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# Tocilizumab reduces the risk of ICU admission and mortality in patients with SARS-CoV-2 infection

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## ABSTRACT

**Objectives.** In some patients the immune response triggered by SARS-CoV-2 is unbalanced, presenting an acute respiratory distress syndrome which in many cases requires intensive care unit (ICU) admission. The limitation of ICU beds has been one of the major burdens in the management around the world; therefore, clinical strategies to avoid ICU admission are needed. We aimed to describe the influence of tocilizumab on the need of transfer to ICU or death in non-critically ill patients.

**Material and methods.** A retrospective study of 171 patients with SARS-CoV-2 infection that did not qualify as requiring transfer to ICU during the first 24h after admission to a conventional ward, were included. The criteria to receive tocilizumab was radiological impairment, oxygen demand or an increasing of inflammatory parameters, however, the ultimate decision was left to the attending physician judgement. The primary outcome was the need of ICU admission or death whichever came first.

**Results.** A total of 77 patients received tocilizumab and 94 did not. The tocilizumab group had less ICU admissions (10.3% vs. 27.6%, *P*=0.005) and need of invasive ventilation (0 vs 13.8%, *P*=0.001). In the multivariable analysis, tocilizumab

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remained as a protective variable (OR: 0.03, CI 95%: 0.007-0.1, *P*=0.0001) of ICU admission or death.

**Conclusions.** Tocilizumab in early stages of the inflammatory flare could reduce an important number of ICU admissions and mechanical ventilation. The mortality rate of 10.3% among patients receiving tocilizumab appears to be lower than other reports. This is a non-randomized study and the results should be interpreted with caution.

**Keywords: COVID-19, tocilizumab, intensive care unit**

## Tocilizumab reduce el riesgo de ingreso en UCI y la mortalidad en pacientes con infección por SARS-CoV-2

## RESUMEN

**Objetivos.** La respuesta inmune en algunos pacientes con infección por SARS-CoV-2 se encuentra desequilibrada desencadenando un síndrome de distrés respiratorio agudo que en muchos casos requiere ingreso en la unidad de cuidados intensivos (UCI). El número limitado de camas de UCI ha sido uno de los mayores retos del manejo a nivel mundial; siendo fundamental, por tanto, el desarrollo de estrategias clínicas que eviten el ingreso en UCI. Nuestro objetivo fue describir la influencia del tratamiento con tocilizumab en la necesidad de traslado a UCI o muerte en pacientes no críticos.

**Material y métodos.** Estudio retrospectivo que incluyó 71 pacientes con infección por SARS-CoV-2 ingresados en planta convencional que no presentaron criterios de traslado a UCI durante las primeras 24h posteriores al ingreso. Los criterios para la administración de tocilizumab fueron el deterioro radiológico, el aumento de la necesidad de oxigenoterapia o el incremento de los parámetros inflamatorios, sin embargo, la decisión final fue tomada por el médico tratante. El resultado primario fue la necesidad de ingreso en UCI o muerte, según lo que ocurriera primero.

**Resultados.** 77 pacientes recibieron tocilizumab y 94 no. El grupo de tocilizumab tuvo menos ingresos en UCI (10,3% frente a 27,6%, *P*=0,005) y menor necesidad de ventilación invasiva (0 frente a 13,8%, *P*=0,001). En el análisis multivariante, tocilizumab permaneció como variable protectora (OR: 0,03, IC 95%: 0,007-0,1, *P*=0,0001) de ingreso en UCI o muerte.

**Conclusiones.** El tratamiento con tocilizumab en estadios precoces de la respuesta inflamatoria podría reducir un número importante de ingresos en UCI y la necesidad de ventilación mecánica. La tasa de mortalidad del 10,3% entre los pacientes que reciben tocilizumab parece ser más baja que en otras series publicadas. No obstante, se trata de un estudio no aleatorizado por lo que los resultados deben interpretarse con cautela.

