JIM Letter to the Editor

doi: 10.1111/joim.13145

# Methylprednisolone added to tocilizumab reduces mortality in SARS-CoV-2 pneumonia: An observational study

**Dear Editor,**

Although there are few randomized controlled trials (RCTs) evaluating the efficacy of drugs to treat COVID-19, different molecules have been used empirically and with great interest in those intended to control the excessive inflammatory response produced by SARS-CoV-2. By blocking the IL-6 receptor, tocilizumab has a role in controlling the inflammatory response. Clinical improvement of respiratory parameters and hospital stay have been described in small series in a series of patients without a control group [1]. There are currently numerous ongoing clinical trials aimed to clarifying the role of this molecule in COVID-19. The guidelines for the treatment of SARS-CoV-2 pneumonia from the Spanish Ministry of Health contemplate the use of tocilizumab as a therapeutic tool for those patients with severe respiratory failure or rapid respiratory deterioration with criteria for admission to the intensive care unit (ICU). However, in clinical practice there are patients who despite treatment with tocilizumab have a torpid evolution with persistent inflammatory response. For this reason, we included methylprednisolone treatment in the local guidelines of our centre based on the study by Wu et al [2]. Our work aimed to analyse the influence on survival of those patients treated with tocilizumab where methylprednisolone was also added.

## Methods

Methylprednisolone treatment was introduced in our local treatment protocol on 27 March 2020 in addition to tocilizumab (administered as a single 400 mg dose) for those patients who display one of the following criteria: $PaO_2/FiO_2 < 300$, $SpO_2 < 92$ (room air), tachypnea, and high ferritin levels. The dosage regimen was methylprednisolone 250 mg administered intravenously daily on the first day followed by 40 mg every 12 h for 4 more days and stopped without tapering. We compared those patients' treatment consecutively with or without methylprednisolone in two different periods of time (before and after the new treatment protocol began). The primary end-point was in-hospital all-cause mortality. A bivariate analysis was performed to identify the characteristics of the population receiving treatment with methylprednisolone versus those who were not. For this, the chi-square test was used with the Yates correction when required, or the Fisher test. Cox proportional hazard regression models were used to calculate between treatments and death. The regression model included demographic factors, comorbidities, radiological and laboratory test, and medications. For survival analysis, the Kaplan–Meier curves were performed comparing the two treatment arms with and without methylprednisolone using the log-rank test. Statistical significance was considered for a value of $P < 0.05$. Statistical analysis was performed with SPSS version 23 software (IBM Corp., Armonk, NY). All retrospective analyses were conducted in accordance with the local institutional review board (Project Number 58/2020).

## Results

We analysed a population of 72 patients diagnosed with SARS-CoV-2 pneumonia using real-time reverse transcriptase–polymerase chain reaction who were treated with tocilizumab, of whom 77.8% (56 cases) also received treatment with methylprednisolone. Clinical characteristics are described in Table 1. Both groups did not present differences regarding comorbidities, radiological characteristics, or laboratory data. The main treatment received by the patients was the combination of hydroxychloroquine and azithromycin (94.4%). We did not observe differences regarding the days from admission to treatment with tocilizumab. Regarding the evolution of the patients, we observed that 59.7% were admitted to the ICU. The overall mortality of the series was 29.2%. Methylprednisolone administered in patients treated with tocilizumab reduces the risk of death (risk ratio: 0.20, 95% CI: 0.08–0.47, $P < 0.01$; Figure 1).

## Discussion

In patients with maximized treatment, who are also especially severe and some with distress criteria, the administration of corticosteroids improved survival in our series.

 

