

## RESEARCH ARTICLE – ARTICLES DE RECHERCHE

**A REDUCED FIXED DOSE OF TOCILIZUMAB 200 MG COMPARED TO 400 MG IN PATIENTS WITH SEVERE COVID-19 DISEASE**Stela COJOCARU<sup>1</sup>, Irina RUSSU<sup>1</sup>, Galina BUTA<sup>1</sup>, Sebastian BERSAN<sup>1</sup>, Valentina POTING-RASCOV<sup>1</sup>, Natalia CULIUC<sup>2</sup>, Lilia BABA<sup>2</sup><sup>1</sup>Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova<sup>2</sup>Toma Ciorba Clinical Hospital of Infectious Diseases, Chisinau, Republic of Moldova

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**Keywords:** COVID-19, Cytokine Storm, Tocilizumab, severe forms, oxygen therapy.**Introduction.** Excessive, deregulated pro-inflammatory cytokine secretion has a detrimental impact on the evolution of COVID-19, aggregating the tissue impairment, organ failure, and an increased risk of death. Several studies have demonstrated the beneficial effect of Tocilizumab (TCZ) in reducing hyperimmune response in severe forms of COVID-19. **Material and methods.** This is an experimental controlled clinical trial, consisting of 66 patients hospitalized with severe COVID-19. **Results.** On average, the decision to administer TCZ was made on average on the 11.34±0.31 day of the disease, when the beginning of Cytokine Storm was suspected in the patients already on dexamethasone treatment. The clinical and paraclinical parameters, including fever, asthenia and dyspnea duration, SpO<sub>2</sub> level, oxygen therapy need, improvement of the radiological picture, and duration of hospitalization were more favorable in patients treated with TCZ 400 mg compared to those treated with TCZ 200 mg ( $p < 0.0001$ ). The relative risk of rapid worsening after TCZ (RR=0.88), the relative risk of decreasing blood pressure (RR=0.29) and the relative risk of transfer to intensive care units for invasive or non-invasive ventilation (RR=0.8) was lower in patients treated with TCZ 200 mg compared to the 400 mg TCZ lot. **Conclusions.** The dose of TCZ had a significant impact on the duration of clinical manifestations, the duration of oxygen therapy and the duration of patient hospitalization, with better results for TCZ 400 mg compared to TCZ 200 mg. Although the risk of worsening after TCZ and the risk of transfer to intensive care were lower in patients treated with TCZ 200 mg. So, the 200 mg fixed dose of TCZ can be a life-saving option for severely ill patients with COVID-19 in the context of IL-6 inhibitor supply shortages.**Cuvinte-cheie:**

COVID-19, furtună de citokine, Tocilizumab, forme severe, terapie cu oxigen.

**DOZĂ REDUSĂ DE TOCILIZUMAB 200 MG, COMPARATIV CU 400 MG, LA PACIENȚII CU FORME SEVERE DE INFECȚIE COVID-19****Introducere.** Eliberarea excesivă a citokinelor proinflamatorii are un impact negativ asupra evoluției infecției COVID-19, sporind afectarea tisulară, insuficiența organică și riscul de deces. Mai multe studii au demonstrat efectul benefic al preparatului Tocilizumab (TCZ) în reducerea răspunsului hiperimun în formele severe de infecție COVID-19. **Material și metode.** Este un studiu experimental, clinic controlat, care include 66 pacienți, internați cu forme severe de infecție COVID-19. **Rezultate.** Decizia privind administrarea de TCZ a fost luată în medie în ziua a 11,34±0,31 de boală, când a fost suspectat debutul furtunii de citokine la pacienții aflați deja în tratament cu dexametazonă. Parametri clinici și paraclinici, precum durata febrei, asteniei și a dispneei, nivelul SpO<sub>2</sub>, necesitatea în terapie cu oxigen, ameliorarea tabloului imagistic radiologic, și durata spitalizării au fost mai favorabili la pacienții tratați cu TCZ 400 mg față de cei tratați cu TCZ 200 mg ( $p < 0.0001$ ). Riscul relativ de agravare rapidă după administrarea TCZ (RR=0,88), riscul relativ de diminuare a tensiunii arteriale (RR=0,29) și riscul relativ de transfer în secțiile de terapie intensivă pentru ventilație invazivă sau non-invazivă (RR=0,8) a fost mai scăzut la pacienții tratați cu TCZ 200 mg, comparativ cu lotul TCZ 400 mg. **Concluzii.** Doza de TCZ a influențat durata manifestărilor clinice, durata terapiei cu oxigen și durata spitalizării pacienților, cu rezultate mai bune pentru TCZ 400 mg față de TCZ 200 mg, deși riscul de agravare după TCZ și riscul de transfer în terapie intensivă au fost mai joase la pacienții tratați cu TCZ 200 mg. Deci, doza de TCZ de 200 mg poate fi o opțiune de salvare a vieții pacienților gravi cu infecție COVID-19, în contextul deficitului de aprovizionare cu inhibitori de IL-6.

