

Does timing matter on tocilizumab administration? Clinical, analytical and radiological outcomes in COVID-19

Raquel Moreno Diaz ¹, Miguel Angel Amor García,¹ Francisco Javier Teigell Muñoz,² Leonardo Ernesto Saldaña Perez,³ María Mateos Gonzalez,² Jose Antonio Melero Bermejo,² Alberto López Hernández,¹ Laura Reyes Marquez,⁴ Maria Teresa De Guzman García-Monge,² Jose Luis Perez Quero,² Marcela Patricia Homez Guzman⁵

¹Pharmacy, Hospital Universitario Infanta Cristina, Parla, Spain

²Internal Medicine, Infanta Cristina University Hospital, Parla, Spain

³Neumology, Getafe University Hospital, Getafe, Madrid, Spain

⁴Radiologist, Hospital Universitario Infanta Cristina, Parla, Madrid, Spain

⁵Critical Care, Hospital Universitario Infanta Cristina, Parla, Madrid, Spain

Correspondence to

Raquel Moreno Diaz, Pharmacy, Hospital Universitario Infanta Cristina, 28981 Parla, Spain; rmorenod@salud.madrid.org

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ABSTRACT

Introduction While there are no pharmacological treatments with proven efficacy for coronavirus disease 2019 (COVID-19), tocilizumab has emerged as a candidate therapy. Some aspects of this therapy are still unknown, including the optimal timing of administration. **Objective** This observational study aimed to compare the 90-day mortality in two cohorts of patients when the drug was administered within the first 10 days from onset of symptoms or after day 11.

Methods Patients hospitalised with severe COVID-19 pneumonia who had received tocilizumab were divided into two groups according to when the medication was administered. The primary outcome was 90-day mortality. Secondary outcomes were 30-day mortality, clinical improvement on a 6-item scale by day 6, biomarker improvement by day 6, radiological image improvement by day 10 and SaO₂ quotient by day 6. The results in the two groups were compared. Additionally, adverse events relating to tocilizumab were recorded.

Results A total of 112 patients were analysed. Both groups were epidemiologically comparable. The results obtained in the primary efficacy variable of the study (90-day mortality) showed a statistically significant difference in the subgroups according to the time of administration of tocilizumab (18.6% vs 5.0%, p=0.048). There was clinical improvement in 24.1% of patients at 6 days, with similar behaviour in both subgroups. No statistically significant differences were found in the percentage of patients who achieved radiological improvement at 10 days or in the other inflammatory parameters, with the exception of significant reductions in lactate dehydrogenase and C-reactive protein. Administration of tocilizumab was not associated with relevant adverse events.

Conclusion To our knowledge, this is the first report of data regarding the timing of administration of tocilizumab in patients with COVID-19 pneumonia. A strategy involving tocilizumab administration after 10 days from onset of symptoms may decrease mortality. Further randomised controlled trials are needed to confirm this emerging hypothesis.

INTRODUCTION

The coronavirus crisis has forced a series of improvised drug therapy decisions based on little scientific evidence, accompanied by little knowledge of

the disease. About 20% of SARS-CoV-2 infected patients suffer from severe illness such as bilateral pneumonia. Some of these cases evolve into acute respiratory distress syndrome (ARDS). This ARDS bears important similarities to cytokine release syndrome (CRS) and secondary lymphohistiocytosis that can be seen in MERS- and SARS-infected patients as well as to CRS of patients with leukaemia who have received modified T-cell therapy (CAR-T). This state of hyperinflammation seems to develop in the first 10 days after the onset of symptoms.^{1,2}

CRS is associated with elevated levels of interferon gamma, interleukin 6 (IL-6) and tumour necrosis factor alpha, among other pro-inflammatory cytokines.³ IL-6 has been identified as the central player in toxicity due to its inflammatory properties through two signalling pathways, the classical pathway and that related to a soluble receptor. In fact, the start of the pro-inflammatory cascade is determined by a pronounced increase in IL-6 levels in the context of CRS.³ Likewise, the plasma levels of IL-6 are directly linked to the increase of other inflammatory parameters in the blood such as C-reactive protein (CRP), lactate dehydrogenase (LDH) and D-dimer.

