and poor prognosis criteria, treated with standard treatment and in which the drug TCZ had also been used at an early stage. Information on participant's sociodemographic characteristics, risk factors, laboratory parameters, medication use, interventions, and clinical outcome was retrospectively assessed from clinical records. Difference in rates for ICU admission, death, recovery of respiratory function, and improvement of biochemical and hematological parameters are considered as study outcomes. The follow-up time of the subjects is from their admission to the hospital until the patients are discharged or they pass away.

2.2. Patients

Adult patients from the University Hospital of Jaén (Spain) and the Hospital Costa del Sol in Marbella (Málaga, Spain), diagnosed with COVID-19, with an oxygen saturation inferior to 92%, baseline process identified as a risk factor, and/or who met at least 3 analytical criteria for poor prognosis (abnormal levels of C-reactive protein, ferritin, D-dimer, IL-6, lymphocytes, and procalcitonin), were included in the study. Patients were not having respiratory distress or multiorganic failure by the time of admission to the hospital. Data from 36 COVID-19 patients treated with TCZ were analyzed. Data from 14 COVID-19 patients that did not receive TCZ was used as a control. For diagnosis, specimens were obtained via throat swabs under aseptic conditions and tested with the real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay. The admission date of these patients was from March 8, 2020 to April 16, 2020.

This study is subjected to the requirements of the Declaration of Helsinki[26] and the Spanish law on protection of patients' rights.[27]

The study was classified as EPA-OD by the Spanish Agency of Medicines and Medical Devices (AEMPS) on May 8, 2020 and was approved by the Ethics Committee for Research with medicinal products of the province of Jaén on May 18, 2020.

2.3. Treatment with tocilizumab

The use of TCZ for this type of patient was permitted by the Spanish Agency of Medicines and Medical Devices (AEMPS) on March 19, 2020, as an available treatment for the management of respiratory infection caused by SARS-CoV-2. It was included in a program for compassionate use, through the application of Medication Management in Special Situations, with specific indications.[28] Patients received a single dose of 400 mg if they weighed <75 kg, or 600 mg if they weighed ≥75 kg.

2.4. Statistical analysis

Continuous measurements are presented as mean ± standard deviation, and categorical variables as count (%). *t* Tests were used for comparison of quantitative variables between experimental groups (with adjustment for variance difference), and 95% confidence intervals for a single group. Chi-square tests were used for comparison of categorical variables between experimental groups, and tests of binomial proportions in the case of a single group. All *P* values are two-sided with a threshold of <.05 for statistical significance. The software used for data processing was Statistical Product and Service Solutions (SPSS) IBM v25.0 (IBM Corp., Armonk, N.Y., USA).

Table 1

Patients characteristics at baseline.

	Tocilizumab (n = 36)	Control (n = 14)
Age years (range)	60·9 ± 10·4 (36–84)	65·2 ± 10·2 (47–78)
Gender		
Male	31/36 (86·1%)	13/14 (92·9%)
Female	5/36 (13·9%)	1/14 (7·1%)
Number of smokers or ex-smokers	10/36 (27·8%)	6/14 (42·9%)
Chronic pathologies		
Hypertension	15/36 (41·7%)	10/14 (71·4%)
Diabetes	12/36 (33·3%)	6/14 (42·9%)
Coronary artery disease	2/36 (5·6%)	3/14 (21·4%)
Atrial fibrillation	2/36 (5·6%)	2/14 (14·3%)
Malignancy	5/36 (13·9%)	0/14 (0·0%)
COPD	2/36 (5·6%)	1/14 (7·1%)
Asthma	2/36 (5·6%)	1/14 (7·1%)
Symptoms		
Fever	32/36 (88·9%)	13/13 (100·0%)
Cough	30/36 (83·3%)	11/13 (84·6%)
Dyspnea	22/36 (61·1%)	10/13 (76·9%)
Arthromyalgia	14/36 (38·9%)	4/13 (30·8%)
Expectoration	5/36 (13·9%)	2/13 (15·4%)
CURB-65		
0	8/36 (22·2%)	0/13 (0·0%)
1	12/36 (33·3%)	3/13 (23·1%)
2	12/36 (33·3%)	6/13 (46·2%)
3	4/36 (11·1%)	3/13 (23·1%)
4	0/36 (0·0%)	1/13 (7·7%)
Bilateral pneumonia	35/36 (97·2%)	14/14 (100·0%)

COPD = chronic obstructive pulmonary disease.

