УДК 616.98:578.834.1]:615.036.275/.357
DOI 10.11603/1681-2727.2024.3.14652

O. V. Oliynyk

COMPARATIVE EFFICACY OF METHYLPREDNISOLONE AND TOCILIZUMAB IN PATIENTS WITH A SEVERE FORM OF COVID-19

O. O. Bogomolets National Medical University, University of Rzeszów (Poland)

Background. *Recently, we have again noted an increase in the incidence of COVID-19. The treatment of patients with severe coronavirus infection poses a significant medical challenge.*

Objectives. *The purpose of this research was to compare the efficacy of standard therapy and pulses of methylprednisolone in combination with or without tocilizumab in patients with a severe form of COVID-19.*

Patients and methods. *In a retrospective study, the medical charts of 220 patients with a severe course of COVID-19 were reviewed. Patients were divided into four groups: those on daily methylprednisolone at a dose of 32 mg enterally; patients who received methylprednisolone pulses (500 mg daily intravenously for three consecutive days, with a subsequent change to the 32 mg of methylprednisolone daily); patients who received a single dose of 400 mg tocilizumab in combination with a 32 mg of methylprednisolone daily; patients who received a single dose of 400 mg tocilizumab in combination with methylprednisolone pulse therapy. At the end of therapy, 28-day mortality and the number of intubations in each group one week after the end of therapy were analyzed.*

Results. *Patients treated with a combination of tocilizumab and pulse methylprednisolone therapy had the lowest risk of death (p<0.001), OR=0.03 (95 % CI 0.01-0.16), compared to patients treated only with 32 mg of methylprednisolone.*

Conclusions. *Methylprednisolone pulses therapy is more effective than therapy with methylprednisolone at a daily dose of 32 mg. The combination of methylprednisolone and tocilizumab is more effective than the isolated administration of methylprednisolone. The combination of tocilizumab with methylprednisolone pulse therapy had the highest therapeutic effect.*

Key words: *COVID-19; methylprednisolone; tocilizumab.*

Despite the decrease in morbidity and mortality in the world from COVID-19, in Ukraine in 2023 it was 40 % more than in 2022. In January 2024, 343 patients died from COVID-19 in Ukraine, including 3 children. On average, in Ukraine in 2024, 4,000 patients were hospitalized with a diagnosis of COVID-19 every week [1]. In most patients, the disease was caused by the Omicron strain, which is characterized by an additional mutation of the spike protein. This strain more often affected people with weakened immune systems. We can say that the problem of COVID-19 has not lost its relevance to this day.

The clinical spectrum of COVID-19 ranges from asymptomatic disease to severe pneumonia and death. Mortality in patients with severe COVID-19 reaches 45-76 % [2, 3]. Treatment of patients with severe and critical forms of COVID-19 is an extremely pressing problem. The range of drugs effective against severe COVID-19 remains very limited [4, 5]. Among the main drugs in the arsenal of medications for the treatment of severe forms of COVID-19 are glucocorticoids and tocilizumab – monoclonal antibodies to the interleukin-6 receptor (IL-6) from the immunoglobulin subclass. Existing views on the use of tocilizumab are contradictory. On December 9, 2021, the European Medicines Agency (EMA) approved the use of tocilizumab for the treatment of patients with severe coronavirus disease, and on August 18, 2021, the WHO recommended tocilizumab for the treatment of severe cases of COVID-19 [6]. The findings were based on 27 clinical studies involving 10,000 patients. Studies have shown that the use of tocilizumab in patients with severe disease reduces mortality by 13 % compared to standard treatment. In addition, the use of tocilizumab reduced the need for mechanical ventilation for severe and critical patients by 28 % compared to standard treatment. At the same time, there is an opinion that tocilizumab is not effective against COVID-19 [7, 8]. There is still no established consensus on glucocorticoid dosing for COVID-19. The traditional recommended dosage of dexamethasone for COVID-19 is 6 mg/day (equivalent to 30 mg methylprednisolone) [9]. This dose of dexamethasone is thought to reduce mortality in patients requiring oxygen or mechanical ventilation [10]. It is known that the

