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Tocilizumab in patients with severe COVID-19 pneumonia in Veracruz, Mexico

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Introduction

After the discovery of Sars Cov 2 a determining factor in the current pandemic called COVID-19 many have been the treatments that have been commented as promising antivirals have unfortunately not been effective so many others came to light in a compassionate way. With the subsequent knowledge of the virulence and pathogenicity of the virus as well as the severity of the symptoms generated by cytokine storm other drugs began to be used of which the IL-6 inhibitors stood out mainly tocilizumab (TCZ).[1,2]

The first beneficial reports on the use of tocilizumab were from small series of patients in which the usefulness as an anti-inflammatory was demonstrated as well as by reducing hospital stay admission to intensive care the need for vasopressors and the need for mechanical ventilation . Some studies showed a modest reduction in mortality and others in contrast a significant reduction in it. In patients hospitalized in the general ward and in intensive care they reported that the former had a 65% survival and the latter 74% with the use of the drug; 77% improved their respiratory condition and 61% showed radiological improvement after the TCZ infusion.[3–9]

In contrast some studies reported some adverse effects (sepsis and added infections) mainly related to the state of immunosuppression that continued after the use of TCZ. Similarly others reported high mortality after using the drug. As strategies to reduce the mentioned adverse effects the subcutaneous route and doses lower than those recommended were instituted.[10–14]

Finally and given the controversies meta-analyzes and systematic reviews came to light with more than 2790 patients analyzed which unfortunately and despite having clinical improvement and critical care parameters the impact on mortality is zero. Similarly a study by the same pharmaceutical company that sells TCZ mentioned that a global randomized double-blind phase III study (COVACTA) did not achieve its primary objective of improving the clinical status of patients with severe COVID-19 pneumonia nor the secondary objective which was to improve the mortality rate. It also reported an infection rate of 38.3% and serious infections of 21%.[15–19]

Material and methods

Descriptive and observational study in critically ill adult patients with data of systemic hyperinflammation and confirmed diagnosis of pneumonia due to COVID-19 by RT-PCR and pulmonary tomography with stay in the critical care unit of the General Hospital 71 of the Veracruz North delegation from the Mexican Social Security Institute who received tocilizumab from April to July 2020.

Results

Twenty patients were analyzed including 5 (25.0%) women and 15 (75.0%) men with a median age of 50.5years. Diabetes mellitus and systemic arterial hypertension were the most frequent comorbidities followed by obesity. (Table 1).

Table 1 Results of the measurement of variables in patients with a confirmed diagnosis of COVID-19 who received tocilizumab

Variable	Result n = 20
Demographic Variables	
Gender.	
Woman, n (%).	5 (25.0)
Man, n (%).	15 (75.0)
Age, years.	50.5 (42.0 – 58.7)

Table continue

Variable	Result n = 20
Previous comorbidities	
Diabetes mellitus, n (%).	7 (35.0)
Systemic arterial hypertension, n (%).	7 (35.0)
Obesity, n (%).	5 (25.0)
Heart disease, n (%).	2 (10.0)
Asthma, n (%).	1 (5.0)
COPD, n (%).	1 (5.0)
Rheumatoid arthritis, n (%).	1 (5.0)
Laboratory variables upon admission to ICU	
Leukocytes, cel/mm^3.	10,250.0 (5,400.0 – 13,275.0)
Lymphocytes, cel/mm^3.	860.0 (707.0 – 1,247.5)
Neutrophils, cel/mm^3.	8,545.0 (3,875.0 – 11,752.5)
Platelets, cel/mm^3.	172,000.0 (156,750.0 – 241,250.0)
Neutrophil-lymphocyte index	7.4 (5.0 – 11.7)
D-dimer, ng/mL.	1,086.0 (779.2 – 2,072.5)
Ferritin, ng/mL.	1,625.6 (1,015.0 – 1,990.0)
PaO_2/FiO_2	162.0 (110.0 – 183.0)
Variables of the clinical status at ICU admission.	
Days of evolution prior to admission to the ICU.	9.0 (7.0 – 11.0)
Organic disease	
Pulmonary failure, n (%).	19 (95.0)
Hematological failure, n (%).	4 (20.0)
Renal failure, n (%).	4 (20.0)
Neurological failure, n (%).	2 (10.0)
ARDS type	
Moderate, n (%).	16 (80)
Serious	4 (20)
Prone position, n (%)	20 (100.0)
Assisted mechanical ventilation, n(%)	12 (60.0)
Medications used prior to ICU	
Azithromycin, n (%).	17 (85.0)
Enoxaparin, n (%).	11 (55.0)
Oseltamivir, n (%).	10 (50.0)
Ivermectin, n (%).	5 (25.0)
Lopinavir, n (%).	3 (15.0)
Chloroquine, n (%).	2 (10.0)
Methylprednisolone, n (%).	1 (5.0)
No drug, n (%).	3 (15.0)
Tocilizumab, n (%)	20 (100.0)
Number of tocilizumab doses, n (%)	1 (85.0)
	2 (15.0)
Evolution day on which tocilizumab was administered.	11.0 (9.0 – 12.0)