3. Results

Overall, 50 patients with COVID-19 were included in this study and distributed in 2 cohorts, the experimental group included 36 patients treated with tocilizumab, while the control group consisted of 14 patients that did not receive this drug. The characteristics of patients are summarized in Table 1. The average age of the patients that received TCZ was 60.9 ± 10.4, and ranged from 36 to 84 years. In the control group, the mean age was 65.2 ± 10.2, and included patients between 47 and 78 years old. Of the 36 patients who were treated with TCZ, 31 were men (86.1%) and 5 women (13.9%), whereas in the control group, 13 were men (92.9%) and 1 was woman (7.1%) (Table 1). The statistical analysis confirmed the homogeneity of the 2 cohorts of patients. From the first group, 10 patients (27.8%) were smokers or ex-smokers, but most of them, 26 patients (72.2%), had never smoked. Similarly, in the control group 8 patients (57.1%) had never smoked. Only one patient from the TCZ group had no described comorbidities, and the most commonly reported ones in both groups were hypertension (41.7% vs 71.4%) and diabetes (33.3% vs 42.9%) (Table 1).

The most frequent symptom presented by patients from the TCZ group was fever (32/36, 88.9%), followed by cough (30/36,

83.3%), dyspnoea (22/36, 61.1%), arthromyalgia (14/36, 38.9%), and expectoration (5/36, 13.9%). Symptomatology in the control group had a similar distribution (Table 1). Thirty four (94.4%) patients from the TCZ cohort needed oxygen therapy or respiratory support of some kind, while all the patients in the control group required it. The average CURB-65 score was 1.33 in the patients that would be treated with TCZ and 2.15 for the patients in the control group. Bilateral pneumonia was present in all patients except for one in the TCZ group (Table 1).

Apart from TCZ, patients from both study cohorts would be treated with antivirals, corticoids, prophylactic, and therapeutic low-molecular-weight heparin, hydroxychloroquine, azithromycin, and ceftriaxone. Additionally, one patient was treated with remdesivir and another with anakinra. The use of corticoids in COVID-19 patients has been associated with increased mortality[29] but that information was not available at the time and only 2 patients in each group were treated with them.

Nine patients (25.0%) of the TCZ group had normal levels of oxygen saturation (≥95%) at the time of their hospital admission (mean, 88.1 ± 10.0), compared with the 2 patients (14.3%) of the control group (mean, 86.7 ± 6.9) (Table 2). Oxygen saturation levels were recovered in most patients after hospitalization (Fig. 1). On average, this recovery was maintained in patients treated with TCZ, with 21 patients achieving normal levels and only 2 with values under 90%. In the controls, this recovery was not sustained, and the mean level of oxygen saturation was reduced, with only 4 patients reaching normal levels before discharge or exitus.

After admission, 26 patients treated with TCZ and 6 controls were not receiving oxygen therapy. However, from the experimental group, only 2 patients prior to treatment and 1 patient after receiving the TCZ treatment did not need any kind of oxygen therapy or respiratory support. 54.8% patients from the TCZ cohort required intubation, whereas in the control group 85.7% required it (Table 2).

At admission, PaFi (PaO_2/FiO_2) levels were reduced in all patients who had it registered. One recovered to normal levels (≥300) during hospitalization and before starting the treatment with TCZ. PaFi levels improved slightly during that time but, in general, were reduced again after TCZ therapy (Fig. 1).

C-reactive protein (CRP) levels were above normal (<5 mg/L) at admission in 35 patients (mean, 148.8 ± 103.7) from the TCZ group and in all patients (mean, 241.3 ± 116.0) from the control group. CRP levels improved in both cohorts during hospitalization, but only patients treated with TCZ (7/36, 19.4%) reached normal rates (Table 2).