## INTRODUCTION

The COVID-19 pandemic caught the medical community by surprise and totally unprepared. After two years of brainstorming, COVID-19 still has many unclarified pathogenetic and therapeutic issues. Cytokines are essential for tissue homeostasis and, as mediators, unleash an effective immune response during infections (1, 2). However, the deregulated excessive pro-inflammatory cytokine secretion has a detrimental impact on the evolution of COVID-19, aggregating the hemodynamic alterations, tissue impairment, organ failure, and increasing the risk for death (3, 4, 5).

It is considered that COVID-19 evolves in several stages, each with its specific pathogenetic and clinical characteristics: early stage – marked by high multiplication of SARS CoV-2; stage IIA – distinct by the appearance of pulmonary pathology; stage IIB – defined by pulmonary involvement with hypoxia and the beginning of systemic inflammation; stage III – expressed by evolution to extrapulmonary systemic hyper inflammation syndrome (6). Interestingly, there is no concluding association between the clinical aggravation of the patients in the second week of the disease and viral load, supporting the primordial role of the immune response in COVID-19 severity (7). Thus, for clinicians is extremely important to understand all pathophysiologic stages in the disease's evolution and correctly appreciate the appropriate moment for antivirals, corticosteroids, and cytokine inhibitors administration.

It is commonly considered that IL-6 plays the fundamental role among pro-inflammatory cytokines in the progression of SARS CoV-2 infection (8, 9, 10). IL-6 signalling in the vascular endothelium has a key role in the imbalance toward the prothrombotic state (11, 12, 13). Pulmonary inflammation could trigger local vascular dysfunction and fibrinolysis, thus contributing to fibrin deposition and dysfunction of alveolar-capillary blood gas exchange (14, 15). In this setting, several studies have demonstrated the beneficial effect of IL-6 inhibitors in reducing hyperimmune response in severe forms of COVID-19 (16 - 20). The therapeutic effect of IL-6 inhibitors in COVID-19 patients with exaggerated systemic inflammatory response was investigated in randomized, controlled platform trials, RECOVERY, and REMAP-CAP, that revealed its beneficial effect on the survival rate (21, 22). These studies

prompted the introduction of Tocilizumab (TCZ), a monoclonal antibody that inhibits the Interleukin-6 (IL-6) receptor in the treatment guidelines for severe COVID-19 (23 - 26). Reminding the pathogenetic stages of disease evolution in SARS CoV-2 infection is essential to realize the significance of the time frame of TCZ administration during COVID-19: not too early, but not too late. Thus, IL-6 inhibitors may not give additional benefits while the patient is already in a critical state and require invasive mechanical ventilation (27, 28). In most studies, TCZ is administered to patients already severely hypoxemic, requiring mechanical ventilation, even in a critical state or within the first hours of life support measures such as invasive or non-invasive ventilation. This may partially be the cause of the lack of plausible results of TCZ treatment in some trials of COVID-19 (29, 30, 31).

Taking into consideration the pathogenesis of excessive systemic inflammatory immune response in severe cases of SARS CoV-2 infection, Tocilizumab was the second drug highly suggested by the WHO for COVID-19 severe or critical cases treatment after dexamethasone recommendation in September 2020. Administration of IL-6 inhibitors for COVID-19 has been prequalified from rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis (SJIA) treatment schedules. The recommended dose of TCZ accepted by most guidelines for COVID-19 is 8 mg/kg up to a maximum of 800 mg, as an intravenous bolus infusion, and a second dose administration can occur 12 to 48 hours later. Other studies proved that a dose of TCZ 400 mg demonstrates an equivalent reduction of inflammation and comparable mortality to a dose of 8 mg/kg (32). The COVIDOSE study concluded that TCZ 4–8 mg/kg dose might be too much for patients with COVID-19 hyper inflammation syndrome. The dose-finding studies, especially of minimal acceptance, and the administration time frame that can provide a valuable anti-inflammatory effect in COVID-19 hypercytokine response have not yet been fully completed.