**Table 1.** *Baseline characteristics and outcomes of patients treated with tocilizumab*

| | All patients ($n$ = 72) | No methylprednisolone group ($n$ = 16) | Methylprednisolone group ($n$ = 56) | $P$ |
|---|---|---|---|---|
| Age (years) | 67.5 (61–76.7) | 68.9 (60.8–78.3) | 67 (61–76.8) | 0.548 |
| Male gender | 45 (62.5) | 12 (75) | 33 (58.9) | 0.242 |
| *Comorbidities* | | | | |
| Hypertension | 43 (59.7) | 12 (75) | 31 (55.4) | 0.158 |
| ACEI/ARB | 35 (48.6) | 6 (37.5) | 29 (51.8) | 0.313 |
| Diabetes | 19 (26.4) | 7 (43.8) | 12 (21.4) | 0.074 |
| COPD | 14 (19.4) | 2 (12.5) | 12 (21.4) | 0.426 |
| Cardiovascular disease | 9 (12.5) | 1 (6.3) | 8 (14.3) | 0.391 |
| Chronic kidney failure | 3 (4.2) | 1 (6.3) | 2 (3.6) | 0.636 |
| Immunosuppression | 9 (12.5) | 2 (12.5) | 7 (12.5) | 1 |
| Symptoms onset to admission | 6.8 (4–9) | 6.1 (4.5–7) | 6.9 (4–9.8) | 0.857 |
| *Chest X-ray* | | | | |
| Bilateral infiltrates | 56 (77.8) | 10 (62.5) | 46 (82.1) | 0.096 |
| Interstitial pattern | 16 (22.2) | 6 (37.5) | 10 (17.9) | 0.096 |
| *Laboratory test, pretocilizumab* | | | | |
| $PaO_2/FiO_2$ | 184 (125–235) | 188 (151–222) | 182 (124–250) | 0.788 |
| $PaO_2/FiO_2 < 250$ | 56 (77.8) | 14 (87.5) | 42 (75) | 0.289 |
| Lymphocyte count ($\times 10^9$/L) | 595 (400–800) | 662 (400–875) | 756 (300–700) | 0.252 |
| Neutrophil count ($\times 10^9$/L) | 8812 (4225–6900) | 7237 (4600–11 650) | 9262 (3950–9775) | 0.551 |
| NLR | 17.4 (6.3–20.8) | 15.5 (5.1–17.9) | 17.9 (7.6–23.6) | 0.646 |
| D-dimer (ng $L^{-1}$) | 1062 (258–1091) | 1521 (552–2200) | 939 (255–1014) | 0.132 |
| Ferritin(μg $L^{-1}$) | 1387 (527–1443) | 1269 (580–1531) | 1418 (509–1432) | 0.772 |
| *Pharmacological treatment* | | | | |
| Lopinavir/ritonavir | 58 (80.6) | 13 (81.3) | 45 (80.4) | 0.937 |
| Interferon beta | 24 (33.3) | 10 (62.5) | 14 (25) | 0.005 |
| Hydroxychloroquine and azithromycin | 68 (94.4) | 15 (93.8) | 53 (94.6) | 0.891 |
| Days from admission to tocilizumab | 2.9 (1–4) | 1.9 (1–3) | 3.2 (1–4) | 0.156 |
| Days from symptoms onset to tocilizumab | 9.2 (6–11) | 8 (6–10) | 9.6 (6.3–12) | 0.165 |
| Days from symptoms onset to corticosteroids | – | – | 10 (6.3–13) | – |
| Days from admission to corticosteroids | – | – | 3.6 (1–5) | – |
| Days from tocilizumab to corticosteroids | – | – | 2.3 (1–3.8) | – |
| *Outcomes* | | | | |

 

**Table 1** (*Continued*)

| | All patients ($n$ = 72) | No methylprednisolone group ($n$ = 16) | Methylprednisolone group ($n$ = 56) | $P$ |
|---|---|---|---|---|
| Duration of viral clearance (survivors) | 20 (13.7–28) | 21.5 (16–30.3) | 19.5 (13.4–28) | 0.713 |
| Hospital stay (days) | 16.4 (11–20) | 12.6 (3.5–22.5) | 17.5 (15–20) | 0.028 |
| Hospital stay survivors (days) | 19.3 (16–21) | 23.2 (16.5–28.3) | 18.8 (15.5–21) | 0.091 |
| ICU admission | 43 (59.7) | 12 (75) | 31 (55.4) | 0.158 |
| Death | 21 (29.2) | 10 (62.5) | 11 (19.6) | 0.001 |

ARB, Angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitors; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio.
Quantitative variables are expressed as median and interquartile range and mean and standard deviation and were calculated using $t$ test.

The role of corticosteroids in reducing host inflammation in response to infection, especially that caused by viruses, is controversial.

A recent meta-analysis assessed the effect of corticosteroids on influenza pneumonia and found that the group treated with corticosteroids had more mortality, a longer ICU stay and more secondary bacterial infections compared with placebo [3]. However, this meta-analysis did not include RCTs, and there is no information in most studies regarding the dose and duration of treatment. On the other hand, pneumonia due to influenza would not be comparable to that produced by SARS-CoV-2, where the pulmonary hyper-inflammation seems to be more relevant [4]. A reduction in the viral clearance without differences in the clinical outcomes was observed