effectiveness of glucocorticoids increases with the use of pulse therapy. There is a study that demonstrated the higher effectiveness of pulse therapy of glucocorticoids compared to the traditional dose in severe forms of COVID-19 [1]. Perhaps such treatment would be more effective for a patients with cytokine storm. From our point of view, the question of the effectiveness or ineffectiveness of tocilizumab is of fundamental importance, due to the limited number of drugs that can improve the condition of patients with severe COVID-19. On the other hand, tocilizumab is a toxic enough drug to be used if it is not indicated for treatment. From our point of view, the comparative effectiveness of various doses of glucocorticoids in severe COVID-19, including pulse therapy, requires a more specific study. In addition, the thesis about the need of repeated studies of the effectiveness of tocilizumab and corticosteroids was repeated in all found randomized studies.

Objectives

The purpose of this research was to investigate the comparative effect of methylprednisolone, used in different doses, and its combination with tocilizumab on the course of severe COVID-19, assessed by disease outcome and by the need for intubation and mechanical ventilation.

Patients and methods

Study design and setting. This is a two-center retrospective observational study. The investigation was performed in the Infectious Diseases Intensive Care Unit of Kyiv City Clinical Hospital №4 and Intensive Care Unit of Ternopil City Hospital №1 during the period from 01.02.2020 to 28.12.2021. This study was approved by the Ethics Committee of O. O. Bohomolets National Medical University (No. 384 of December 18, 2019). This study was a part of clinical research "Optimization of respiratory support methods for patients with severe forms of respiratory insufficiency, including acute respiratory distress syndrome" conducted in the Department of Anesthesiology and Intensive Care of NMU and registered in the Clinical Trials Register of the State Expert Centre of the Ministry of Health of Ukraine (Registration number 0119U100684). The study was conducted according to the guidelines of the Declaration of Helsinki. Since the study was a retrospective one, informed consent for participation in the study was not required under Ukrainian law. The size of the study was determined by the time it was conducted.

220 adult patients with a severe COVID-19 and severe acute respiratory failure. The medical records of these patients were analyzed.

Inclusion criteria:

• SARS-CoV-2 infection (confirmed with a positive reverse transcription polymerase chain reaction (RT PCR) test);

• bilateral interstitial pneumonia confirmed with a computed tomography (CT) scan;

• respiratory failure with arterial partial pressure of oxygen (PaO2) <60 mmHg when breathing ambient air;

• hyperinflammatory syndrome, accompanied by the presence of two of three hyperinflammation biomarkers (elevation of C-reactive protein above 100 mg/L, ferritin above 900 μg/L, D-dimer above 1500 μg/L).

Exclusion criteria:

• systemic connective tissue diseases,
• cardiogenic pulmonary edema,
• brain stroke,
• malignancies,
• decompensated diabetic ketoacidosis,
• decompensated chronic kidney or liver diseases,
• pregnancy or breastfeeding,
• participation in another clinical study,
• patients with Do Not Attempt Resuscitation or Do Not Intubate orders.

Treatment strategy

Depending on the prescribed treatment, patients were divided into four groups:

Group 1 (n=72): patients who received oral methylprednisolone (Methylprednisolone-PS, Acino Inc., Switzerland) in a daily dose of 32 mg, referred to as M32;

Group 2 (n=48): patients who received methylprednisolone pulses (Solu-Medrol, Pfizer, Inc., USA), 500 mg daily intravenously for three consecutive days, with a subsequent change to 32 mg of methylprednisolone daily (during 11 days), referred to as MP;

Group 3 (n=48): patients who received a daily dose of 32 mg of methylprednisolone in combination with a single dose of 400 mg tocilizumab (Actemra, Roche), referred to as T+M32,

Group 4 (n=52): patients who received methylprednisolone pulses 500 mg daily intravenously for three consecutive days, with a subsequent change to 32 mg of methylprednisolone daily) in combination with a single dose of 400 mg tocilizumab, referred to as T+MP.