*The study aimed* to compare physiological responses and clinical outcomes of IV TCZ 200 mg vs. 400 mg fixed dose bolus in patients with severe COVID-19 that do not require invasive ventilation at the moment of administration. The study was also reasoned by the shortages of IL-6 inhibi-

tors supply in the Republic of Moldova during the pandemic period.

## MATERIAL AND METHODS

A controlled experimental clinical trial was conducted. This study was carried out with the approval of the Ethics Committee no. 02/02.10.2020 of the *Nicolae Testemitanu* State University of Medicine and Pharmacy, Republic of Moldova. After obtaining the patients' agreement to participate in the research, two groups of patients with COVID-19 infection, severe form, hospitalized between December 2020 and June 2021 in the Toma Ciorba Clinical Hospital for Infectious Diseases, Republic of Moldova, were made. A total of 66 patients were included in the study. Group ratio 1:1 (L1=33, L2=33). Patients in the research group (L1) were treated with a single intravenous dose of Tocilizumab at 200 mg. Those in the control group (L2) received a single intravenous dose of Tocilizumab at 400 mg. The TCZ dose decision was made randomly.

The diagnosis of COVID-19 was confirmed by detecting SARS-CoV-2 RNA by PCR tests. Patients were not COVID-19 vaccinated, and no one received monoclonal antibodies targeting the spike glycoprotein or antiviral treatment against SARS CoV-2 during the study period. Criteria for inclusion in the study were: people over the age of 18 with severe forms of COVID-19 who developed signs of cytokinic storm. The data from the patients' medical records were processed according to a unified, pre-established form that included epidemiological, socio-demographic, clinical, para-clinical, laboratory data, and information on therapeutic management. Data were collected from the day of hospitalization till the date of discharge or transfer to ICU.

A decision regarding TCZ administration was made when the beginning of Cytokine Storm (hypercytokinemia) was suspected in the patients already on dexamethasone treatment.

Criteria for TCZ administration were the combination of fever  $>38^{\circ}\text{C}$ , prolonged or reappearance in the second wave, exacerbation of asthenia, intensification of dyspnea, advancing hypoxemia  $\text{SpO}_2 \leq 94\%$  at rest on room air, bilateral lung involvement with progressive negative evolution of imaging over the last 24-48 hours, requirement of oxygen supplementation 10 L/min within 24-48 hours of commencement of respiratory support

on nasal oxygen, absence of general improvement following treatment with corticosteroids (dexamethasone).

Exclusion criteria for the study group were: age below 18 years old, pregnancy, pre-existing treatment resulting in ongoing immunosuppression, co-existing diseases that might be worsened by IL-6 inhibitors, such as systemic fungal or bacterial co-infection, patients in shock, a necessity in non-invasive/invasive ventilation before TCZ administration, patients with poor prognosis indicating an unlikely survival of over 48 h.

Clinical and paraclinical parameters of patients at admission and during treatment, the presence of comorbidities, the persistence of fever after treatment with TCZ and its duration, the rate of patients with low oxygenation ( $\text{SpO}_2 < 94\%$ ) and the terms of improvement of  $\text{O}_2$  saturation, the proportion of patients transferred to intensive care department for invasive or non-invasive ventilation, as well as the duration of hospitalization were evaluated. The accumulated data were entered into Excel. The statistical evaluation of the data obtained was performed using the MedCalc program. To estimate the efficacy of treatment in the compared groups, tests were evaluated: Arithmetic mean  $\pm$  mean error ( $M \pm m$ ), p-significance coefficient ( $p < 0.05$ ), Relative Risk (RR), 95% Confidence Interval (95%CI) and Number Needed to Treat (NNT).