Taking into consideration the therapeutic approach of CRS in patients undergoing advanced therapies (CAR-T), the use of anti-cytokine antibodies was extended, mainly IL-6 and IL-1, which are also responsible for the tissue damage.^{3,4} One of the advantages of tocilizumab is its long half-life and irreversible action on IL-6 receptors, both membrane-bound and soluble-form. Several studies suggest that the time of administration of the drug may influence its effectiveness in controlling this hyperinflammation secondary to SARS-CoV-2 infection.^{5,6}

The objective of this study is to describe the differences in the results (clinical, analytical and radiological) obtained in patients with COVID-19 infection treated with tocilizumab within the first 10 days after the onset of symptoms compared with those who received the drug from day 11.

METHODS

Design and inclusion of participants

This observational and retrospective study included all consecutive patients admitted to the Infanta

Cristina Hospital with COVID-19 confirmed by PCR or with a high clinical suspicion. Patients should have received at least one dose of tocilizumab as an anti-COVID-19 treatment between 19 March and 13 April 2020. Our hospital is the referral health centre for a population of 168 000 inhabitants in 2020. All patients gave informed consent to data collection and to compassionate use of tocilizumab. Patients were followed up until hospital discharge or death within 90 days after drug administration.

The following criteria were defined for the prescription of tocilizumab: interstitial pneumonia with severe respiratory distress, progressive respiratory deterioration requiring ventilation, signs of systemic inflammation (defined by high levels of IL-6 (>40 pg/mL) or D-dimer (>1500 ng/mL) or progressive increase of the latter) as well as patients who were candidates for admission to the ICU. A starting intravenous dose of 400 mg tocilizumab was administered to patients with body weight <75 kg or 600 mg in those with body weight \geq 75 kg as a 1-hour infusion. A second dose of 600 or 400 mg was administered 12 hours later, and a third dose of 400 mg at 24 hours in case of incomplete or partial clinical response until change of protocol.

Variables register

Demographic variables (age, sex and race), comorbidities, previous treatments, analytical parameters (at the beginning and 6 days after administration), anti-COVID-19 treatments (antiviral or immunosuppressant), oxygen therapy and outcome variables were recorded. Respiratory function was evaluated by measuring oxygen saturation by pulse oximetry/inspired oxygen fraction ($\text{SaO}_2/\text{FiO}_2$), which shows a good correlation with the arterial partial pressure index of oxygen ($\text{PaO}_2/\text{FiO}_2$).

The date of tocilizumab administration was considered as day 0 for analysis purposes. The date of onset of symptoms was recorded, as well as the date of hospital admission. The patients were stratified into two subgroups according to the time elapsed from the onset of symptoms to the administration of the drug: group 1 with patients who received it in the first 10 days and group 2 with those who received it from day 11 onwards.

The primary efficacy endpoint was mortality within 90 days of tocilizumab administration. Mortality at 30 days after administration of tocilizumab was also evaluated, as well as other secondary variables: clinical improvement defined as hospital discharge and/or a decrease of at least 2 points on the oxygen therapy scale 6 days after tocilizumab administration (recommended by WHO R&D Blueprint Group⁷). The 6-point scale contains the following categories: 1, non-hospitalised; 2, hospitalised without supplemental oxygen; 3, hospitalised with supplemental oxygen; 4, hospitalised with high-flow supplemental oxygen; 5, hospitalised, requiring invasive mechanical ventilation (IMV), extracorporeal membrane oxygenation system (ECMO), or both; and 6, death. The other secondary efficacy variables were: improvement in oxygen therapy status and in the $\text{SaO}_2/\text{FiO}_2$ ratio at 6 days, length of hospital stay, radiological improvement at day 10, ICU admission, length of ICU stay and change in analytical parameters. The change in LDH, CRP, total lymphocyte count and D-dimer at 6 days after administration compared with baseline was recorded in both groups of patients.

The chest radiographs performed during admission were retrospectively reviewed, identifying the date on which signs of radiological improvement were observed. Radiological improvement was considered as the disappearance or absence of radiological signs (lesions) compatible or suggestive of COVID-19 in the context of the current pandemic: decrease in the size of

consolidations/opacities, decrease in the number of opacities/infiltrates, decrease in the number of lobes with lung disease, disappearance of diffuse reticular pattern and resolution of complications (pleural effusion, pneumomediastinum and pneumothorax). The Radiology Service recorded the time required for radiological improvement. Subsequently, the proportion of patients who showed radiological improvement at 10 days after administration of tocilizumab was analysed.

Possible adverse events associated with the administration of tocilizumab were recorded: elevation of transaminases, infections or intestinal perforation, as well as all those not related to the rest of the concomitant treatments or that could not be linked to the administration of tocilizumab.

