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FROM PUBLICATIONS TO EVERY DAY CLINICAL PRACTICE: TOCILIZUMAB IN PATIENTS WITH SEVERE COVID-19

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Abstract **Introduction**: there is evidence on the effectiveness and safety of tocilizumab (TZC) used in combination with systemic corticosteroids for severe SARS-CoV-2 pneumonia treatment. The purpose of this study was to describe epidemiological, clinical, and laboratory features as well as clinical outcome of patients receiving this combination therapy compared with those receiving only corticosteroids. **Methods**: a retrospective cohort study, which included adults with severe SARS-CoV-2 pneumonia, was conducted between March and August 2021. Enrolment included 101 patients, 46 with corticosteroids and 55 with corticosteroids plus tocilizumab. **Results**: median age was 58 years old and 63.9% were females. High blood pressure was present in 36.1% and obesity in 54.6%. Survival in the cohort was 81.4%, with a median hospital stay of 19.0 days. Secondary infections were present in 47.4% of the cohort. Patients in the TZC group had a lower C reactive protein (CRP) at discharge, lower rate of multiple organ failure, better functional status at discharge and shorter hospital stay. In a bivariate analysis, no differences were found in mortality rate and secondary infections occurrence. When assessing clinical status as per WHO Ordinal Scale there was a significant difference in its variability from worsening to discharge (or 14 days), evidencing a better functional status in patients receiving TCZ. **Discussion**: we were able to demonstrate its efficacy in reducing inflammatory biomarkers and a trend towards fewer days of hospitalization, with no impact on mortality.

Key words: tocilizumab, pneumonia, SARS-CoV-2, Covid-19

Resumen ***De las publicaciones a la práctica cotidiana: tocilizumab en pacientes con COVID-19 grave*** **Introducción**: existe evidencia sobre la efectividad y seguridad de tocilizumab (TZC) utilizado en combinación con corticosteroides sistémicos para el tratamiento de la neumonía grave por SARS-CoV-2. El propósito de este estudio fue describir las características epidemiológicas, clínicas y de laboratorio, así como el resultado clínico de los pacientes que recibieron esta terapia combinada en comparación con los que recibieron solo corticosteroides. **Métodos**: se realizó un estudio de cohorte retrospectivo, que incluyó adultos con neumonía grave por SARS-CoV-2, entre marzo y agosto de 2021. Se incluyeron 101 pacientes, 46 con corticosteroides y 55 con corticosteroides más tocilizumab. **Resultados**: la mediana de edad fue de 58 años y el 63.9% eran mujeres. La hipertensión arterial estuvo presente en el 36.1% y la obesidad en el 54.6%. La supervivencia en la cohorte fue del 81.4%, con una mediana de estancia hospitalaria de 19.0 días. Las infecciones secundarias estuvieron presentes en el 47.4% de la cohorte. Los pacientes del grupo TZC tenían valores menores de proteína C reactiva (PCR) al alta, una tasa más baja de insuficiencia multiorgánica, un mejor estado funcional al alta y una estancia hospitalaria más corta. En un análisis bivariado, no se encontraron diferencias en la tasa de mortalidad y la ocurrencia de infecciones secundarias. Al evaluar el estado clínico según la Escala Ordinal de la OMS hubo una diferencia significativa en su variabilidad desde el empeoramiento hasta el alta (o 14 días), evidenciando un mejor estado funcional en los que recibieron TCZ. **Discusión**: pudimos demostrar su eficacia en la reducción de biomarcadores inflamatorios y una tendencia a menos días de hospitalización, sin impacto en la mortalidad.

Palabras clave: tocilizumab, neumonía, SARS-CoV-2, Covid-19

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KEY POINTS

- The safety and effectiveness of combination therapy with tocilizumab and corticosteroids in severe SARS-CoV-2 pneumonia is known.
- In this cohort tocilizumab showed an adequate safety profile.
- Its efficacy in decreasing inflammation parameters has been demonstrated, although decreased in mortality doesn't seem to be as effective.

SARS-CoV-2 infection has a wide variety of clinical presentations as well as systemic involvement; respiratory failure being the most severe one. Respiratory distress syndrome is the main cause of mortality, and massive release of pro-inflammatory cytokines may contribute to poor prognosis[1].