## RESULTS

The average age of the patients included in the study was  $58.22 \pm 1.38$  years, L<sub>1</sub> group -  $58.6 \pm 2.3$  y/o, L<sub>2</sub> group -  $57.8 \pm 1.6$  [95%CI (0.17-1.77),  $p=0.11$ ]. The male/female ratio in the total group was 0.83, L<sub>1</sub> group - 0.5 and L<sub>2</sub> group - 1.35. Feminine gender predominates in the L<sub>1</sub> group - 22 (66.7%) patients, L<sub>2</sub> group - 14 (42.4%) patients [95%CI (0.99-7.38),  $p=0.05$ ], while masculine gender predominate in the L<sub>2</sub> group - 19 (57.6%) patients, L<sub>1</sub> group - 11 (33.3%) patients [95%CI (0.14-1.0),  $p=0.05$ ]. Contact with the patients with COVID-19 was confirmed in 28 (42.4%) cases.

Patients were hospitalized during the different periods of disease evolution. The average day of hospitalization from the onset of the disease was  $7.86 \pm 0.38$  (2-14) days. The main clinical manifestations of the patients in the total group while entering the hospital were fever, fatigue, cough, dyspnea and headache (fig. 1).

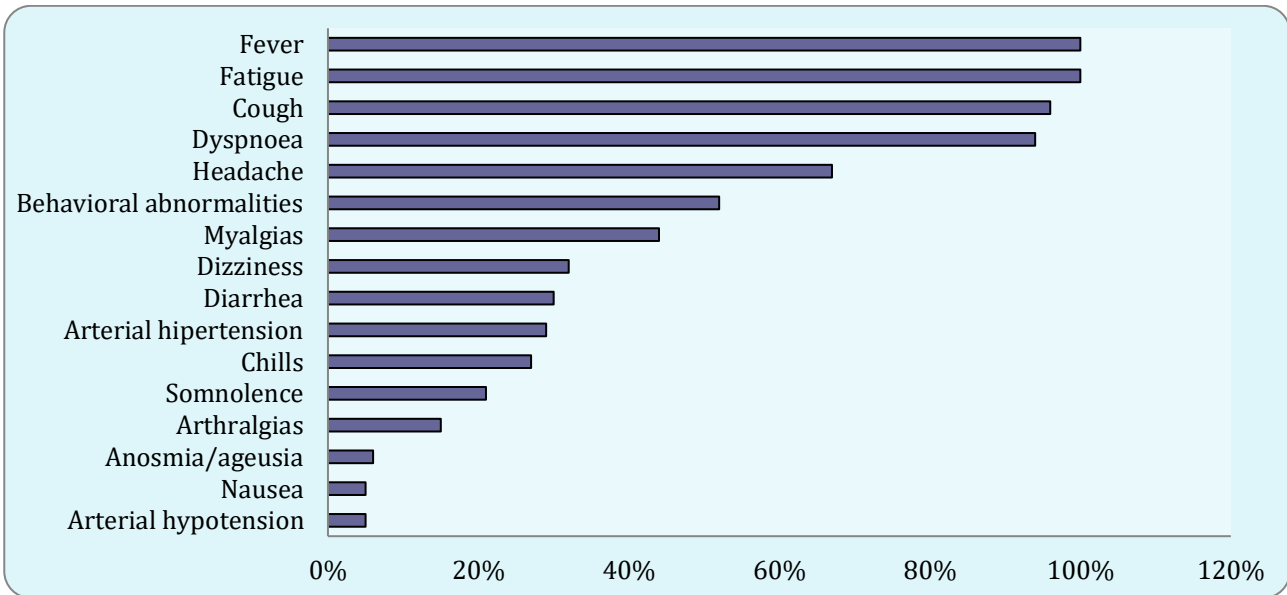


Figure 1. The main clinical manifestations in the total group while entrance to the hospital.

Patients also suffered from different comorbidities with negative potentiality on the evolution of COVID-19, such as arterial hypertension and chronic cardiovascular diseases 33 (50.0%) patients, diabetes mellites 21 (31.8%) patients, severe obesities 20 (30.3%) patients. Only 10 (15.15%) patients, average age 57.93±1.6 y.o.,

were without confirmed comorbidities at the moment of hospitalization. There wasn't a statistically significant difference in the L<sub>1</sub> and L<sub>2</sub> groups in the prevalence of comorbidities that could substantially influence the evolution of COVID-19 (tab. 1).