Lymphocytes count at the time of admission showed that 22 patients (22/36, 61.1%) had an abnormal value in the TCZ cohort (mean, 1.05 ± 0.49), with 8 patients (8/14, 57.1%) from the control group in the same situation (mean, 1.01 ± 0.62). Lymphocytes count decreased after TCZ treatment, as opposed to the increase observed in control patients, with 10 (27.8%) and 8 (88.9%) patients within the normal range, respectively (Table 2).

The median procalcitonin value at admission was 0.47 ± 1.52 (n = 28) in the TCZ group, with only 2 patients (7.1%) presenting a normal level, and 0.73 ± 0.82 (n = 10) in the control group, with none of those patients testing within the standard parameters (Table 2). After treatment with TCZ, even though only 2 patients had acceptable levels of procalcitonin, only 4 had levels higher than 5 ng/mL.

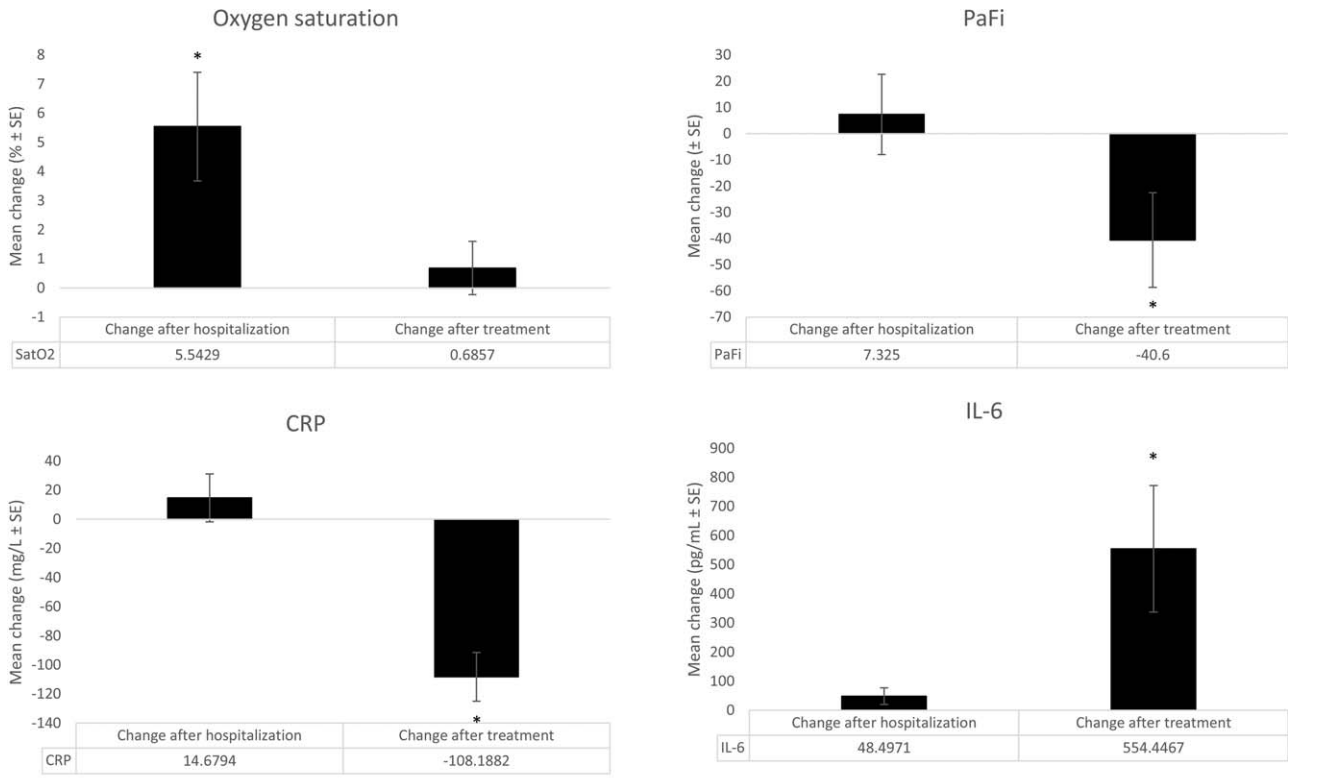
Pro-brain natriuretic peptide (Pro-BNP) levels were increased in most patients at the time of admission and they did not show

Table 2

Laboratory tests at different time points.