**Palabras clave: COVID-19, tocilizumab, unidad de cuidados intensivos.**

## INTRODUCTION

Infection by Coronavirus 2 (SARS-CoV-2) emerged in December 2019 in Wuhan and rapidly spread around the world. SARS-CoV-2 pneumonia evolves in 2 different phases, the first one is characterized by a high viral replication and classical symptoms of a respiratory virus infection, including fever, malaise, myalgia, and cough [1]. About 80% of the patients control the infection within a week but 15-20% of them develop a severe respiratory failure fulfilling the definition of acute respiratory distress syndrome (ARDS) with many requiring intensive care management [2]. The blood tests reveal lymphopenia, and high levels of C-reactive protein (CRP), ferritin, and D-dimer values [1], all related with the activity of different cytokines (IL-1beta, IL-2, IL-6, IL-8, IL-17, IFN-gamma or TNF-alpha) [3]. Therefore, the main therapeutic objective during the first days of treatment is to stop the viral replication while afterwards blocking the tissue damage induced by the cytokine storm is paramount [4].

In agreement with the immunopathogenesis, it has been proposed to treat patients during the inflammatory flare with IL-6 inhibitors [5,6]. The first description included 21 patients admitted to a Chinese hospital who received tocilizumab, a recombinant humanized anti-IL-6 receptor monoclonal antibody. In a few days, symptoms improved remarkably, 75% had lowered their oxygen intake and no patient died [7]. From that communication, a meta-analysis of observational studies including 9850 patients showed a significant reduction in mortality among patients receiving tocilizumab (aRR 0.77; 95%CI 0.63-0.95) [8]. However, a meta-analysis of clinical trials including 1310 patients did not supported this finding [9]. Potential explanations for this discrepancy are the low number of patients with low mortality rate included in these trials, or the fact that the majority of the studies evaluated mortality at 28 days but the observed reduction in the risk of ICU admission or mechanical ventilation observed as secondary endpoints in some clinical trials [10,11] probably will impact in later mortality. More recently, a not peer-reviewed publication of preliminary results of RECOVERY trial showed a significant reduction in the mortality rate and in the need of mechanical ventilation [12].

The main objective of the present article is to describe our experience during pandemic with tocilizumab in non-critically ill patients and its impact on the prognosis, defined as eventual need of transfer to the ICU or death.

## MATERIAL AND METHODS

From February 19th to April 16th patients with respiratory symptoms and radiological evidence of pneumonia (uni or bilateral interstitial infiltrates) and those with respiratory symptoms without pneumonia but with co-morbidity (hypertension, diabetes mellitus, cancer, chronic liver diseases, chronic obstructive pulmonary disease or immunosuppression) were admitted to Hospital Clínic of Barcelona in the context of SARS-CoV-2 pandemic. Definitive diagnostic was stablished by a positive polymerase chain reaction (PCR) from a nasopharyngeal swab during the first two weeks of pandemic but once the prevalence of positive tests was >70%, the diagnosis was based on clinical criteria. Clinical criteria for defining a case of

SARS-CoV-2 were the presence of respiratory symptoms with uni or bilateral interstitial infiltrate in the chest-X ray without evidence of other potential causes (e.g. heart failure). During the study period, 171 patients that did not qualify as requiring transfer to the ICU during the first 24h after admission to a conventional hospital ward, were included.

For ARDS, the Berlin definition [13] was applied. When $PaO_2$ was not available, $SpO_2/FiO_2 \leq 315$ suggested ARDS (including in non-ventilated patients) [14].