The Kyiv City Clinical Hospital and Ternopil City Hospital № 1 have a local treatment protocols for COVID-19, which recommended the preferential use of methylprednisolone over other glucocorticoids. All treatment regimens were prescribed at the disease terms corresponding to days 7-20 from the onset of the disease. Methylprednisolone at a dose of 32 mg was administered from the first day of admission. Methylprednisolone pulse therapy was started from days 6 to 14 from admission as a continuation of previous use of 32 mg of methylprednisolone. After completion of pulse therapy, the dose was returned to 32 mg. Generally, the total duration of therapy with methylprednisolone was 14 days. In addition, all patients had a complication in the form of bacterial pneumonia and received antibiotic therapy and enoxaparin sodium at a dose of 0.4 ml daily. The model of treatment with methylprednisolone was determined by the physicians' preference and previous

experience in the methylprednisolone use in the treatment of patients with other pathologies.

Tocilizumab was recommended to all patients with the hyperinflammatory syndrome. Patients were informed about the possible side effects of tocilizumab therapy. In the case of acceptance of the tocilizumab therapy, patients signed informed consent for its use. Tocilizumab therapy usually started on days 6-14 after admission to the unit. Tocilizumab was not administered until day 5 because it took 1-2 days to establish the indication for tocilizumab i.e. (presence of hyperinflammatory syndrome).

Data collection

To compare estimate the initial condition of the patients, the following pre-treatment data were assessed: age, sex, temperature, respiratory index (PaO_2/FiO_2), the number of white blood cells, lymphocytes, platelets, erythrocytes, plasma levels of fibrinogen, D-dimer, ferritin, interleukin-6 (IL-6), C-reactive protein (CRP), procalcitonin. Pre-treatment intubation (Intubation 1) was defined as the need for intubation within the first five days from admission to the department. Intubation 1 was used as one of the factors in assessing the severity of the patients' preliminary condition.

Outcomes

Primary endpoint:

• 28-day mortality rate

Secondary endpoint:

• 28-day quantity of intubated patients (we designated this number as Intubation 2).

Statistical methods

MedCalc® Statistical Software version 20.109 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022) was used in the analysis. The median (Me) and interquartile range (QI-QIII) were calculated to represent quantitative data, the distributive law differed from normal by the Shapiro-Wilk test. Frequency (%) was calculated for qualitative measures. The Kruskal-Wallis test was used to compare quantitative features in the four groups, subsequent comparisons were made using the Dunn's test. For qualitative comparisons of more than two groups, the Chi-square test was used and subsequent comparisons were performed using the Fisher's exact test with Bonferroni correction. To quantify the degree of influence of factor signs on mortality risk, the method of logistic regression model construction and analysis was used. The prognostic quality of the models was assessed by ROC-curve analysis. The area under the ROC curve (AUC) and its 95 % CI were calculated. The influence of the factor signs was assessed by the value of odds ratios (OR), for which a 95 % CI was computed. The p-value <0.05 was considered significant for all statistical tests.

Our efforts to address potential sources of bias were: obtaining complete data, complete reporting of all prespecified outcomes.

Research results and their discussion

The basic demographic and medical data of the studied groups are presented in the Table 1. The patients were the oldest in the T+MP group (mid age 71 years) and the youngest in the MP group (mid age 67 years) (p<0.001). Patients did not differ in gender and the need for mechanical ventilation prior to treatment. 50-65 % of patients were on mechanical ventilation prior to treatment (Intubation 1). Such a significant number of patients intubated at the beginning of treatment can only be explained by their initially severe general condition.