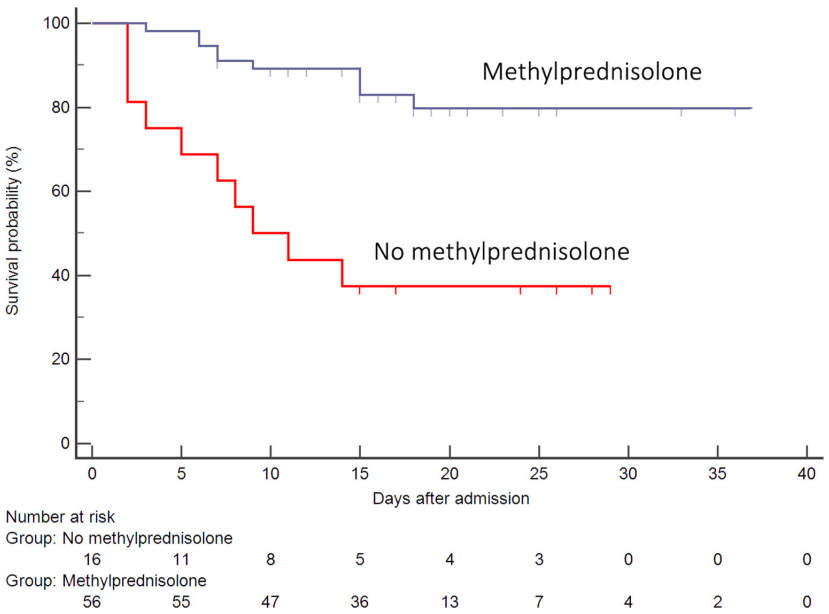


**Fig. 1** *Survival curve in patients treated with tocilizumab who did and did not receive methylprednisolone treatment. Methylprednisolone administered in patients treated with tocilizumab reduces the risk of death (hazard ratio: 0.20, 95% CI: 0.08–0.47,* P < *0.01). Log-rank* < *0.01.*

 

with the administration of high doses of methylprednisolone in a small RCT during SARS infection [5]. Mortality was not influenced by corticosteroid treatment in MERS patients, but delayed virus clearance and adverse effects were observed [6]. However, this study was carried out only in patients admitted to the ICU with very severe respiratory failure.

On the other hand, in an observational study, Wu et al. recently reported a decrease in mortality in those patients with SARS-CoV-2 acute respiratory distress syndrome (ARDS) who were treated with methylprednisolone, although it is not possible to rule out a selection bias [2]. A recent published study has observed that an early short course of methylprednisolone in patients with moderate-to-severe COVID-19 improved clinical outcomes preventing the development of complications and improving survival [7]. Our study has serious limitations since it is an observational single-centre study and it is not a randomized trial. However, we observed an effect on survival without notable adverse effects attributed to the dose and duration of treatment. On the other hand, the precocity in its establishment is one of the facts that we consider key when it comes to impacting the evolution of the patients. We cannot rule out a deleterious effect of interferon in our series.

Our work offers modestly encouraging signs concerning this open question and how important it would be to confirm these data in large randomized controlled trials.

### Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

### Funding

None.

### Author contribution

**Francisco Sanz:** Conceptualization (lead); Data curation (lead); Formal analysis (lead); Investigation (lead); Methodology (equal); Project administration (lead); Resources (equal); Software (lead); Supervision (lead); Validation (lead); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Francesc Puchades:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Pilar Ortega:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Carolina Ferrer:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Dolores Ocete:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Miguel Garcia Deltoro:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal).

**F. Sanz Herrero[1]; F. Puchades Gimeno[2]; P. Ortega García[3]; C. Ferrer Gómez[4]; M. D. Ocete Mochón[5] & M. García Deltoro[6]**

*From the, [1]Pulmonology Department; [2]Internal Medicine Department; [3]Hospital Pharmacy Department; [4]Anesthesiology Department and Intensive Care Unit; [5]Microbiology Department; and [6]Infectious Diseases Department, Consorci Hospital General Universitari, València, Spain*

### References

1 Xu X, Han M, Li T *et al.* Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA* 2020; **117:** 10970–5.

2 Wu C, Chen X, Cai Y *et al.* Risk factors associated with acute respiratory distress syndrome and death in patients with

 

coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Internal Med* 2019; **2020:** e200994.
3 Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care* 2019; **23:** 99.
4 Huang C, Wang Y, Li X *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *China. Lancet.* 2020; **395:** 497–506.
5 Lee N, Allen Chan KC, Hui DS *et al.* Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. *J Clin Virol* 2004; **31:** 304–9.
6 Arabi YM, Mandourah Y, Al-Hameed F *et al.* Corticosteroid therapy for critically Ill patients with middle east respiratory syndrome. *Am J Respir Crit Care Med* 2018; **197:** 757–67.
7 Fadel R, Morrison AR, Vahia A *et al.* Early short course corticosteroids in hospitalized patients with COVID-19. *Clin Infect Dis* 2020;**ciaa601. https:**//doi.org/10.1093/cid/ciaa601.

*Correspondence*: Francisco Sanz Herrero, Av. Tres Cruces, 2, 46014 València, Spain.
(e-mail: sanz_fraher@gva.es).

 