The standard protocol included antiviral treatment that consisted of lopinavir/ritonavir 400/100 mg BID for 7-14 days plus hydroxychloroquine 400 mg/12h on the first day, followed by 200 mg/12h for the next 4 days. From the 18th of March onwards, azithromycin 500 mg the first day and 250 mg/24h for 4 additional days was added to the regimen. In addition, a clinical trial with remdesivir was enrolling patients in our institution during the study period. All patients with risk factors for thrombosis received prophylactic doses of low molecular weight heparin [15]. Intravenous methylprednisolone was recommended for patients with disease progression to ARDS. The local protocol suggested the use of tocilizumab for patients with pneumonia, progressive respiratory failure (increasing fraction of inspired oxygen) and CRP ≥ 8 mg/dL or ferritin ≥800 ng/mL or lymphocyte count < 800 cells/$mm^3$. The dose was 400 mg/24h iv for patients with ≤75 kg and 600 mg/24h iv for those with >75 kg with the possibility to repeat the dose every 12h up to 3 doses in case of only partial response. However, due to the lack of evidence to support its efficacy, the ultimate decision about using tocilizumab was left to the judgement of the attending physician.

Patients with severe comorbidity and a life expectancy <6 months were considered no tributary of advanced life support (ALS). The outcome variable was a composite of the need of ICU admission or death whichever came first. The last revision of medical charts was April 26th.

The Institutional Ethics Committee of the Hospital Clínic of Barcelona approved the study and due to the nature of retrospective chart review, waived the need for inform consent from individual patients (Comité Ètic d'Investigació Clínica; HCB/2020/0273).

**Statistical analysis.** Categorical variables were described using the absolute number and percentage and continuous variables using the mean and standard deviation (SD). Categorical variables were compared using a Chi-squared test or Fisher exact test when necessary, and means by using the Student-t test. For multivariable analysis, variables with a *P*-value ≤ 0.2 in the univariable analysis were subjected to further selection by using a backward logistic regression procedure. Interactions between variables were explored. In order to reduce the effect of selection bias, we estimate the propensity score (PS) to receive tocilizumab as the predicted probability from a logistic regression model using tocilizumab as the dependent variable. The PS was included in the multivariable analysis of the main outcome. The calibration of the model was assessed by means of the Hosmer-Lemeshow goodness-of-fit test. Statistical significance was defined as a two-tailed *P* value <0.05. The analysis was performed in SPSS version 23 (SPSS Inc., Chicago, IL).

## RESULTS

The cohort included 171 patients, of whom 77 received tocilizumab while staying in a conventional ward and 94 did not, with a mean (SD) age of 61.5 (12.4) and 61.4 (16) years, respectively. The proportion of males and the main comorbidities were similar between both groups (Table 1). Patients in the tocilizumab group had more frequently fever, pneumonia (interstitial infiltrate) and at day 1 they needed more often oxygen therapy. C-reactive protein levels were significantly higher in the tocilizumab group (9.7 mg/dL vs. 7.5 mg/dL, *P*=0.04) but other biological parameters were similar in both groups. During patients' stay in a conventional ward, corticosteroid therapy was more frequently administered in the tocilizumab group (50.6% vs. 27.7%, *P*=0.002). A total of 26 patients were not candidates to ALS, 10 (12.9%) in the tocilizumab group and 16 (17%) among controls. The mean (SD) time from symptoms onset to hospital admission in tocilizumab group was 6.5 (3.3) days while it was 5 (6.5) days in the control group.

The outcome of both groups, with all patients discharged alive or dead, showed that patients in the tocilizumab group had significantly less ICU admissions (10.3% vs. 27.6%, *P*=0.005) and less need of invasive ventilation (0 vs 13.8%, *P*=0.001). The univariable analysis of our composite outcome (ICU admission or death whichever came first) showed that comorbidities (hypertension, heart diseases and lymphoma), the need of oxygen at day 1, a CRP > 16 mg/dL and the development of cardiovascular, renal or respiratory (ARDS, invasive ventilation) complications were significantly associated with the primary outcome. In contrast, tocilizumab was the only one protective variable (Table 2). In the multivariable analysis, including the PS estimate to receive tocilizumab as a potential confounder, tocilizumab remained as a strong protective variable (OR: 0.03, CI 95%: 0.007-0.1, *P*=0.0001) of ICU admission or death (Table 3).