In Argentina, since March 2021, an increase in coronavirus infection, which continued until end of August, has been observed, with peaks of approximately 40 000 daily cases by end of May[2]. This increase in COVID cases resulted in a larger number of severe cases and deaths, as well as a high occupancy rate at Intensive Care Units.

Until that moment, standard of care (SOC) for patients with severe or critical infection (WHO Severity Ordinal Scale, category 6-7)[3] included oxygen support (non-rebreather mask, high flow nasal oxygen [HFNO] or invasive ventilation [IMV]), thromboembolic prophylaxis and 6 mg of systemic dexamethasone (oral or intravenous)[4, 5].

The RECOVERY[6] and REMAP-CAP 5[7] studies demonstrated that using tocilizumab (TCZ) in combination with systemic corticosteroids decreased mortality in people with SARS-CoV-2 pneumonia with high oxygen requirements.

Based on these publications, United States' National Institutes of Health (NIH)[8] and Infectious Diseases Society of America (IDSA)[9] made recommendations for its use.

In May 2021, Argentina's Health's Ministry published a TCS assessment report, which concluded that its use may potentially decrease mortality and need for invasive mechanical ventilation (IMV) in patients with severe COVID-19[10].

This study intended to investigate about the clinical and laboratory features, potential impact on mortality, occurrence of secondary infections and clinical outcome as per WHO Ordinal Scale at discharge (or at 14 days, whichever occurs first).

Materials and methods

Between March and August 2021, an observational and analytical study of a retrospective cohort of adult patients with severe or critical SARS-CoV2 pneumonia (WHO Ordinal Scale[3] categories 6 and 7) hospitalized at Sanatorio Finochietto was conducted. Patients were classified according to whether they received standard of care (SOC) treatment (dexamethasone 8 mg or equivalent plus oxygen therapy, high flow nasal oxygen [HFNO] or IMV) or SOC plus TCZ (8 mg/kg, single dose).

TCZ was administered based on the following criteria:

- SARS-CoV2 pneumonia confirmed by PCR.
- requirement of being hospitalized and requiring oxygen by non-rebreather mask, high flow nasal oxygen or invasive mechanical ventilation.
- corticosteroid treatment for at least 24 hours prior to clinical worsenig (dexamethasone, at least 8 mg daily or equivalent).
- rapidly progressive clinical worsening (requiring more than 5 L/min of high flow nasal oxygen or non-rebreather mask).
- plus any of the following factors: increasing CRP or a total value of more than 75 mg/dL, 60 years or older, diabetes, chronic obstructive pulmonary disease, high blood pressure, obesity.

The following were considered contraindications for use:

- neutropenia (neutrophils less than 1000/mm^3),
- liver enzymes (ALT/TGP: glutamic pyruvic transaminase and AST/TGO: glutamic-oxaloacetic transaminase) at least five times the normal value,
- severe immunosuppression (oncological disease receiving chemotherapy treatment, patients with solid organ or bone marrow transplant) and/or
- suspected or confirmed secondary infection (bacterial or fungal) at time of clinical worsening.

Sanatorio Finochietto, in Buenos Aires City, Argentina, is a Level 3 health center that provides health care services for prevalent clinical and surgical conditions present. This institution has an Emergency Department, Maternity Ward, General Ward and Intensive Care Unit, with a total of 180 beds; electronic clinical records and high-complexity complementary services.

Treatment protocol was approved by Sanatorio Finochietto's Ethics Committee under Number 5489 and registered in ClinicalTrials.gov (No. NCT05057962).

Statistical analysis

In the descriptive analysis, quantitative data is expressed as median and interquartile range (IQR) 25-75. Qualitative data is expressed as absolute frequency and relative percentage. Chi^2 method or Fisher test were used to compare groups. For comparison between measures in each treatment group Wilcoxon signed rank test was used.

Multiple organ failure was analyzed using logistic regression. Multiple logistic regression incorporating all significant baseline variables was used to derive a propensity score or the predicted probability that an individual patient belonged to each treatment group. The propensity score included: age, obesity, arterial hypertension, CRP worsening and HFNO. Comparisons between groups regarding outcome variables was then performed adjusted for significant baseline variables and propensity score in multivariable regression analysis. The percent variation in the WHO Ordinal Scale was analyzed using lineal regression. Significant level was set less of 5% and software R was used for analysis.

