de otras terapias (por ejemplo, hidroxicloroquina) y que, además, es posible que se haya producido algún cambio no farmacológico en el tratamiento de los pacientes, durante el periodo de estudio, de acuerdo con la evolución del conocimiento de la fisiopatología de la COVID-19. No obstante, y debido a la falta de medicamentos específicos contra esta infección, la mayoría de los pacientes recibieron un tratamiento similar y, por lo tanto, creemos que los resultados del estudio actual todavía tienen cierta importancia clínica.

En conclusión, la incidencia de TIH observada en pacientes con COVID-19, en tratamiento tromboprofiláctico con HBPM, es elevada (6,9%) aunque de moderada intensidad. Por tanto, en aquellos pacientes en los que exista fuerte sospecha de TIH, se debe suspender el tratamiento con heparina y/o continuarlo con un anticoagulante alternativo, para evitar el alto riesgo de trombosis inducida por TIH.

Bibliografía

1. Llitjos J-F, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost. 2020;18:1743–6, http://dx.doi.org/10.1111/jth.14869.
2. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:311–37.
3. Xuan L, Xiaopeng Z, Yongjiu X, Ting G, Guangfei W, Zhongyi W, et-al. Heparin-induced thrombocytopenia is associated with a high risk of mortality in critical COVID-19 patients receiving heparin-involved treatment. medRxiv. 10.1101/2020.04.23.20076851.
4. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18:1094–9, http://dx.doi.org/10.1111/jth.14817.

Roberto Lozano [a,*] y María-Esther Franco [b]

[a] *Hospital Real de Nuestra Señora de Gracia, Servicio de Farmacia, Zaragoza, España*
[b] *Hospital Real de Nuestra Señora de Gracia, Servicio de Hematología, Zaragoza, España*

* Autor para correspondencia.
Correo electrónico: rlozano@salud.aragon.es (R. Lozano).

Tocilizumab plus glucocorticoids in severe and critically COVID-19 patients. A single center experience

Tocilizumab más glucocorticoides para tratar pacientes graves y en situación crítica infectados por COVID-19. Experiencia de un centro

Dear Editor:

The cytokine storms (CS) mediated by overproduction of proinflammatory cytokines have been observed in a large population of critically ill patients infected with COVID-19.[1]

In previous studies, severe patients that have been hospitalized for COVID-19 have had laboratory results that show an increased level of cytokines, specifically interleukin 6 (IL-6). Tocilizumab is a recombinant humanized monoclonal antibody that has an antagonist effect on the IL-6 receptor, and could play a role in treatment for severely ill patients with COVID-19.[2] Corticosteroids such as methylprednisolone (MP) are the conventional agents used to treat CS, but usually are related with risk of side effects, the most common the secondary bacterial superinfection. There are observational studies on the frontline in China and Italy that suggest the use of methylprednisolone was associated with better clinical outcomes in severe patients with COVID-19 pneumonia.[3,4]

This was a single centre observational study. We report the outcomes of patients tretaed with tocilizumab plus glucocorticoids in severe and critical severe COVID-19 patients between March 26 and April 17, 2020 in a Intensive Care Unit (ICU) Hospital in Barcelona, Spain. We included patients with high suspicion of CS (persisten fever, increase in inflammatory parameters (CPR, D-dimer, ferritine), and excluded patients with confirmed bacterial superinfection at the start of the tretament.

All patients enrolled met the severe or critical severe criteria defined by the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (6th interim edition) sponsored by National Health Commission of the People's Republic of China.[5]

The diagnose of severity was defined if any of the following conditions was met[1]: respiratory rate $\geq$ 30 breaths/min [2]; $SpO_2 \leq 93\%$ while breathing room air[3]; $PaO_2/FiO_2 \leq 300$ mmHg. A critical case was diagnosed if any of[1]: respiratory failure which requiring mechanical ventilation[2]; shock[3]; combined with other organ failure, need to be admitted to ICU.

A single dose of tocilizumab was administered in 21 patients and two doses in 4 patients. Methylprednisolone were adminsterd 1 mg/kg/day during the inflammatory phase. Afther that, decreasing doses were administered.

Twenty five patients (14 males and 11 females) with COVID-19 were included in this study. The characteristics of patients, status, laboratory and clinical outcomes are summarized in Table 1. The media age of the patients was 62.4 years. Eight (32%) patients were severe ill, and 17 were critical severe ill (68%), 15 of them with invasive mechanical ventilation, 2 with non invasive ventilation and 8 with high doses of oxigen (O_2 mask more than 50% FiO_2, or high flow oxygen) at the start of the treatment.

The body temperature of 19 patients (76%) returned to normal in the first 72 h after receiving the treatment. The total number of lymphocytes increases in 17 (68%) patients and CRP decreased significantly in 92% patients at 72 h after the start of treatment. At the same time this was related to a clinical improvement of most patients (Appendix A).

There were 8 (32%) patients with subsequent bacterial superinfection, all these patients with long ICU admission. The median of days of hopitalization was 25 (8–52) days.

At this time (May 31, 2020), 18 (72%) patients were discharged from hospitalization, 2 patients remain hospitalized, 1 patient in ICU, and 5 deaths (20%).

The time that the anti-inflammatory treatment with tocilizumab was started since the hospital admission was variable among patients, the treatment were started earlier in patients who survived than those who died (7.6 ± 5 vs. 13.6 ± 7.7 days; *p*: 0.03).

In our study we observed a significant decrease in fever, CPR, D-dimer, ferritine, and an increase in the total number of lymphocytes at 72 h after ther start the anti-inflammatory treatment in critical COVID patients.