Table 1. Distribution of patients by study groups and main comorbidities.

Comorbidities	L <sub>1</sub> group TCZ 200 mg	L <sub>2</sub> group TCZ 400 mg	p	RR	95%CI (RR)	NNT
<b>Arterial hypertension and chronic cardiovascular diseases</b>	17 (51.5%)	16 (48.5%)	0.81	1.06	0.65-1.72	33.0
<b>Diabetes mellites</b>	9 (27.3%)	12 (36.4%)	0.43	0.75	0.37-1.53	11.0
<b>Severe obesities</b>	8 (24.2%)	12 (36.4%)	0.29	0.67	0.31-1.41	8.25
<b>Chronic renal diseases</b>	5 (15.1%)	5 (15.1%)	1.0	1.0	0.26-3.84	-
<b>Chronic hepatitis</b>	3 (9.1%)	4 (12.1%)	0.69	0.75	0.18-3.09	33.0
<b>Chronic pulmonary diseases</b>	1 (3.0%)	3 (9.1%)	0.32	0.32	0.04-2.96	16.3
<b>Autoimmune thyroiditis</b>	1 (3.0%)	3 (9.1%)	0.32	0.32	0.04-2.96	16.3

Note: RR and NNT were computed for the experimental group

The duration of fever before TCZ administration was 7.89±0.32 (1-14) days in the total group: L<sub>1</sub> group - 7.81±0.38 (3-13) days, L<sub>2</sub> group - 7.69±0.53 (1-14). This was on average on the 11.34±0.31 day of the disease, L<sub>1</sub> group - 11.36±0.44 (5-16), L<sub>2</sub> group - 11.33±0.43 (7-16), [95%CI (0.18-0.24), P=0.78].

The level of SpO<sub>2</sub> (%) before TCZ administration was 85.02±0.77 (68-94) in the total group, L<sub>1</sub> group - 85.09±1.03 (78-94), L<sub>2</sub> group - 84.94±1.15 (68-94), [95%CI (0.39-0.69), P=0.58]. It is necessary to mention that TCZ typically leads

to the temporary worsening of the patients' general state within several days, usually manifested by the progression of asthenia and temporary reduction of SpO<sub>2</sub>, usually by 5-7%. The first symptom of patient improvement was the decrease in the level of fever, then the increase of SpO<sub>2</sub>, after that - asthenia reduction, and the last - dyspnea disappearance. Subsequently, administration of an IL-6 inhibitor, the improvement in the general state of the patients was TCZ-dose-dependent, with better results registered for the L<sub>2</sub> group, which also led to a shorter duration of oxygen therapy (tab. 2).



**Table 2.** Duration of clinical manifestations subsequently administration of TCZ.

Manifestations	L <sub>1</sub> group TCZ 200 mg	L <sub>2</sub> group TCZ 400 mg
Fever duration, days (minimum-maximum days)	2.09±0.25 (1-5)	0.28±0.09 * (1-2)
On what day post-TCZ the general state improves according to the patients' appreciation, (minimum-maximum days)	7.29±0.74 (1-8)	5.26±0.53 * (2-8)
Average of minimal SpO <sub>2</sub> , % (minimum-maximum %)	88.7±0.64 (78-94)	90.15±0.6 * (80-94)
On what day does SpO <sub>2</sub> start to increase (minimum-maximum days)	4.95±0.46 (1-10)	4.08±0.46 * (1-14)
On what day does SpO <sub>2</sub> ≥95 (minimum-maximum days)	9.44±0.97 (3-22)	7.13±0.75 * (2-19)
Duration of asthenia, days (minimum-maximum days)	7.29±0.74 (2-16)	5.26±0.53 * (1-15)
Duration of oxygen therapy, days (minimum-maximum days)	10.9±0.94 (2-23)	7.87±0.75 * (1-19)
Duration of dyspnea, days (minimum-maximum days)	16.04 ±1.08 (6-29)	11.66±0.82 * (3-23)

Note: \*p-significance coefficient (p< 0.0001)

At the same time, after TCZ administration 11 (33%) patients in L<sub>1</sub> group maintained fever for 1-5 days and 8 (24.2%) patients in L<sub>2</sub> group - for 1-2 days. Worsening of the general condition by intensification of dyspnea and general asthenia was established in 15 (45.5%) patients from L<sub>1</sub> group on average for 3.5 days and in 17 (51.5%) - from L<sub>2</sub> group for 2.8 days. Hypotension below 90/60 mmHg was recorded in 2 (6.0%) patients in L<sub>1</sub> group and in 7(21.2%) - in L<sub>2</sub> group. SpO<sub>2</sub> < 94% was maintained in 31 (93.9%) patients in L<sub>1</sub> group (during 3-22 days) and in 27 (81.8%) - in L<sub>2</sub> group (during 2-19 days)(tab.3).