This study was conducted following national and international regulatory standards on research on human subjects; and following Health Ministry Resolutions, Helsinki Declaration including all its amendments and Clinical Practice Guidelines (ICH E6). All study data was collected from electronic clinical records and was managed following high confidentiality standards, and anonymously, with restricted access and only for study purposes as per the current legislation on National Personal Data Protection Laws (Habeas Data Law) and Law 26529/09 of Argentine Republic. The study was approved by Sanatorio Finochietto's Independent Ethics Committee.

Results

During the analyzed period, 101 patients with severe or critical SARS-CoV-2 pneumonia were hospitalized. Of these patients, 45.5% (n = 46) (Ci95% 35.6-55.7) received SOC and 54.5% (n = 55) (Ci95% 44.2-64.4) SOC plus TCZ. Of the latter, 92.7% (n = 51) were analyzed and 7.3% (n = 4) were excluded due to missing data as they were transferred to other health care centers. On admission, patients had median values of 6.00 [6.0-7.0] on WHO Ordinal Scale, 119.0 mg/dL [65.0-171.0] on CRP, 1661.0 ng/mL [931.0-2644.0] on ferritin and 0.30 ug/mL [0.23-0.45] on D-dimer. High flow nasal oxygen (HFNO) was required by 59.8% (58) (Ci95% 49.3-69.2) of patients as only treatment or prior to invasive mechanical ventilation, which was necessary in 55.7% (54) (Ci95% 45.2-65.7) of the cases. Patients received systemic dexamethasone 8 mg for a median of 13.0 days [10.0-17.0].

Shock, requiring vasoactive drugs for more than 24 hours, was present in 28.1% (27) (Ci95% 19.2-37.8) of patients, and 18% (18) (Ci95% 11.3-27.7) had multiple organ failure.

Survival rate was 81.4% (83) (Ci95% 76.9-91.8); with a median hospital stay of 19.00 days [13.0-28.0].

There were similar features between both groups (asthma, COPD, diabetes, arterial hypertension, coronary artery disease, heart failure, cancer, HIV) and some differences (age and obesity). Severity at time of admission, APACHE II score and WHO Ordinal Scale were similar in both groups, as well as ferritin and D-dimer values. CRP values were different in both groups, although this difference could be related to criteria for TCZ indication (CRP >75 mg/dL). All data is shown in Table 1.

TABLE 1.– Comparison of demographic, comorbidities, ventilatory, biochemical parameters and outcomes in patients based on whether they received tocilizumab treatment or not

Characteristics	No TCZ n = 46	TCZ n = 51	p
Age[1]	62.0 (49.2-68.7)	53.0 (42.0-63.0)	0.012
Female[2]	25 (54.3)	37 (72.5)	0.098
BMI[1]	32.4 (31.3-32.5]	28.5 (26.7-29.1)	< 0.001
Comorbidities			
Asthma[2]	3 (6.5)	3 (5.9)	0.999
COPD[2]	5 (10.9)	3 (5.9)	0.602
DBT[2]	9 (19.6)	10 (19.6)	0.999
High blood pressure[2]	21 (45.7)	14 (27.5)	0.098
Obesity[2]	43 (93.5)	10 (19.6)	< 0.001
Apache II[1]	10.0 (6.0-12.5)	8.0 (6.0-10.0)	0.132
Coronary heart disease[2]	5 (10.9)	2 (3.9)	0.251
Heart Failure[2]	1 (2.2)	0 (0.0)	0.474
Solid tumor[2]	5 (10.9)	2 (3.9)	0.251
Onco-haematology disease[2]	1 (2.2)	0 (0.0)	0.474
HIV[2]	2 (4.3)	0 (0.0)	0.222
N° of corticosteroid days[1]	13.0 (11.0-16.5)	13.0 (10.0-17.5)	0.814
Methylprednisolone[2]	0 (0.0)	4 (7.8)	0.119
Ventilatory parameters			
IVM[2]	29 (63.0)	25 (49.0)	0.237
IVM days[1¥]	11.0 (2.5- 22.7)	14.0 (9.0-28.0)	0.128
HNF[2]	21 (45.7)	37 (72.5)	0.013
HFN days[1†]	1.0 (0.00-3.0)	3.0 (1.0- 4.0)	0.015
Biochemical parameters			
Ferritin ng.mL[1]	1660.5 (961.2-2818.5)	1674.0 (855.0-2374.0)	0.646
D Dimer ug/mL[1]	0.3 (0.2-0.5)	0.3 (0.2-0.4)	0.680
CRP at admission mg/dLl[1]	77.3 (42.2-131.2)	147.8 (107.0-180.3)	< 0.001
CRP at discharge or death mg/dL[1]	19.4 (9.1-165.6)	3.5 (1.4-19.4)	< 0.001
WHO score[1]			
Admission WHO Score[1]	6.0 (6.0-7.0)	6.0 (6.0-6.0)	0.575
WHO score worsening or discharge[1]	6.50 [2.50, 7.00]	1.00 [1.00, 7.00]	0.004
Change in WHO score[1]	0.0 (-3.7-1.0)	-5.0 (-5.0-0.0)	0.002