Statistical analysis

Continuous variables were expressed as median and IQR and categorical variables as frequencies and percentages. The Wilcoxon sign test was used for comparisons between continuous variables and the χ^2 test or Fisher's exact test was used to compare categorical variables. A p value of <0.05 was considered statistically significant. Statistical analyses were performed using Stata IC-14 software.

RESULTS

In the analysed period, 112 patients who received at least one dose of tocilizumab were included. The median time from tocilizumab administration to outcome (death or hospital discharge) was 10 days (IQR 6–22).

The baseline epidemiological characteristics of the study population are shown in table 1. All patients received some type of anti-COVID-19 treatment.

A total of 47 patients received tocilizumab within the first 10 days of symptoms (group 1) and 65 after that period (group 2).

Clinical results

For the analysis of the primary efficacy variable, 103 patients were included as nine were transferred to other centres without being able to record the final outcome. Eleven deaths were recorded (10.7%), 8/43 (18.6%) in group 1 and 3/60 (5.0%) in group 2, showing a statistically significant difference ($p=0.048$). Analysis of the clinical efficacy results by subgroups is shown in table 2.

Regarding the analysis of the clinical improvement variable, 108 patients were included as four were transferred before day 6 post-tocilizumab. The proportion of patients who experienced clinical improvement at 6 days was 24.1% (26/108), with 16 patients (14.8 %) discharged in that period and 10 (9.3 %) who had their oxygen supplementation needs reduced. The median score of oxygen therapy requirements was reduced from 4 (IQR 3–5) to 3 (IQR 2–4) for both subgroups of patients, with significant differences in the comparison between repeated measures from baseline to day 6 ($p=0.003$ for group 1 and $p=0.001$ for group 2). No statistically significant differences were found when comparing the proportion of patients in each of the different oxygen therapy stages (table 3).

Regarding the rest of the clinical variables, the value of the $\text{SaO}_2/\text{FiO}_2$ ratio increased from 116 (IQR 94–207) at the time of tocilizumab administration to 217 (IQR 128–352) at 6 days ($p<0.001$). These significant differences were maintained regardless of the time of administration of tocilizumab. Ninety-two patients (82.1%) were discharged from hospital and nine (8.0%) transfers to other centres were registered after the

Table 1 Baseline and treatment characteristics and comparison by subgroups

Variable	Total (n=112)	Group 1 (n=47)	Group 2 (n=65)	P value
Days from symptom onset to tocilizumab administration	11 (9–13)	8 (7–10)	13 (12–16)	<0.001
Days from onset of symptoms to admission	7 (6–10)	6 (5–7)	9 (7–10)	<0.001
Days from admission to administration of tocilizumab	3 (2–5)	2 (1–3)	5 (2–7)	<0.001
Age, years	58 (48–85)	56 (45–67)	60 (49–64)	0.777
Men, n (%)	83 (73.2)	39 (83.0)	43 (66.2)	0.047
Race, n (%)				
Caucasian	76 (67.9)	31 (66.0)	45 (69.2)	0.714
Latin	31 (27.7)	15 (31.9)	16 (24.6)	0.394
Afro-American	3 (2.7)	1 (2.1)	2 (3.1)	0.759
Asian	2 (1.8)	–	2 (3.1)	0.225
Confirmed PCR for SARS-CoV-2, n (%)	77 (68.8)	34 (72.3)	43 (66.1)	0.586
Active smoker, n (%)	4 (3.6)	2 (4.3)	2 (3.1)	0.74
Presence of at least one comorbidity, n (%)	51 (45.5)	23 (48.9)	28 (43.1)	0.539
Comorbidities, n (%)				
HT	72 (64.3)	21 (44.7)	19 (29.2)	0.092
DM	22 (19.7)	10 (21.3)	12 (18.5)	0.711
COPD	7 (6.3)	3 (6.4)	4 (6.2)	1
CVD	6 (5.4)	2 (4.3)	4 (6.2)	1
ESRD	5 (4.5)	2 (4.3)	3 (4.6)	1
Asthma	4 (3.6)	2 (4.3)	2 (3.1)	1
Active cancer	4 (3.6)	–	4 (6.2)	0.138
Corticosteroid treatment, n (%)	76 (67.9)	33 (70.2)	43 (66.2)	0.65
Use of pulsed corticosteroids, n (%)	65 (58.0)	29 (61.7)	36 (55.4)	0.504
Concomitant treatments, n (%)				
HCQ	110 (98.2)	46 (97.9)	64 (98.5)	1
Ceftriaxone	106 (94.6)	43 (91.5)	63 (96.9)	0.236
LPV/r	106 (94.6)	45 (95.7)	61 (93.9)	1
Azithromycin	105 (93.8)	44 (93.6)	61 (93.9)	1
β-interferon 1b	8 (7.1)	3 (6.4)	5 (7.7)	1
Immunoglobulins	3 (2.7)	1 (2.1)	2 (3.1)	1
No of tocilizumab doses, n (%)				
1	78 (69.6)	31 (66.0)	47 (72.3)	0.471
2	31 (27.7)	15 (31.9)	16 (24.6)	0.394
3	3 (2.7)	1 (2.1)	2 (3.1)	1

ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HCQ, hydroxychloroquine; HT, hypertension; LPV/r, lopinavir/ritonavir; RI, renal insufficiency.

administration of tocilizumab (4/47 (8.5%) in group 1 and 5/65 (7.7%) in group 2).

There were 30 ICU admissions, 14 (12.5%) were admitted after tocilizumab administration and 16 (14.3%) were in the ICU at the time of administration. For ICU candidates, no significant differences were found in the proportion admitted after

Table 2 Clinical efficacy results

	Total (n=112)	Group 1 (n=47)	Group 2 (n=65)	P value
Mortality at 90 days	10.7%	18.6%	5.0%	0.048
Mortality at 30 days	9.4%	15.6%	4.9%	0.093
Clinical improvement at 6 days	24.1%	28.9%	20.6%	0.323
Length of hospital stay (days)*	14 (10–25)	11 (9–18)	15 (11–28)	0.044
% of patients with radiological improvement after 10 days*	67.9%	71.4%	65.3%	0.554
Admission to the ICU after tocilizumab†	14.6%	15.0%	14.3%	0.922
Length of stay in ICU (days)	16 (11–28)	18 (11–28)	13 (11–23)	0.600

6-day efficacy results are based on patients with follow-up at the indicated period.

*Excluding patients transferred to other centres or deaths.

†Excluding patients who were already in the ICU at the time of administration.

Table 3 Total oxygen therapy status and by subgroup

	Total (n=112)	Group 1 (n=45)	Group 2 (n=63)	P value
Not hospitalised, n (%)				
Day 0	–	–	–	–
Day 6	23 (21.3)	10 (22.2)	13 (20.6)	0.843
Hospitalised without supplemental oxygen, n (%)				
Day 0	–	–	–	–
Day 6	8 (7.4)	5 (11.1)	3 (4.8)	0.274
Hospitalised with supplemental oxygen, n (%)				
Day 0	33 (29.5)	13 (27.7)	20 (30.8)	0.751
Day 6	28 (25.9)	9 (20.0)	19 (30.2)	0.235
Hospitalised with supplemental high-flow oxygen, n (%)				
Day 0	65 (58.0)	29 (61.7)	36 (55.4)	0.444
Day 6	23 (21.3)	10 (22.2)	13 (20.6)	0.843
Hospitalised, requiring IMV, ECMO or both, n (%)				
Day 0	14 (12.5)	5 (10.6)	9 (13.9)	0.628
Day 6	22 (20.4)	10 (22.2)	12 (19.1)	0.686
Death				
Day 0	–	–	–	–
Day 6	4 (3.7)	1 (2.2)	3 (4.8)	0.639

IMV, invasive mechanical ventilation; ECMO, extracorporeal membrane oxygenation.

tocilizumab had been administered as well as in the days of stay in the unit.

Analytical results

For the total population, the parameters related to inflammation are summarised in table 4. Statistically significant reductions were found in LDH and CRP and in the increase in the total lymphocyte count 6 days after administration ($p < 0.001$). When comparing both subgroups, no statistically significant differences were found in the rest of the inflammatory parameters both at baseline and on day 6 from the administration of tocilizumab, except for the baseline CRP value (table 4).

Safety

An increase in transaminases (aspartate aminotransferase (AST) or alanine aminotransferase (ALT)) was recorded in 30 patients (26.8%), together with tocilizumab-related infections in three patients (2.7%) and a hospital-acquired infection in one patient (0.9%). The median AST on day 6 for these patients was 70.5 U/L (IQR 44.0–106.5) and ALT was 197.0 U/L (IQR 127.0–258.0). When analysing the total population, statistically significant differences were found for ALT on day 6 ($p < 0.001$), but not for AST. Grade 3 or 4 transaminase elevations were not reported in any patient.