	Tocilizumab				Control			
	Admission	Before treatment	Δ*P* value (95% CI)	After treatment	Δ*P* value (95% CI)	Admission	After ICU admission	Discharge/Exitus
Oxygen saturation (%)	88.1 ± 10.0 (n = 36)	93.6 ± 4.0 (n = 35)	*P* < .05 (2.20, 9.71)	94.3 ± 3.3 (n = 36)	NS (−1.16, 2.43)	86.7 ± 6.9 (n = 14)	95.2 ± 4.6 (n = 13)	89.8 ± 10.7 (n = 10)
PaFi	140·7 ± 50·6 (n = 13)	182.5 ± 67.0 (n = 14)	NS (−24.54, 37.56)	133.1 ± 51.1 (n = 14)	*P* < .05 (−80.26, −8.20)	157.9 ± 46.4 (n = 6)	177.2 ± 60.9 (n = 11)	151.4 ± 130.7 (n = 5)
C-reactive protein, mg/L	148.8 ± 103.7 (n = 36)	167.5 ± 127.3 (n = 34)	NS (−20.29, 46.32)	61.8 ± 94.9 (n = 36)	*P* < .05 (−140.15, −75.33)	241.3 ± 116.0 (n = 14)	201.6 ± 100.6 (n = 14)	98.7 ± 111.7 (n = 9)
Procalcitonin, ng/mL	0.47 ± 1.52 (n = 28)	0.78 ± 1.73 (n = 28)	*P* < .05 (0.06, 0.84)	5.73 ± 20.09 (n = 30)	NS (−0.04, 15.81)	0.73 ± 0.82 (n = 10)	2.68 ± 5.20 (n = 14)	1.26 ± 1.62 (n = 9)
Ferritin, ng/dL	1863.1 ± 1541.2 (n = 20)	1850.2 ± 1637.0 (n = 22)	NS (−23.34, 686.84)	1719.0 ± 1688.1 (n = 22)	NS (−331.14, 106.50)	793.4 ± 398.6 (n = 5)	2569.5 ± 2708.9 (n = 2)	1132 (n = 1)
IL-6, pg/mL	222.9 ± 689.5 (n = 19)	333.2 ± 645.5 (n = 29)	NS (−2.14, 111.66)	883.7 ± 1197.2 (n = 26)	*P* < .05 (186.69, 1023.93)	217.7 ± 198.0 (n = 4)	98.5 ± 125.0 (n = 4)	183.6 ± 144.7 (n = 3)
Lymphocytes ($\times 10^3/\mu L$)	1.05 ± 0.49 (n = 36)	1.11 ± 1.65 (n = 34)	NS (−0.34, 0.61)	0.85 ± 0.48 (n = 36)	NS (−0.89, 0.18)	1.01 ± 0.62 (n = 14)	0.83 ± 0.39 (n = 14)	1.49 ± 0.54 (n = 9)
High-sensitivity troponin, ng/L	24.74 ± 30.29 (n = 14)	22.20 ± 27.35 (n = 23)	NS (−11.60, 5.03)	26.50 ± 35.30 (n = 27)	NS (−4.32, 11.00)	37.62 ± 31.89 (n = 6)	25.67 ± 27.27 (n = 11)	65.14 ± 91.77 (n = 9)
Pro-BNP, pg/mL	1107.6 ± 1537.2 (n = 5)	832.0 ± 829.2 (n = 15)	NS (−1173, 225)	752.8 ± 920.4 (n = 19)	NS (−349.64, 185.97)	379.5 ± 385.4 (n = 6)	824.9 ± 896.2 (n = 13)	1441.3 ± 2529.4 (n = 9)

BNP = brain natriuretic peptide, IL-6 = Interleukin 6, NS = not significant, PaFi = (PaO_2/FiO_2).



*p<0.05.
CRP, C-reactive protein; IL-6, Interleukin 6; PaFi, (PaO_2/FiO_2).