TZC: tocilizumab; BMI: body mass index; DBT: diabetes; COPD: chronic obstructive pulmonary disease; HIV: human inmunodeficiency virus; IMV: invasive mechanical ventilation; HNF: high nasal flow oxygen; CRP: C reactive protein; WHO: World Health Organization

[1]*Median (interquartile range)*

[2]*Absolute frequency (relative frequency in %)*

TCZ was administered in 52.6% (51) (Ci95% 42.2-62.8) of cases as a single 800 mg [600.0-800.0] dose within 24 hours of clinical worsening, and with an average time of administration of 10.0 days [9.0, 11.5] from symptom onset. None of these had to be discontinued due to acute adverse effects during infusion. The 15.6% (Ci 95% 7.0-28.5) 8/51 of patients had side effects in the following days (48 hours or 7 days, increased liver enzymes at least five times the normal value with no liver failure). Neutropenia was not observed in any case.

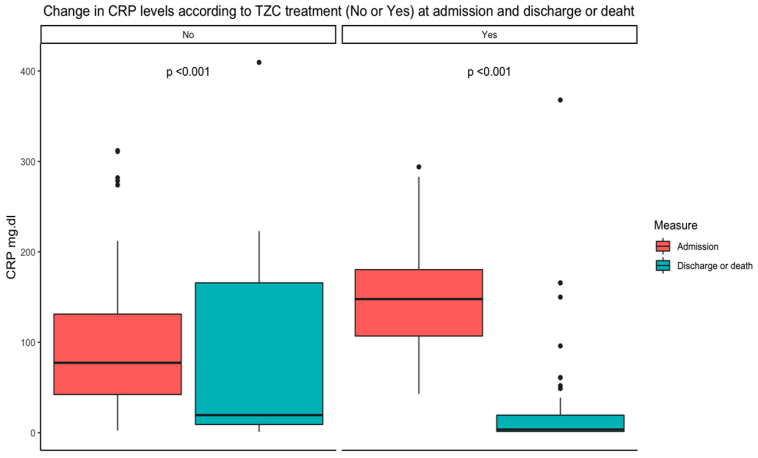
Patients in the TZC group had a lower CRP value at discharge with a higher delta from time of worsening to discharge (Fig. 1), lower rate of multiple organ failure, better functional status at discharge and shorter hospitalization period.

Bivariate analysis of primary objective showed no differences in mortality rate and secondary infection occurrence. When assessing clinical status as per WHO Ordinal Scale there was a significant difference in its variability from worsening to discharge (or 14 days), evidencing better functional status in patients receiving TCZ (Fig. 2).

Regarding secondary objectives, there were no difference on mechanical ventilation days or shock occurrence. Data about primary and secondary objectives are shown in Table 2.