Table 1
Clinical characteristics of the patients.

Characteristics	All patients (25)
Age, years, mean ± SD	62.4 ± 8.8
Male gender, n (%)	14 (56)
Hypertension, n (%)	12 (48)
Diabetes Mellitus, n (%)	3 (12)
COPD, n (%)	4 (16)
Cardiovascular disease, n (%)	2 (8)
Chronic renal failure, n (%)	1 (4)
Status	
Severe	8 (32)
Critical severe	17 (68)
Oxygen therapy	
Mechanical ventilation	17 (68)
Invasive, n (%)	15 (60)
Noninvasive, n (%)	2 (8)
Mask oxygen, n (%)	6 (24)
High flow oxygen, n (%)	2 (8)
Laboratory basal, 72 h after the treatment start	
CPR (mg/dl) basal, mean ± SD	21.4 ± 16.3
CPR (mg/dl) 72 h, mean ± SD	5.3 ± 7.3
Lymphocytes (mm³), basal	784 ± 374.8
Lymphocytes (mm³)	1256 ± 950
Ferritin (ng/ml), basal, mean ± SD, basal	2017 ± 1465
Ferritin (ng/ml), 72 h, mean ± SD, basal	1614 ± 1008
D-Dimer (μg/l), mean ± SD, basal	2190 ± 987
D-Dimer (μg/l), mean ± SD, 72 h	1457 ± 706
Clinical outcomes	
Discharge from hospital, n (%)	18 (72)
Hospitalization, n (%)	2 (8)
Intensive Care Unit, n (%)	1 (4)
Deaths, n (%)	5 (20)

COPD: chronic obstructive pulmonary disease; CPR: C-reactive protein; SD: standard deviation.

The reported mortality in critically ill patients infected by COVID-19 is high between 18 and 66%.[5] For this reason, pharmacological strategies should be sought to mitigate the inflammatory phase.

Although data from several ongoing randomized, controlled trials will soon provide more evidence regarding the different treatments, the outcomes observed in this report specifically the improvements in the inflamamatory parameter, with a 72% of the patients discharge from the hospitalization and overall mortality of 20%, suggest that tocilizumab plus glucocorticoids appears to be an effective treatment option in COVID-19 patients to attenuate the CS.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.medcli.2020.07.001.

Bibliografía

1. Fu B, Xu X, Wei H. Why tocilizumab could be an effective treatment for severe COVID-19? J Transl Med. 2020;18:164, http://dx.doi.org/10.1186/s12967-020-02339-3.
2. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents. 2020;29:105954.
3. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan China. JAMA Intern Med. 2020;180:1–11.
4. Nicastri E, Petrosillo N, Bartoli TA, Lepore L, Mondi A, Palmieri F, et al. National institute for the infectious diseases "L. Spallanzani" IRCCS. Recommendations for COVID-19 clinical management. Infect Dis Rep. 2020;12:8543.
5. Zhonghua Yi Xue Za Zhi. Interpretation of "Guidelines for the diagnosis and treatment of novel coronavirus (2019-nCoV) infection by the National Health Commission (Trial Version 5)"; 2020 February 7.

Gustavo Jiménez-Brítez [a,b,*], Pablo Ruiz [a], Xavier Soler [a]

[a] Intensive Care Unit, Centro Médico Teknon, Quironsalud, Barcelona, Spain
[b] Facultad de Ciencias de la Salud, Universidad Nacional del Este (FACISA-UNE), Paraguay

* Corresponding author.
E-mail address: gustavo.jimenezb@quironsalud.es
(G. Jiménez-Brítez).

https://doi.org/10.1016/j.medcli.2020.07.001

Características y evolución de los pacientes con cáncer de pulmón e infección Covid-19 en un hospital de segundo nivel durante los 3 primeros meses de pandemia

Characteristics and outcome of lung cancer patients and Covid-19 infection in a second-level hospital during the first 3 months of the pandemic

Sr. Editor:

El 31 de enero de 2020 el nuevo coronavirus SARS-CoV-2 tocó por primera vez tierra española. No fue hasta principios de marzo cuando se detectó transmisión intracomunitaria, convirtiéndose en un importante problema de salud pública y provocando una alerta sanitaria sin precedentes. Durante este periodo, los pacientes oncológicos junto a otros con patologías crónicas graves han sido los únicos en los que se ha mantenido la asistencia habitual. Por este motivo, junto con su estado de inmunosupresión, parece haberse observado una mayor incidencia de Covid-19, como hemos podido evidenciar en distintas series de China[1-3]. Además, nosotros mismos observamos mayor incidencia acumulada de casos entre la población oncológica general en nuestro centro durante el primer mes de pandemia[4], con un aumento de mortalidad[1-4], siendo aún mayor en pacientes con cáncer de pulmón, como exponen en el estudio TERAVOLT[5].

En nuestro estudio, describimos de forma retrospectiva las características y la evolución de los pacientes con cáncer de pulmón que han desarrollado Covid-19, desde el 5 de marzo al 2 de junio de 2020. Además, observamos si existe una mayor mortalidad entre los pacientes con cáncer de pulmón con respecto a la población general de referencia de nuestro centro.

Veinticuatro pacientes con cáncer de pulmón fueron diagnosticados de Covid-19. Su mediana de edad fue de 70 años (rango 49-84), tratándose en su mayoría de varones (n = 16, 66,7%). El subtipo de cáncer de pulmón más frecuente fue carcinoma no microcítico (n = 21, 87,5%), presentando la mayoría enfermedad