The transfer rate to the ICU remains high in the total group, without statistically significant difference depending on the administration of TCZ dose.

In the ICU department was transferred 18 (27.3%) patients from the total group, L<sub>1</sub> group – 8 (24.2%) patients, L<sub>2</sub> group – 10 (30.3%) patients, [95%CI (0.36-1.77), p=0.62]. According to the significance index "p", no statistically significant differences were established between the studied groups (tab. 3) although the relative risk of worsening after TCZ treatment (RR=0.88), relative risk of blood pressure drop (RR=0.29) and relative risk of transfer to intensive care unit (RR=0.8) were lower in L<sub>1</sub> patients compared to the control group. Based on the statistical indicators below, the TCZ 200 mg dose was not found to be less effective than the TCZ 400 mg dose. At the same time, the NNT is quite high according to all manifestations for the dose of TCZ 200mg compared to 400mg.

**Table 3.** Clinical status of patients after TCZ administration.

Manifestations	L <sub>1</sub> group TCZ 200 mg	L <sub>2</sub> group TCZ 400 mg	P	RR	95%CI (RR)	NNT
Presence of fever after TCZ treatment, patients	11	8	0.41	1.37	0.64-2.97	11.0
Post TCZ aggravation (dyspnea, asthenia), patients	15	17	0.46	0.88	0.54-1.45	11.0
Hypotension < 90/60 mmHg, patients	2	7	0.1	0.29	0.06-1.27	6.6
SpO <sub>2</sub> < 94%, patients	31	27	0.14	1.14	0.96-1.38	8.2
Transfer to intensive care wards, patients	8	10	0.62	0.80	0.36-1.77	16.5

Note: RR and NNT were computed for the experimental group

Radiological changes were registered in all patients from both groups before TCZ administration. The improvement of the radiological picture in L<sub>1</sub> patients was established on average

13.13±0.92 days after the administration of TCZ 200 mg, and in patients from the control group – at 11.33±0.83 days, significantly earlier (p≤0.0001).

The duration of hospitalization in non-transferred to ICU patients was on average  $15.97 \pm 1.17$  (8-30) days, statistically significantly longer in the L<sub>1</sub> group  $17.5 \pm 1.53$  (9-30), compared with the 2-nd group  $14.5 \pm 1.69$  (8-30), [95%CI (2.21-3.79),  $p \leq 0.0001$ ].

## DISCUSSIONS

In the Republic of Moldova, TCZ is included in the off-label treatment guidelines for COVID-19 for severe and critical cases. The usefulness of IL-6 inhibitors depends on the optimal time of administration: too early can inhibit the effectiveness of the host immune answer; too late – aggravate the clinical manifestation, leading to invasive ventilation in critically ill patients. That is why the clinical thinking of physicians, their knowledge proficiencies in understanding the COVID-19 evolution, and hypercytokinemia expectation, experience aptitudes in finding the proper time for TCZ administration is essential for the life of the patients.

## CONCLUSIONS

1. The improvement of general condition by decreasing febrile period, asthenia, disappearance of dyspnea and increase of SpO<sub>2</sub> level, improvement of radiological picture, as well as duration of hospitalization showed better results in patients treated with TCZ 400 mg, although the relative risk of rapid worsening after TCZ treatment (RR=0.88), relative risk of blood pressure decrease (RR=0.29) and relative risk of transfer to intensive care unit for invasive or non-invasive ventilation (RR=0.8) were lower in patients treated with TCZ 200 mg compared to the TCZ 400 mg.
2. The 200 mg fixed dose of Tocilizumab may be considered an alternative and life-saving drug for severely ill patients at the beginning of the hypercytokinemia phase of COVID-19 in the context of IL-6 inhibitor supply deficiency can provide benefits to a larger number of patients.
3. Further randomized trials are needed to confirm the efficacy of a low dose of Tocilizumab and the frame time of IL-6 inhibitor administration in larger populations.

## CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

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There is no information.

## REFERENCES

1. Kany S, Vollrath JT, Relja B. Cytokines in Inflammatory Disease. *Int J Mol Sci.* 2019; 20(23):6008. doi:10.3390/ijms20236008
2. Zhang JM, An J. Cytokines, inflammation, and pain. *Int Anesthesiol Clin.* 2007;45(2):27-37. doi:10.1097/AIA.0b013e318034194e
3. Rabaan AA, Al-Ahmed SH, Muhammad J, et al. Role of Inflammatory Cytokines in COVID-19 Patients: A Review on Molecular Mechanisms, Immune Functions, Immunopathology, and Immunomodulatory Drugs to Counter Cytokine Storm. *Vaccines (Basel).* 2021;9(5):436. doi:10.3390/vaccines9050436
4. Jamilloux Y, Henry T, Belot A, et al. Should we stimulate or suppress immune responses in

We are confident of our study limitations, but despite these, we confirm that most baseline characteristics were similar between the two groups, and the main standard of management was identical. In our study, both doses of TCZ demonstrate its efficiency in severely ill patients with COVID-19, which is essential in a pandemic situation, especially during periods of TCZ supply shortages. We cannot prove that the dose of TCZ influences the percentage of patients transferred to the ICU for invasive or non-invasive ventilation. However, we demonstrate that the TCZ dose significantly impacts the duration of patients' disabilities, with better efficiency for TCZ 400 mg compared to 200 mg. That is why TCZ 200 mg may not be a cost-effective solution in COVID-19, as it leads to longer hospitalization and NNT is quite high according to all manifestations than TCZ 400 mg. However, reducing the TCZ dose can be a life-saving option in the context of ongoing supply shortages.

## ETHICAL APPROVAL

This study was carried out with the approval of the Ethics Committee no. 02/02.10.2020 of the *Nicolae Testemitanu* State University of Medicine and Pharmacy, Republic of Moldova.

- COVID-19? Cytokine and anti-cytokine interventions. *Autoimmun Rev.* 2020;19(7): 102567.  
doi:10.1016/j.autrev.2020.102567
5. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microbe.* 2020. doi:10.1016/j.chom.2020.04.009
  6. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. *J Heart Lung Transplant.* 2020;39(5):405-407. doi:10.1016/j.healun.2020.03.012
  7. Dadras O, Afsahi AM, Pashaei Z, et al. The relationship between COVID-19 viral load and disease severity: A systematic review. *Immun Inflamm Dis.* 2022;10:e580. doi:10.1002/iid3.580
  8. Shekhawat J, Gauba K, Gupta S, et al. Interleukin-6 Perpetrator of the COVID-19 Cytokine Storm. *Indian J Clin Biochem.* 2021; 36(4):1-11. doi:10.1007/s12291-021-00989-8
  9. Santa Cruz A, Mendes-Frias A, Oliveira A, et al. Interleukin-6 Is a Biomarker for the Development of Fatal Severe Acute Respiratory Syndrome Coronavirus 2 Pneumonia. *Front. Immunol.* 12:613422. doi:10.3389/fimmu.2021.613422
  10. McGonagle D, Sharif K, O'Regan A, Bridge-wood C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. *Autoimmun Rev.* 2020;19(6): 102537. doi:10.1016/j.autrev.2020.102537
  11. Zhang Y, Zhang Z, Wei R, et al. IL (Interleukin)-6 Contributes to Deep Vein Thrombosis and Is Negatively Regulated by miR-338-5p. *Arterioscler Thromb Vasc Biol.* 2020;40(2): 323-334. doi:10.1161/ATVBAHA.119.313137
  12. Kerr R, Stirling D, Ludlam Ch. Interleukin 6 and Haemostasis. *BJHaem.* 2008. doi:10.1046/j.1365-2141.2001.03061
  13. Pons S, Fodil S, Azoulay E. et al. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. *Crit Care* 24. 2020. doi:10.1186/s13054-020-03062-7
  14. Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. *Intensive Care Med.* 2020;46(6): 1105-1108. doi:10.1007/s00134-020-06059-6
  15. Stenmark KR, Frid MG, Gerasimovskaya E, et al. Mechanisms of SARS-CoV-2-induced lung vascular disease: potential role of complement. *Pulm Circ.* 2021;11(2): 20458940211015799. doi:10.1177/20458940211015799
  16. Xu X, Han M, Li T, Sun W, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA.* 2020; 117(20):10970-10975. doi:10.1073/pnas.2005615117
  17. San-Juan R, Fernández-Ruiz M, López-Medrano F, et al. Analysis of the factors predicting clinical response to tocilizumab therapy in patients with severe COVID-19. *Int J Infect Dis.* 2022. doi:10.1016/j.ijid.2022.01.040
  18. Roumier M, Paule R, Vallée A, et al. Tocilizumab for Severe Worsening COVID-19 Pneumonia: a Propensity Score Analysis. *J Clin Immunol.* 2021;41(2):303-314.
  19. Somers E, Eschenauer G, Troost J, et al. Tocilizumab for Treatment of Mechanically Ventilated Patients With COVID-19. *Clinical Infectious Diseases.* 2021;73(2):e445-e454. doi:10.1093/cid/ciaa954
  20. Chamber D, Aksak-Waş B, Bobrek-Le-siakowska K, et al. Effectiveness of Tocilizumab in Patients with Severe or Critical Lung Involvement in COVID-19: A Retrospective Study. *J Clin Med.* 2022;11(9):2286. doi:10.3390/jcm11092286
  21. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *The Lancet.* 2021;397. doi:10.1016/S0140-6736(21)00676-0
  22. Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med.* 2021;384:1491-1502. doi:10.1056/NEJMoa2100433
  23. WHO. A living WHO guideline on drugs for covid-19. *BMJ.* 2020;370:m3379.
  24. NIH Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available from: <https://www.covid19treatmentguidelines.nih.gov/> [Accessed 02.06.2022].