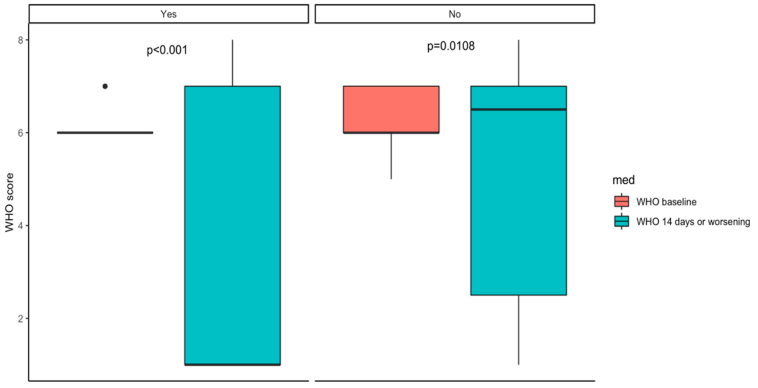
Multivariate analysis showed no differences in multiple organ failure and TZC treatment after adjustment by HFNO and propensity score (odds ratio 2.81 Ci 95% 0.62-14.62 p = 0.196). There were no differences in WHO Ordinal Scale score variation after adjusted for obesity, high blood

Fig. 1.– Change in C Reactive Protein level based on tocilizumab treatment (No or Yes) on admission and at discharge or death



CRP: C reactive protein; TZC: tocilizumab
TCZ NO: CRP admission: 77.3 (IQR 42.2-131.2); CRP discharge or death: 19.4 (IQR 9.1-165.6)
TCZ Yes: CRP admission: 147.8 (IQR 107.0-180.3); CRP discharge or death: 3.5 (1.4-19.4)
p values compare measures in each group or treatment

Fig. 2.– Change in WHO Ordinal Scale based on tocilizumab treatment on admission and at discharge or death



TZC: tocilizumab; WHO: World Health Organization
TCZ Yes: WHO score at baseline (admission) 6.0 (6.0- 7.0); WHO 14 days or worsening: 1.0 (IQR 1.0-7.0)
TCZ NO: WHO score at baseline (admission) 6.0 (IQR 6.0-7.0); WHO 14 days or worsening: 6.50 (IQR 2.5-7.0)

pleasure, CRP on admission and HFNO (beta -1.20 Ci95% -2.76-0.23 p = 0.096) neither.

About half of the patients (47.4%-n: 46) presented secondary infections, but no significant differences were found between both groups (SOC 50.0% (23) vs. SOC + TZC 45.1% (23) (Ci95%31.1-59.6, p: 0.78) (Fig. 3).

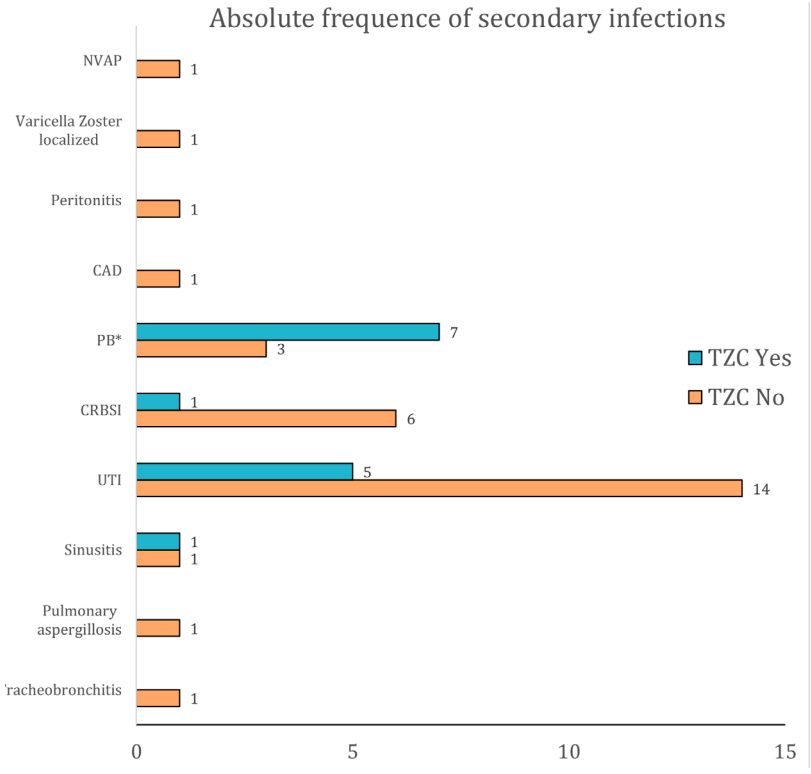
When classifying infections by type of event and comparing them between groups, there were no differences in early-and late-onset ventilator-associated pneumonia (Fig. 4), but there was higher incidence of urinary tract infections and catheter-related infections in SOC group, and of primary bacteremia in SOC + TCZ group.