DISCUSSION

This study describes the clinical, analytical and radiological results of a Spanish cohort of patients treated with tocilizumab as an anti-COVID-19 treatment. The objective is to assess if the time of administration of tocilizumab has a critical role in its efficacy. To our knowledge, this is the first cohort reporting data regarding the timing of administration of tocilizumab.

The use of tocilizumab became very common during the first wave of the pandemic, despite the lack of randomised clinical trials on this subject. So far, the only drugs that have proved to be useful in reducing mortality have been corticosteroids, as published in the RECOVERY study,⁸ which showed benefit in the use of dexamethasone. The proportion of patients treated

Table 4 Baseline inflammatory parameters at 6 days

	Total (n=112)	Group 1 (n=47)	Group 2 (n=65)	P value
LDH (U/L)				
Day 0	364 (295–455)	368 (299–443)	359 (295–463)	0.684
Day 6	281 (215–410)	290 (219–431)	274 (209–403)	0.428
CRP (mg/dL)				
Day 0	171.2 (94.9–265.0)	208.7 (118.0–270.0)	153.0 (61.2–238.1)	0.035
Day 6	4.2 (2.3–8.3)	6.0 (3.0–9.6)	3.8 (2.0–7.4)	0.067
Total lymphocytes (10 ⁹ /L)				
Day 0	0.7 (0.5–0.9)	0.7 (0.4–0.9)	0.7 (0.5–0.9)	0.782
Day 6	1.0 (0.5–1.5)	0.9 (0.4–1.3)	1.1 (0.7–1.6)	0.169
D-dimer (µg/mL)				
Day 0	1150 (590–2500)	1080 (500–2220)	1450 (670–2540)	0.346
Day 6	3720 (1230–10040)	2980 (1280–11490)	4165 (1230–9530)	0.819

LDH, lactate dehydrogenase; CRP, C-reactive protein.

with corticosteroids was similar in the two subgroups, which indicates that it is not a confounding factor in the comparison between subgroups. However, only 68% of our patients received some type of corticosteroid treatment and this could affect the final efficacy results.

In our case, all the patients included met the criteria for severe disease due to COVID-19 and had a median age similar to the rest of the studies published to date with an age range from 47 to 73 years.^{1,9–11} Likewise, the presence of comorbidities, highlighting arterial hypertension and diabetes, coincided with that reported in other scientific publications.^{1,5,9} However, the proportion of men, especially in subgroup 1 with 83%, was clearly higher than the 60–65% described in the bibliography.^{1,9,12} At the time of tocilizumab administration (with a median of 3 days from admission), all patients had a clearly hyperinflammatory state characterised by increased levels of CRP, LDH and D-dimer, as well as lymphopenia.

The results obtained in the primary efficacy variable of our study (90-day mortality) reflected a statistically significant difference in the subgroups according to the time of administration of tocilizumab (18.6% vs 5.0%, $p=0.048$). These subgroups presented comparable demographic and clinical characteristics as well as a similar loss rate, with only a higher proportion of men and higher baseline CRP values being reported in the group that received tocilizumab in the first 10 days of symptoms. These two variables should not have enough weight to justify the difference in mortality. On the other hand, mortality at 30 days (9.4%) did not reach statistical significance when comparing both subpopulations (15.6% vs 4.9%). These mortality rates have been studied (at 28 days) in the recently published EMPACTA¹³ and COVACTA¹⁴ trials with figures of 10.4% and 19.7%, respectively. In these cases, the inclusion criteria for patients were wider, with different stages of the disease and without stratification by signs of hyperinflammation. Therefore, the mortality rates reported in our study are at the lower limit, except for the subgroup that received tocilizumab in the first 10 days of symptoms. Other comparable sources reported mortality rates at 30 days in the group treated with tocilizumab of 7.7% in the study by De Rossi *et al*,¹⁵ 16% in the series by Campochiaro *et al*¹⁶ and 27.7% by Gupta *et al*.¹⁷ The mortality rate reported by Salvarani *et al*¹⁸ of 3.3% could not be used for comparison because it excluded all patients with criteria for future admission to the ICU. The meta-analysis by Kaye *et al*¹⁹ reported an overall mortality rate of 16% in 34 studies of the use of tocilizumab. The study by Rojo *et al*⁹ in 6424 Spanish patients reported a

mortality rate of 21% in hospitalised patients. Our data show an improvement in this figure in the two groups, despite the fact that they were patients with poor prognostic factors and severe disease.