## DISCUSSION

Monoclonal antibodies directed against key inflammatory cytokines represent a class of potential adjunctive therapies for SARS-CoV-2 infected patients. The rationale for their use is that the underlying pathophysiology of significant lung damage is caused by a cytokine storm being IL-6 one of the main drivers. Therefore, monoclonal antibodies against IL-6 or its receptor could theoretically improve clinical outcomes mainly by reducing the need of ICU admission and consequently the associated mortality. Tocilizumab, a monoclonal antibody IL-6 receptor antagonist, was administered to 77 patients admitted to a conventional ward in our hospital and the outcome was compared with 94 patients also admitted in a conventional ward during the same period of time that did not

**Table 1** **Characteristics and outcome of patients that received or did not received tocilizumab in a conventional ward.**

| Variables | Tocilizumab group (N=77) | Control group (N=94) | *P* - value |
|---|---|---|---|
| Mean (SD) age in years | 61.5 (12.4) | 61.4 (16.0) | 0.957 |
| Age > 62 years old (%) | 40 (52) | 52 (55.3) | 0.660 |
| Male (%) | 53 (68.8) | 59 (62.7) | 0.406 |
| Comorbidities (%) | | | |
| Hypertension | 35 (45.4) | 43 (45.7) | 0.960 |
| Heart diseases | 12 (15.5) | 21 (22.3) | 0.265 |
| Chronic respiratory disease | 8 (10.3) | 12 (12.7) | 0.630 |
| Diabetes Mellitus | 12 (15.6) | 14 (15) | 0.900 |
| Mean (SD) days from symptoms onset to admission | 6.5 (3.3) | 5 (6.5) | 0.061 |
| Initial characteristics (%) | | | |
| Fever | 86 (98.7) | 80 (85) | 0.002 |
| Dyspnea | 33 (43) | 47 (50) | 0.352 |
| Cough | 64 (83) | 70 (74.5) | 0.172 |
| Normal chest x-ray at admission | 3 (4) | 14 (15) | 0.017 |
| Need of oxygen therapy at day 1 | 56 (72.7) | 50 (53.8) | 0.011 |
| Positive PCR from a nasal swab | 68 (88.3) | 82 (87.2) | 0.831 |
| Laboratory at admission mean (SD) | | | |
| D-dimer (ng/mL)[a] | 918.6 (1354.8) | 1503.9 (2175.4) | 0.100 |
| Lymphocytes count (cell/mm$^3$) | 878.9 (452.8) | 910.1 (534.6) | 0.686 |
| C-Reactive protein (mg/dL)[b] | 9.7 (7.4) | 7.5 (5.7) | 0.044 |
| Serum ferritin (ng/dL)[c] | 867.8 (871) | 904.1 (809.9) | 0.842 |
| ARDS at any given time (%) | 24 (31.1) | 26 (27.6) | 0.616 |
| Treatments received (%) | | | |
| Antiviral agents[d] | 77 (100) | 91(96.8) | 0.164 |
| Steroid prior ICU admission | 39 (50.6) | 26 (27.7) | 0.002 |
| Not candidate to ALS (%) | 10 (12.9) | 16 (17) | 0.465 |
| Mean (SD) days of follow up | 11.2 (6.2) | 14.7 (10.6) | 0.027 |
| Outcomes (%) | | | |
| Need of ICU | 8 (10.3) | 26 (27.6) | 0.005 |
| Need of no invasive MV | 3 (3.9) | 1 (1) | 0.198 |
| Need of invasive MV | - | 13 (13.8) | 0.001 |
| Extubation | - | 9 (9.6) | - |
| Discharge from ICU | 5 (6.5) | 21 (22.3) | - |
| Hospital discharged | 69 (89.6) | 77 (81.91) | 0.156 |
| Still in the hospital | 0 (0) | 0 (0) | - |
| Mortality (%) | | | |
| Global mortality | 8 (10.3) | 17 (18) | 0.156 |
| Mortality in: | | | |
| Not candidates to ALS | 6 (60) | 12 (75) | 0.420 |
| Candidates to ALS | 2 (3) | 5 (6.4) | 0.337 |

