L. Bermúdez Barrezueta*, M. Brezmes Raposo,
I. Sanz Fernández, P. López Casillas, C. Villa Francisco,
A. Pino Vázquez

*Unidad de Cuidados Intensivos Pediátricos y Neonatales,
Servicio de Pediatría, Hospital Clínico Universitario de
Valladolid, Valladolid, Spain*

*Corresponding author.
E-mail address:* bermudezlorena@hotmail.com
(L. Bermúdez Barrezueta).

Combined therapy of tocilizumab and corticosteroids in severe SARS-CoV-2 disease[☆]

Terapia combinada de tocilizumab y corticoides en la enfermedad grave por SARS-CoV-2

Dear Editor,

Diseases due to SARS-CoV-2 is characterized by cytokine storm mediated by the overproduction of proinflammatory cytokines that can be expressed with a higher level of interleukin 6 (IL-6). On the other hand, infection can cause pneumonia, and eventually progress into acute respiratory distress syndrome being one of the leading causes of death in these patients.[1,2]

The basis of treatment of critically ill patients with pneumonia due to SARS-CoV-2 is symptomatic and supportive: only the use of corticoids has proven capable of reducing mortality[3] while the effects of tocilizumab as a recombinant humanized monoclonal antibody antagonizing the IL-6 receptor have been confirmed.[4]

During this pandemic a great number of patients have received a great variety of therapies in all sorts of combinations. Some of these combinations—based on the premises described before—have been the combined use of tocilizumab and corticoids.

We wanted to analyze the impact that a combined therapy of tocilizumab and corticoids in this context has on the short-term survival (28 days) of patients admitted to an intensive care unit (ICU) due to SARS-CoV-2. Therefore, we conducted a retrospective study that included cases hospitalized due to SARS-CoV-2 infection admitted from March 10, 2020 through December 5, 2020. Patients were categorized into 4 groups based on the different combinations used: group A: did not receive corticoids or tocilizumab; group B: received combined therapy with corticoids and tocilizumab; group C: received tocilizumab only; group D: received corticoids only.

Tocilizumab was used in patients with disease progression with a PaO_2/FiO_2 ratio <300, and D-dimer levels >1500 ng/mL (or in gradual increase) or IL-6 levels >40 pg/mL or elevated ferritin levels. The dose administered in patients of >75 kg of weight was a single dose of 600 mg, and in patients of <74 kg of weight, the dose administered was 1 single dose of 400 mg. Five patients received a second dose of tocilizumab, 6 patients received 3 doses of tocilizumab, and 2 patients received 4 doses of tocilizumab.

The use of corticoids was registered as a binary variable (Yes or No) if patients received, at least, 40 mg of methylprednisolone or its equivalence for, at least, 3 days to treat inflammation associated with viral pneumonia.

A descriptive analysis of the sample was initially conducted and then followed by Cox regression and a 28-day survival analysis using the Kaplan-Meier method for the variable of time of death. Survival curves were compared using the log-rank test.

In the study period a total of 254 patients were admitted. A total of 46 patients were excluded from the study due to lack of data or no confirmation of the presence of SARS-CoV-2. A total of 208 patients were analyzed. The main characteristics of the 4 groups of patients are shown on Table 1.

Using Cox regression analysis (method: intro; state: dead at ICU; covariates used: age, sex, patients' comorbidities, therapies involved in the management of these patients, the SOFA score, the PaO_2/FiO_2 ratio at admission, and the analytical values and ventilatory support therapies). The PaO_2/FiO_2 ratio at the ICU admission behaved as a protector factor against mortality (HR, 0.98; 95%CI, 0.97−0.99; *P* = .01). Out of all the therapies analyzed, the combined use of corticoids and tocilizumab was associated with a better survival rate at the ICU setting (HR, 9.623; 95%CI, 2.39–38.69; *P* = .001). No significant differences were seen with the remaining variables analyzed.

In the 28-day survival analysis, the group on a combined therapy of tocilizumab and corticoids had more chances of survival after 28 days (OR, 2.83; 95%CI, 1.24–6.44) compared to the nonuse of tocilizumab and corticoids. This significant difference was not observed compared to the other 2 groups analyzed: OR, 1.26; 95%CI, 0.54–2.94 vs therapy with tocilizumab; OR, 1.31; 95%CI, 0.57–3.01 vs corticoid therapy (Fig. 1).

Currently, the most consistent and recent studies that assessed tocilizumab in monotherapy against COVID-19 revealed no beneficial effects whatsoever.[5–7] This data proves that blocking one single cytokine is not enough to have a significant clinical impact in these patients.