25. IDSA. Guidelines on the Treatment and Management of Patients with COVID-19. Available from: <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/> [Accessed 02.06.2022].
26. MSMPS. Infectia cu coronavirus de tip nou (COVID-19) [New type of coronavirus infection (COVID-19)], PCN 371. Available from: <https://ms.gov.md/legislatie/covid-19/protocoale-si-ghiduri-covid-19/> [Accessed 02.06.2022].
27. Ercan S, Ergan B, Özuygur S, Korkmaz P, et al. Clinical Predictors of Response to Tocilizumab: A Retrospective Multicenter Study. *Turk Thorac J.* 2022;23(3):225-230. doi:10.5152/TurkThoracJ.2022.21179
28. De Rossi N, Scarpazza C, Filippini Ch. Early use of low dose tocilizumab in patients with COVID-19: A retrospective cohort study with a complete follow-up. *EClinicalMedicine.* 2020;25:100459. doi:10.1016/j.eclinm.2020.100459
29. Hermine O, Mariette X, Porcher R, et al. Effect of Interleukin-6 Receptor Antagonists in Critically Ill Adult Patients with COVID-19 Pneumonia: two Randomised Controlled Trials of the CORIMUNO-19 Collaborative Group. *European Respiratory Journal.* 2022;2102523. doi:10.1183/13993003.02523-2021
30. Cardona-Pascual I, Berlana D, Martinez-Valle F, et al. Effect of tocilizumab versus standard of care in adults hospitalized with moderate-severe COVID-19 pneumonia. *Med Clin (Engl Ed).* 2022;158(7):301-307. doi:10.1016/j.medcle.2021.03.036
31. Rosas I, Brau N, Waters M, et al. Tocilizumab in patients hospitalised with COVID-19 pneumonia: Efficacy, safety, viral clearance, and antibody response from a randomised controlled trial (COVACTA). *eClinicalMedicine.* 2022;47:101409. doi:10.1016/j.eclinm.2022.101409
32. Stukas S, Joshua G, Kinkade A, et al. Reduced fixed dose tocilizumab 400 mg IV compared to weight-based dosing in critically ill patients with COVID-19: A before-after cohort study. *Lancet Reg Health Am.* 2022;11:100228. doi:10.1016/j.lana.2022.100228

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