PCR, polymerase chain reaction. ADRS, adult distress respiratory syndrome. ICU, intensive care unit. ALS, advanced life support. MV, mechanical ventilation. [a]Measured in 110 patients; [b]Measured in 168 patients: [c]Measured in 86 patients; [d]See material and methods for antivirals used in our protocol.

**Table 2** Variables associated with ICU admission and/or death whichever came first.

| Variables | No ICU admission and/or death, N=121 | ICU admission or death, N=50 | *P* - value |
|---|---|---|---|
| Age >62 years (%) | 57 (47) | 35 (70) | 0.006 |
| Male sex (%) | 77 (63.6) | 35(70) | 0.426 |
| Mean (SD) follow-up, days | 12 (8.347) | 16.6 (9.858) | 0.006 |
| Comorbidities (%) | 98 (81) | 48 (96) | 0.012 |
| Hypertension | 49 (40.5) | 29 (58) | 0.037 |
| Diabetes Mellitus | 20 (16.5) | 6 (12) | 0.453 |
| Heart diseases | 17 (14) | 16 (32) | 0.007 |
| Chronic respiratory disease | 11 (9) | 9 (18) | 0.099 |
| Neoplasia | 11(9) | 6(12) | 0.580 |
| Dyslipemia | 8 (6.6) | 6 (12) | 0.356 |
| Lymphoma | 2 (1.7) | 5 (10) | 0.012 |
| Solid organ transplantation | 5 (4) | 3 (6) | 0.693 |
| Human Immunodeficiency Virus | 1(0.8) | - | 1 |
| Mean (SD) days from symptoms onset to admission | 5.98 (6.124) | 4.86 (3.084) | 0.223 |
| Initial characteristics (%) | | | |
| Fever | 112(92.6) | 44 (88) | 0.337 |
| Dyspnoea | 59 (48.8) | 21 (42) | 0.420 |
| Cough | 98 (81) | 36 (72) | 0.222 |
| Normal chest x-ray at admission | 12 (10) | 5 (10) | 0.987 |
| Need of oxygen therapy at day 1 | 68 (56.7) | 38 (76) | 0.018 |
| Positive PCR from nasal swab | 105 (86.8) | 45 (90) | 0.559 |
| Laboratory at admission (%) | | | |
| Lymphocytes count <700 cell/mm$^3$ [a] | 36 (29.8) | 18 (36) | 0.424 |
| C-Reactive protein >9 mg/dL [b] | 39 (32.5) | 20 (41.7) | 0.261 |
| C-Reactive protein >16 mg/dL [b] | 23 (19) | 25 (50) | 0.0001 |
| Treatments received (%) | | | |
| Antiviral agents[c] | 118 (97.5) | 50 (100) | 0.261 |
| Steroids prior ICU admission | 44 (36.4) | 21 (42) | 0.490 |
| Tocilizumab | 65 (53.7) | 12 (24) | <0.0001 |
| Complications (%) | | | |
| Cardiovascular | 5 (4) | 13 (7.6) | 0.012 |
| ARDS in the conventional ward | 14 (11.6) | 30 (60) | 0.0001 |
| Acute Kidney Injury | 3 (1.8) | 12 (24) | 0.0001 |
| Invasive ventilation | - | 13 (26) | 0.0001 |
| Not candidate to ALS | 8 (6.6) | 18 (36) | 0.0001 |

PCR, polymerase chain reaction. ICU, intensive care unit. ADRS, adult distress respiratory syndrome. ALS, advanced life support.
[a]Measured in 110 patients; [b]Measured in 168 patients; [c]See material and methods section for antivirals used in our protocol.