Similarly, it could be interpreted that one single fixed dose of steroids regardless of disease severity, the cytokine storm released or the presence of acute respiratory distress syndrome would be insufficient in many of these patients.[8]

Our results are consistent with those reported in the REMAP-CAP study[9] that analyzed the use of tocilizumab in a population of patients admitted to the ICU for organ support. This study confirmed that the addition of tocilizumab to the use of dexamethasone improved the mortality of the sample. Consistent with this, the study conducted by Mikulska et al. confirmed that the negative impact of the immune response to COVID-19 might mitigate through the early administration of corticoids plus tocilizumab.[10]

On the other hand, we wish to mention that the group that only received tocilizumab had worse oxygen levels at admission, required more vasopressor drugs and renal replacement therapies during the ICU admission. Also, they developed more nosocomial over-infections, among them, ventilator-associated tracheobronchitis and pneumonia (VAT/VAP). In this sense,

Table 1 Main differences between patients treated with tocilizumab and corticoids of the sample studied.

Variables	Group A (n = 72)	Group B (n = 49)	Group C (n = 29)	Group D (n = 58)	P
Age, mean (SD)	64 (13)	67 (11)	57 (18)	65 (8)	<.05
Sex					
Men, n (%)	53 (74)	38 (77)	20 (69)	50 (86)	.93
Comorbidities					
AHT, n (%)	38 (53)	27 (55)	14 (48)	33 (57)	.94
DM, n (%)	17 (24)	14 (28)	5 (17)	13 (22)	.63
Obesity, n (%)	8 (11)	12 (24)	6 (21)	19 (32)	.07
Dyslipidemia, n (%)	29 (40)	21 (43)	8 (27)	25 (43)	.63
Smoker, n (%)	18 (25)	15 (31)	11 (38)	25 (43)	.36
SOFA score, median (SD)	5 (3)	5 (4)	7 (3)	4 (2)	.12
PaO2/FiO2 ratio at the ICU admission, mean (SD)	155 (92)	150 (63)	106 (40)	146 (58)	<.05
Lab data at the ICU admission					
CK, mean (SD)	549 (1032)	199 (287)	983 (1246)	156 (562)	<.05
DD, mean (SD)	8959(19975)	7347(25248)	13061(28630)	6634(19335)	<.05
IL-6, mean (SD)	57 (51)	92 (131)	148 (168)	88 (132)	<.05
CRP, mean (SD)	27(11)	22 (14)	20 (7)	29 (8)	.37
LDH, mean (SD)	469 (512)	369 (114)	643 (536)	395 (141)	<.05
Ferritin, mean (SD)	1299 (1140)	1203 (814)	1312 (775)	1112 (947)	.41
Decubitus position	36 (50)	32 (65)	23 (79)	29 (50)	.35
HFNO, n (%)	24 (33)	22 (45)	7 (24)	39 (67)	<.05
IMV, n (%)	48 (66)	42 (85)	28 (96)	48 (82)	<.05
Need for vasopressors, n (%)	33 (46)	22 (45)	20 (69)	13 (22)	<.05
ECMO, n (%)	0 (-)	1 (0.2)	1 (0.3)	0 (-)	–
iNO, n (%)	3 (0.4)	0 (-)	3 (0.1)	3 (0.5)	–
Need for RRT, n (%)	6 (8.3)	1 (2)	3 (10)	2 (3.4)	<.05
Nosocomial over-infection, n (%)	20 (28)	17 (35)	18 (62)	14 (24)	<.05
VAT/VAP, n (%)	15 (21)	13 (26)	15 (52)	5 (9)	<.05
Germs					
Aspergillus, n (%)	2 (10)	2 (12)	1 (5)	–	–
Candida, n (%)	1 (5)	2 (12)	3 (15)	3 (21)	<.05
E. coli, n (%)	1 (5)	5 (29)	–	2 (14)	–
Pseudomonas, n (%)	3 (15)	1 (6)	2 (10)	3 (21)	<.05
MRSA, n (%)	1 (5)	2 (12)	3 (15)	–	
Stay at the ICU, mean (p25–p75)	11 (3—17)	14 (6—28)	17 (9—33)	11 (5—18)	<.05
Mortality at the ICU setting, n (%)	27 (37)	7 (14)	8 (27)	10 (17)	.16

AHT, arterial hypertension; CK, creatine kinase; CRP, C-reactive protein; DD, D-dimer; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; HFNO, high flow nasal oxygen; IL-6, interleukin-6; IMV, invasive mechanical ventilation; iNO, inhaled nitric oxide; LDH, lactate dehydrogenase; MRSA, methicillin-resistant *Staphylococcus aureus*; RRT, renal replacement therapies; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis.
Group A: did not receive corticoids or tocilizumab; group B: received combined therapy with corticoids and tocilizumab; group C: received tocilizumab only; group D: received corticoids only.
Reference values: CK (46—171 U/L); DD (0–500 (ng/mL); IL6 (<5 pg/L); CRP (<0.5 g/dL); LDH (120—246 U/L); ferritin (22—322 ng/mL).
The table shows the OR values with its corresponding 95% confidence interval.