Figure 1. Change in oxygen saturation, PaFi, CRP, and IL-6 after hospitalization and after tocilizumab treatment. $^{*}P < .05$. CRP = C-reactive protein, IL-6 = interleukin 6, PaFi = (PaO_2/FiO_2).

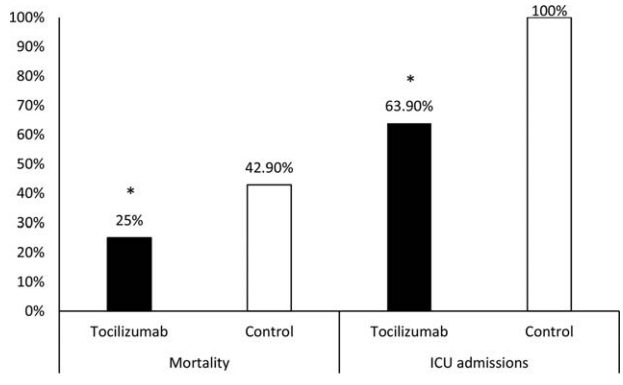
any significant variation after TCZ treatment. However, 6 patients out of 18 (33.3%) reduced their Pro-BNP levels to within the reference range.

High-sensitivity troponin values were stable for TCZ treated patients, with 9, 15, and 16 patients within acceptable levels at the admission, pre-treatment and post-treatment time points, respectively. In comparison, the troponin mean level was increased in the control group at the last time point, but the difference was not significant between cohorts, and 1, 5, and 4 patients had adequate values at the corresponding admission, pretreatment and posttreatment time points.

In addition, all patients who were analyzed for IL-6 levels presented increased values in both groups of patients (means, 222.9 ± 689.5, n = 19 in the TCZ group; 217.7 ± 198.0, n = 4 in the control group). As expected, IL-6 levels went up significatively in the cohort of patients treated with TCZ (554.45; CI 95% 186.69, 1032.93; $P < .05$) (Fig. 1) but not in the control group (Table 2). However, no significant differences could be found when both cohorts were compared.

Whereas all the patients (14/14) from the control group had to be treated in the ICU, only 63.9% of patients (23/36) receiving TCZ required admission ($P = .021$) (Fig. 2). At the time that the data for this study was gathered, 22 (61.1%) patients who had been treated with TCZ had been discharged, 2 (5.6%) were still in ICU, and 9 (25.0%) patients had died. Comparatively, in the control group, 3 (21.4%) patients had been released from the hospital, 3 (21.4%) were still in ICU, and 6 (42.9%) had died. Mortality difference between cohorts was statistically significant ($P = .021$) (Fig. 2). For patients treated with TCZ, the median duration of hospital stay was 21.61 days and 15.80 days in the ICU. This is similar to the 24.89 days of hospitalization and the 16.45 days of ICU for the control group patients (Table 3).

44.1% of patients treated with TCZ showed a favorable radiological evolution, in contrast to 15.4% of those from the control group. Meanwhile, 61.5% of the control patients had an



*p=0.021.

Figure 2. Percentages of mortality and ICU admissions. ICU = intensive care unit. $^{*}P = .021$.

Table 3

Time in hospitalization and ICU.

	Tocilizumab	Control	*P* value
Hospitalization days (range)	21.61 ± 10.31 (3–47) (n = 31)	24.89 ± 13.70 (6–43) (n = 9)	*P* = .021
ICU days (range)	15.80 ± 5.68 (5–39) (n = 20)	16.45 ± 12.04 (1–41) (n = 11)	*P* = .021

ICU = intensive care unit.

adverse radiological outcome. This is similar to the patients that received TCZ, of which 55.6% had this unpropitious result.

In the TCZ cohort, from the 11 patients that had serology done, 11 were positive for IgM and 9 for IgG, whereas in the control group, of the 6 subjects with serology, 5 were positive for IgM and all 6 for IgG.

4. Discussion

In this retrospective study, we evaluated the effect of tocilizumab, an IL-6 blocker, in a cohort of 36 patients affected by COVID-19 presenting severe pneumonia and poor prognosis, and compared their outcomes with a control group of 14 patients with the same characteristics who did not receive this medication. Our findings supported the effectiveness of TCZ in the prevention or treatment of cytokine storms induced by COVID-19. In the majority of cases, acute phase reactant levels were reduced, and the patients were reaching a stable condition reflected by a later progressive decrease of IL-6 after TCZ administration.