receive tocilizumab. Although this study was not randomized, the characteristics of both groups did not differ in terms of demographics and comorbidities. Moreover, the tocilizumab group had more severe infection (pneumonia, need of oxygen at day 1 or higher CRP). Furthermore, all the patients were evaluated during the same period of time so the same criteria for being transferred to the ICU was applied. After adjusting for potential confounders, including the PS for receiving to-

**Table 3** Variables significantly associated with the risk of being admitted in the ICU and/or death in the multivariable analysis.

| Variables[a] | Adjusted odd ratio (95% CI) | *P* - value |
|---|---|---|
| Lymphoma | 16.7 (1.7-157.3) | 0.01 |
| Heart disease | 2.9 (0.9-9.4) | 0.07 |
| Need of oxygen at day 1 | 3.4 (1.1-10.5) | 0.03 |
| ARDS prior to ICU admission | 50.7 (10.4-245.7) | 0.0001 |
| Not candidate to ALS | 3.8 (1.2-11.7) | 0.01 |
| Tocilizumab | 0.03 (0.007-0.1) | 0.0001 |

**ARDS, Adult respiratory distress syndrome. ICU, intensive care unit. ALS, advanced life support.**

**[a] Variables included in the analysis: age > 62 years, chronic respiratory disease, hypertension heart disease, lymphoma, C-reactive protein >16 mg/dL, need of oxygen at day 1, cardiovascular complications, ARDS in the conventional ward, not candidate to ALS, tocilizumab administration, propensity score to receive tocilizumab. Acute kidney injury and invasive ventilation were complications that occurred after being admitted in the ICU, therefore, they were not included for the main outcome analysis since this include the need of being admitted in the ICU.**

cilizumab, the multivariable analysis revealed that tocilizumab was an independent factor associated with a reduction in the need of ICU admission and death. The need of ICU in the tocilizumab group was almost 3 times lower (10.3% vs. 27.6%) than in controls and it was lower than the one reported in Wuhan hospitals (26%) [1,16] or more recently in New York (14%) [17]. The availability of ICU beds is critical for the management of patients that develop a severe ARDS in few hours, therefore, reducing the need of ICU beds using tocilizumab impacted directly not only on the outcome of patients that received the treatment but also of those that not receiving tocilizumab or arriving too late in a critically ill condition had more chances of being admitted in the ICU. In line with this, the mortality of our cohort, including patients not candidates to ALS, was 14.2% which seems lower than that showed in previous reports, regularly >20% [1,16,17].

Although from the beginning of the pandemic tocilizumab was recommended in the general protocol, the heterogenicity of its prescription could be explained by the lack of clinical randomized trials supporting its usefulness.

Our results suggest that tocilizumab should be administered in early phases of the inflammatory flare. It is reasonable to hypothesize that other strategies directed to inhibit other specific inflammatory pathways (including IL-1 with anakinra or INF-gamma with JAK inhibitors), or a broad-spectrum inhibition with steroids with or without therapeutic strategies to reduce the pro-coagulant status, could be also effective [18-20]. On the other hand, although in non-severe cases after one week from symptoms onset the viral viability is significantly reduced, there is data supporting the continuous viral replication in severe cases [21] that could be the trigger for the inflammatory flare and its maintenance. Accordingly, we consider that antiviral agents should be associated with immunomodulators.

In conclusion, our findings support that the administration of tocilizumab in the early stages of the inflammatory flare, particularly before the need of ICU admission, is more convenient and could potentially avoid an important number of ICU admissions and mechanical ventilation use. Consequently, the mortality rate of 10.3% among patients receiving tocilizumab appears to be lower than that described by others in previously published series. However, this is a non-randomized study and, therefore, the results should be interpreted with caution.

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The authors declare that they have no conflicts of interest

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