according to the medical literature it is a known fact that upper airway infections are the most common side effects of tocilizumab.[11,12]

Our study has several limitations. it is a relatively small series of patients from a single hospital. On the other hand, the results were obtained in the middle of a pandemic with saturated hospital units and, often with non-expert medical and nursing personnel. None of the treatments were implemented randomly, but according t the health professionals' best clinical judgement. Also, we should mention that there are specific contraindications for the use of tocilizumab like the presence of hepatic failure or previous infections that may lead to aprioristic patient selection bias.

Currently, the indication for a combined therapy of tocilizumab plus corticoids could be considered premature meaning that new randomized clinical trials would be needed before establishing better options of treatment, duration, and limitations.
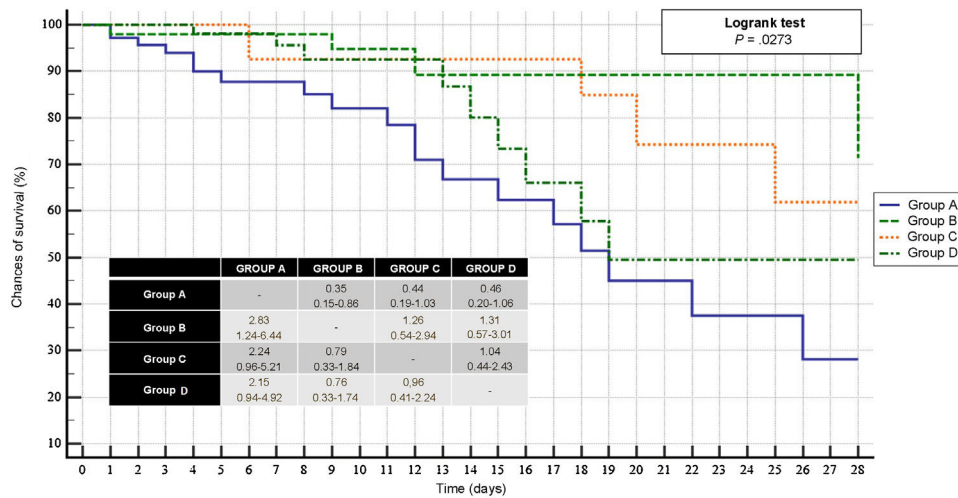
Figure 1 Survival analysis (Kaplan–Meier) regarding the 28-day survival in the 4 groups established. Group A: did not receive corticoids or tocilizumab; group B: received combined therapy with corticoids and tocilizumab; group C: received tocilizumab only; group D: received corticoids only.

Conflicts of interest

None.

References

1. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46:846–8.
2. Fu B, Xu X, Wei H. Why tocilizumab could be an effectivetreatment for severe COVID-19? J Trans Med. 2020;18:164.
3. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. N Engl J Med. 2021;84:693–704 https://doi.org/10.1056/NEJMoa2021436
4. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) ofsevere COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab maybe the key to reduce the mortality. Int J Antimicrob Agents. 2020;29:105954.
5. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. JAMA Intern Med. 2021;181:24–31.
6. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med. 2020;383:2333–44.
7. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med. 2021;384:20–30.
8. Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA, et al. Dexamethasone in ARDS network. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020;8:267–76.
9. The REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report. medRxiv 2021. 01.07.21249390; https://doi.org/10.1101/2021.01.07.21249390.
10. Mikulska M, Nicolini LA, Signori A, Di Biagio A, Sepulcri C, Russo C, et al. Tocilizumab and steroid treatment in patients with COVID-19 pneumonia. PLoS ONE. 2020;15:e0237831.
11. Smolen JS, Beaulieu AD, Dikranian A, Fenton I, Fisheleva E, Alecock E, et al. Safety of tocilizumab in patients with rheumatoid arthritis: Pooled analysis of five phase 3 clinical trials. Arthritis Rheum. 2008;589:1669.
12. Rueda Gotor J, Blanco Alonso R. Tocilizumab en artritis reumatoide. Reumatol Clin. 2011;6:S29–32, http://dx.doi.org/10.1016/j.reuma.2011.01.001.

A. González-Castro*, E. Cuenca Fito, A. Fernandez, P. Escudero Acha, J.C. Rodríguez Borregán, Y. Peñasco

Servicio de Medicina Intensiva, Hospital Universitario Marqués de Valdecilla, Santander, Spain

*Corresponding author.
E-mail address:* e409@humv.es (A. González-Castro).