There was clinical improvement in 24.1% of our patients at 6 days, with similar behaviour in the two subgroups. The association of this effect with the use of the drug has been described in numerous observational studies.^{2,12,20–24} Clinical improvement at 28 days was the main objective on a 7-level ordinal scale in the COVACTA clinical trial²⁴ in which statistical significance was not reached. Likewise, it appears as one of the secondary variables of the EMPACTA clinical trial according to the first published information,¹³ and in this case the objective was achieved. The lack of consistency in the results of the published studies makes us doubt the existence of some type of variable in the selection of patients that has not been identified.

With regard to the other secondary variables, the SaO₂/FiO₂ ratio increased at 6 days in the two groups. The length of hospital stay was not significantly reduced, with a median of 15 days in group 2 and 11 days in group 1. This duration is between the mean values of 6 days in the EMPACTA trial and 20 days in the COVACTA trial for the tocilizumab group.^{13,14} The proportion of patients admitted to the ICU after administration of tocilizumab was 14.6% of the total, which is far from the 23.6% registered in the COVACTA trial²⁴ for the intervention group but is similar to the results reported by Moreno-García *et al* (10%),² Stone *et al* (15.9%)²⁵ and Salvarani *et al* (10%).¹⁸ The criteria for admission to the intensive care service varied depending on the availability of beds, which could have a negative impact on the interpretation of the results.

The median values in the parameters related to inflammation in our sample show a behaviour similar to that described in other series,^{10,26} with a clear and expected reduction in LDH and CRP from day 0 to 6 after the administration of tocilizumab, as well as an increase in lymphocyte values. The D-dimer values of the two groups showed a significant increase after the administration of tocilizumab, an aspect expected by the displacement that IL-6 undergoes from its receptor.^{3,5,26}

No differences were found in the percentage of patients who achieved radiological improvement at 10 days. Toniati *et al*,²³ using chest x-ray, showed an improvement in lung opacity 10 days after administration of tocilizumab in 61% of the patients, similar to our series.

With regard to the safety profile, the administration of tocilizumab was not associated with the appearance of relevant

adverse events. An increase in liver enzymes occurred in 26.8% of patients, which is higher than that described in other studies.^{8 17 21 27} However, this increase in enzymes had no clinical impact. No case of intestinal perforation was reported, reinforcing the idea of a favourable safety profile described by Malgic *et al* in their systematic review.²⁰ In our study, the infection rate was 2.7% up to the end of follow-up, which is consistent with the literature.^{8 15 26}

The limitations of this study are those inherent to an observational study due to the absence of randomisation and a control group. Furthermore, due to the retrospective nature of the study, not all the laboratory parameters studied were determined in all patients.

CONCLUSION

In our experience, the efficacy of tocilizumab could be affected by the time of administration, presenting a difference in mortality rates. Based on the results of this work, administration after 10 days from the onset of symptoms is associated with better outcomes in patients. However, due to the methodological design of the study, the results should be treated with caution until the publication of clinical trials that definitively clarify the efficacy of tocilizumab in SARS-CoV-2.

What this paper adds

What is already known on this subject

- Some patients with SARS-CoV-2 infection have severe illness such as bilateral pneumonia and some of these cases progress to acute respiratory distress syndrome. This acute respiratory distress syndrome bears important similarities to cytokine release syndrome.
- The start of the pro-inflammatory cascade is determined by a pronounced increase in IL-6 levels.
- Tocilizumab is an IL-6 receptor antagonist, both membrane-bound and soluble-form.
- This state of hyperinflammation seems to develop in the first 10 days after the onset of symptoms.
- Tocilizumab was approved for the treatment of cytokine release syndrome in 2018.
- Protocols in some countries (eg, in Spain) still include tocilizumab as a therapeutic option in patients with severe COVID-19 pneumonia.
- The results of the different observational studies are inconsistent and the clinical trials that are being published are also inconclusive.
- Although the use of interleukins appears to be beneficial, this relationship has not always been demonstrated.

What this study adds

- Several studies suggest that the timing of administration of tocilizumab may influence its effectiveness in controlling hyperinflammation secondary to SARS-CoV-2 infection. To our knowledge, this is the first cohort reporting data regarding the timing of administration of tocilizumab.
- We have studied the 90-day mortality rate, taking into account the slow recovery of patients after the acute episode of those who survive, as well as the secondary effects of the infection. These events can put at risk the actual survival of these patients after the first 28 days from infection.
- This study provides a multidisciplinary view of outcomes.

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ORCID iD

Raquel Moreno Diaz <http://orcid.org/0000-0002-8177-0351>

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