TABLE 2.– Comparison of outcomes in patients based on whether they received tocilizumab treatment or not

Outcomes	No TCZ n = 46	TCZ n = 51	p
Secondary infections[2]	23 (50.0)	23 (45.1)	0.780
Length of stay[1]	19.5 (13.0-29.5)	17.0 (13.0- 27.0)	0.654
Convalescence plasma[2]	46 (100.0)	50 (98.0)	0.999
Shock[2]	17 (37.0)	10 (20.0)	0.074
Multiple organ failure[2]	13 (28.3)	5 (9.8)	0.038
Death[2]	12 (26.1)	6 (11.8)	0.121

[1]*Median (interquartile range)*
[2]*Absolute frequency (relative frequency in %)*

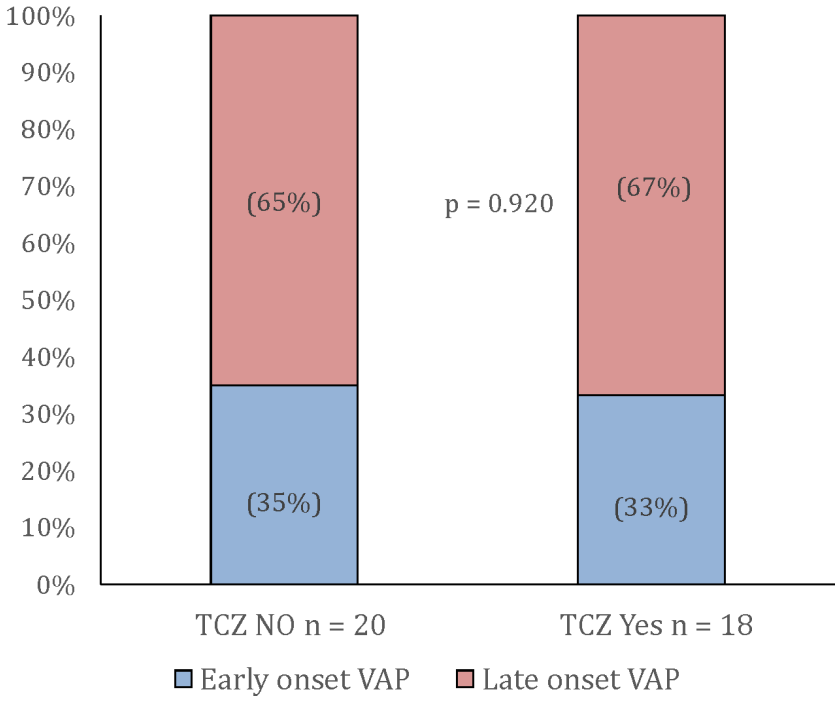
Fig. 3.– Secondary Infections (except ventilator associated pneumonia). Comparison between patients based on whether they received tocilizumab treatment or not



PB: primary bacteriemia*; CRBSI: catheter related blood stream infection.; UTI: urinary tract Infection; CAD: clostridium associated diarrhea; NVAP: non-ventilator associated pneumonia; UTI: urinary tract infection; TZC: tocilizumab; VAP: ventilated associated pneumonia

**Significant difference between treatment groups p = 0.002*

Fig. 4.– Early and late-onset ventilator associated pneumonia. Comparison between patients based on whether they received tocilizumab treatment or not



VAP: ventilated associated pneumonia; TZC: tocilizumab

Discussion

This study is the continuation of our recent report on our initial experience using TZC in 30 patients hospitalized due to severe or critical SARS-CoV-2 pneumonia[11].

Regardless of the treatment administered, in this cohort we observed a lower mortality compared with prior publications in Argentina[12]. This could be related to better knowledge and experience gained in the management of these patients. Locally, this might also be related to the fact that patients involved in the second wave in our country were younger, but it does not seem to be related to tocilizumab use.

Patients that received TZC in the analyzed period did not present any of the most frequently reported adverse effects (reaction during administration, neutropenia or liver toxicity); confirming its safety profile.