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Table continue

Variable	Result n = 20
Image Variables (CO-RADS Categories) %	
Basal CT	
CO-RADS 1	1 (5.0)
CO-RADS 3	8 (40.0)
CO-RADS 4	7 (35.0)
CO-RADS 5	4 (20.0)
CT at ICU admission	
CO-RADS 6	20 (100.0)
CT at day 5 post TCZ	
CO-RADS 3	9 (45.0)
CO-RADS 4	9 (45.0)
CO-RADS 5	1 (5.0)
CO-RADS 6	1 (5.0)
Patients who had improvement in CO-RADS post TCZ	19 (95.0)
Outcomes	
Days of hospital stay	16.0 (15.0 – 18.7)
NIV patients who did not require AMV, n (%)	8 (40)
Patients with AMV who were successfully extubated	12 (60)
Deaths, n (%).	2 (10.0)

* Results expressed with medians and interquartile ranges (IQR 25 - 75), except when otherwise specified.

COPD, chronic obstructive pulmonary disease; INL, neutrophil lymphocyte index; ICU, intensive care unit; ARDS, acute respiratory distress syndrome. NIV, non-invasive ventilation; VMA, Assisted mechanical ventilation

Regarding the determination of laboratory tests upon admission to the ICU we found that the median of the leukocytes neutrophils and platelets were within normal parameters; however the lymphocytes had a median of 860 cel/mm^3. Additionally we found that the median neutrophil-lymphocyte index was 7.4 D-dimer was 1086ng/mL ferritin was 1625.6ng/mL and the PaO_2/FiO_2 index with a median of 162.

Concerning the severity we found that 95.0% of the patients had pulmonary failure hematological failure in 20.0% kidney failure in 20.0% and neurological failure in 10.0%. Furthermore 80% of the patients had moderate ARDS and 20% had severe ARDS; all patients remained in the prone position 60% received mechanical ventilation and 40% non-invasive ventilation.

Regarding the administration of tocilizumab 17 (85.0%) patients received one dose (15.0%) patients received two doses (8mg/kg/dose) and the median number of days of evolution from the onset of symptoms to the administration of tocilizumab was 11.0 (9.0 - 12.0) days.

Concerning to the chest tomography we found that in the baseline evaluation (24 - 48 h after the onset of symptoms) the most frequent imaging findings were compatible with CO-RADS 3 (40.0%) CO-RADS 4 (35.0%) CO-RADS 5 (20.0%) and CO-RADS 1 (5.0%). The tomography at ICU admission we found that all patients had CO-RADS 6. In the evaluation after the administration of TCZ 19 (95.0%) patients had a decrease in the CO-RADS category with respect to the CT of admission to ICU CO-RADS 3 and 4 were the most frequent (45.0% respectively); the remaining patients had CO-RADS 5 and 6 (5.0% respectively).

Regarding the quantified outcomes there were 2 (10%) patients who died. No adverse events were reported after drug administration.

Conclusion

In this series of cases clinical and tomographic improvement is reported as well as low mortality lower mechanical ventilation requirements and a higher rate of successful extubation. Randomized controlled studies are needed to define more precisely these results and a precise usefulness of the drug.

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