Similarly to what has been previously reported,[12] in our study more men than women needed admission into the hospital due to COVID-19. Furthermore, most of them had some chronic underlying conditions, mainly cardiovascular diseases or diabetes. Old age, obesity, and the presence of comorbidities might be associated with increased morbidity. All patients included in the study presented at least one of those characteristics.

As previously mentioned, COVID-19 is clinically manifested by fever, cough, and dyspnea,[6] which were common among the patients analyzed in this investigation. After the treatment with TCZ, symptomatology improved in most patients and, in line with what has been observed in similar retrospective studies,[3,30] oxygen saturation increased and remained stable. In addition, there was a consistent difference between the number of patients discharged in the TCZ cohort in comparison with the control group, and significatively, many of the subjects from the experimental cohort (12/22) did not need an ICU admission, as opposed to the control group. In fact, of the 11 patients receiving tocilizumab who were not admitted to the ICU, only one did not survive. Furthermore, a robust contrast in favor of TCZ therapy can be observed between both cohorts in terms of mortality (25.0% vs 42.9%, $P = .021$). Similar outcomes were observed in another retrospective case-control study, where the percentage of patients with TCZ that died and/or needed ICU admission was lower than that of the standard group.[31] Since only 2 patients from each group received corticoid treatment, it does not seem to have influenced these outcomes. Improvement of chest radiographic evidence was also more frequently seen in patients that were treated with TCZ than those who were not.

Although elevated CRP levels were reduced significatively (–108.19; CI 95% –140.15, –75.33; $P < .05$) (Fig. 1), similar to what was observed in the Chinese retrospective study,[3] a parallel reduction was also detected in control patients, questioning if this change is really caused by the TCZ therapy. Interestingly, more patients (4/30, 13.3%) had high levels of procalcitonin, which can be indicative of infection, after TCZ treatment than before treatment (2/28, 7.1%). TCZ therapy did not change the level of ferritin, even though it has been reported that it can be reduced in patients with rheumatoid arthritis.[32] However, the IL-6 level increase matches the elevated serum levels found in rheumatoid arthritis patients that were treated with TCZ, which is explained by the inhibition of IL-6 receptor consumption of IL-6.[33] In the study from Xu et al[3] around 50% of those studied returned to a normal lymphocytes percentage. The results presented here showed that only 10 patients (27.8%) had lymphocytes counts within an acceptable range after TCZ administration and the median value decreased, while this parameter was raised in the control group, indicating a better recovery of the immunologic system in TCZ patients. The median level of high-sensitivity troponin increased in the control group, but it was stable in the TCZ cohort. Something similar happened with the Pro-BNP levels.

In the current pandemic situation, this work provides some insights that can help to decide the therapy of COVID-19 patients and to design clinical trials to find better approaches for these patients.

This study may have some limitations, some of which are common to all retrospective, observational, cohort studies. The number of cases reported may be small, and could lack the statistical power to draw stronger conclusions. The relatively small sample size/data sets for some laboratory parameters are also a potential limitation and may hinder the interpretation of certain data. Also, as study data are collected retrospectively from clinical records, information bias is a possibility (as a result of incorrect or inexact recording). It was a single observational study, and a significant bias could have possibly existed. However, although our results should be evaluated with caution, we reported a good response in patients with TCZ, and, therefore, the data in this study permits an early assessment of the efficacy of TCZ in severe COVID-19 patients. Observation with a sufficient number of COVID-19 patients and randomized controlled trials are still needed to document the effectiveness of TCZ.

In summary, tocilizumab improves clinical symptoms and subdues deterioration observed in severe COVID-19 patients, enhancing the survival rate. In addition, since it decreases the need for ICU admissions, it may help reduce the workload in hospitals during an emergency situation. Therefore, tocilizumab, like other drugs that might also be useful against infection-induced cytokine storms, could be considered as an effective therapeutic option in severe COVID-19 patients who develop a significant inflammatory response to the disease.

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