In hospitalized patients with severe COVID, variable rates (3.7 up to 43%) of secondary infections have been reported. The impact of using immunosuppressive or immunomodulatory drugs in their occurrence is under discussion. Several controlled trials demonstrated that the number of infections was not higher with its use[13]. Secondary infections in our cohort are closer to the upper levels of these values.

A recently published multicenter retrospective cohort report[14], described a higher probability of bacteremia when using the combination of corticosteroids plus tocilizumab [OR 2.13, 95% CI 1.2–4.05, p-value 0.0217]. In a similar way, our combination therapy group (dexamethasone plus TCZ) presented a higher incidence of primary bacteremia. This doesn't seem to be a prognostic factor since it was not associated with an increase in multiple organ failure, shock or mortality. Regarding other kinds of infections, ventilator-associated pneumonia rate was similar in both groups; and we did not find an association between tocilizumab and developing fungal, viral or other multidrug-resistant germ infections.

Secondary infections do not seem to be a worse prognostic factor; mortality was not affected by the presence of secondary infections and remained relatively low when compared to averages in our country, and in international reports[15].

CRP values were significantly higher in the group receiving TCZ. This was expected since having a CRP value over 75 mg/dL was an eligibility criterion. There is a clear evidence of Its activity as moderator of the hyper inflammatory response since, in spite of having initial higher levels, the values of this biomarker at time of discharge were significantly lower in the combination therapy group, with a delta between time of clinical worsening and discharge, favoring the latter.

Regarding severity, both groups were similar as its shown in Apache II and WHO Ordinal Scale values at time of worsening. As previously mentioned, TCZ group had a lower average age and BMI.

In a bivariate analysis, we found a difference in development of multiple organ failure and condition at discharge, favoring combination therapy group, with an important improvement in WHO Ordinal Scale score. When performing a multimodal analysis with these mentioned variables, this apparent protective effect disappears, reflecting what is well described in the literature about age and obesity being poor prognostic factors for patients with severe SARS-CoV-2 pneumonia[16-20].

In May and June, due to sustained high number of cases, prolonged hospitalizations and limited resources, Intensive Care Unit occupancy rate was 90% at national level[21]. In this context, number of hospital stay days were also a factor to be considered. In combination therapy group we observed an average of 2.5 less days of hospitalization.

This study has limitations, the most important ones, being those related to the retrospective and observational cohort design and that the number of patients included in the analysis, may be little to draw solid conclusions. However, we believe it adds information on the use of tocilizumab and raises the question on whether its use is equally effective in our setting to that reported in other case series. In order to answer this question, it would have been interesting to propose a prospective cohort, which was not possible in that epidemiological setting.

In conclusion, the use of tocilizumab in combination with systemic corticosteroids is considered a safe and efficacious therapy to treat severe or critical SARS-CoV-2 pneumonia.

In our cohort, adding a single dose (8 mg/kg) of tocilizumab to systemic corticosteroids in patients with severe or critical SARS-CoV-2 pneumonia seems to maintain that described safety profile. However, we were able to demonstrate its efficacy only in decreasing inflammation biomarkers and a tendency to fewer hospital stay days; with no impact on mortality or clinical outcome. This raises the question of the cost-benefit of its use in our setting.

Conflict of interests: None to declare

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Simply gathering data without having any specific question in mind is an approach to science that many people are doubtful about. Modern science is supposed to be mostly 'hypothesis driven' –you have a hunch about how the world works, and do experiments that ask if your hunch is right. If it is, you can make predictions about how the world might work in other, similar situations. My first studies in the worm lineage didn't require me to ask a question (other than 'What happens next?'). They were pure observation, gathering data for the sake of seeing the whole picture. Making a worm map would be the same. This is sometimes called 'ignorance drive' or, more grandly, 'Baconian science'. The seventeenthcentury philosopher Francis Bacon suggested a system for understanding the world that began with the accumulation of sets of facts, based on observations. Naturalists who collect and classify living species or astronomers who map the stars in the sky are examples of Baconian scientists. This kind of project suits me –it's never bothered me that it doesn't involve bold theories or sudden leaps of understanding, or indeed that it doesn't usually attract the same level of recognitions as they do.

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