Table 1

Basic clinical and laboratory data in the study groups, median (QI–QIII) for continuous variables, and numerical values (%) for categorical variables

	M32 (n=72)	MP (n=48)	T+M32 (n=48)	T+MP (n=52)	p
1	2	3	4	5	6
Age, years	68* (65.5-68.0)	67* (66.0-71.5)	68* (66.0-69.0)	71 (68.0-72.0)	**<0.001**
Sex, female, %	16 (44.4)	11 (45.8)	21 (43.7)	26 (50.0)	0.918
Intubation 1, %	38 (52.8)	24 (50.0)	31 (64.6)	29 (55.8)	0.492
Temperature, °C	37.8* (37.4-38.1)	38.1 (37.6-38.1)	37.7 (37.4-38.2)	38.1# (38.1-38.1)	**0.02**
Interleukin-6, pg/mL	71 (41-73.5)	54.5 (50-72.5)	62.5 (48-68)	55 (53-64)	0.70
Procalcitonine ng/mL	0.2 (0.1-0.4)	0.2 (0.1-0.250)	0.25* (0.2-0.3)	0.1& (0.1-0.2)	**0.009**
CRP, mg/L	39 (31.5-55)	53 (32-56)	42.5 (32-56)	41 (32-55)	0.266
Fibrinogen, g/L	1.6$ (1.6-1.8)	1.85# (1.6-2.1)	1.85 (1.6-2.5)	1.7 (1.6-2)	**0.007**
Ferritin, ng/mL	2650.5 (1022-5473)	3350 (3055-3830)	1534 (1044-5941)	3531 (1400-3998)	0.998

Continuation of the Table 1

1	2	3	4	5	6
D-dimer, μg/L	2174 (1527-2637)	1767 (1542-2448)	1928 (1427-2506)	1876 (1282-3335)	0.702
Leukocytes, $\times 10^9$/L	1.8$^{\$}$ (1.7-2.5)	2$^{\#}$ (2-2.9)	2 (1.8-3.5)	2.3 (1.8-2.8)	**0.010**
Thrombocytes $\times 10^9$/L	88* (72.5-136)	87.5* (76-125)	88* (78.5-126)	71$^{\#\$\&}$ (58-87)	**<0.001**
Lymphocytes, %	17$^{\$\&}$ (16-23.5)	20.5$^{\#}$* (18-26)	20.5$^{\#}$ (17-24.5)	18$^{\$}$ (17-22.5)	**<0.001**
Erythrocytes, $\times 10^{12}$/L	2.2 (2.2-2.6)	2.3 (2.250-2.7)	2.45 (2.2-3.2)	2.3 (2.3-2.5)	0.187
PaO_2/FiO_2	96* (88-112)	108.5 (92-119)	105.5 (91-117.5)	112$^{\#}$ (96-122)	**0.002**

Laboratory test reference ranges: interleukin-6 <4.0 pg/mL, procalcitonin <0.02 ng/mL, CRP <5.0 mg/L, fibrinogen 2.0-4.0 g/L, ferritin 8-143 ng/mL, D-dimer <500 μg/L, leukocytes 4.0-9.0×10^9/L, lymphocytes 19-37 %, thrombocytes 200-400×10^9/L, erythrocytes 3.6-4.2×10^{12}/L, PaO_2/FiO_2 454-495 mmHg

– difference from the rate in persons treated with M32, statistically significant, p<0.05;

$ – difference from the rate in persons treated with MP, statistically significant, p<0.05;

& – difference from the rate in persons treated with T+M32, statistically significant, p<0.05;

* – difference from the rate in persons treated with T+MP, statistically significant, p<0.05.

The analysis indicates the presence of differences between groups in few certain parameters (p<0.05 according to the Kruskal-Wallis test). The temperature in the T+MP group was higher (p<0.02) than in the M32 and T+M32 groups. The platelets count in the T+MP group was lower than in the other three groups (p<0.001). The number of lymphocytes in the group M32 was lower (p<0.001) than in the MP and T+M32 groups. The level of procalcitonin was the lowest in the group T+MP (p=0.009), the level of fibrinogen – in the group M32 (p=0.007). Respiratory index was the lowest in the M32 group (p=0.002).

Table 2 presents an analysis of the risks of treatment outcomes depending on the types of treatment. The smallest number of patients who required mechanical ventilation a week after the beginning of treatment and the number of patients who died were in the T+MP group, the largest in the M32 group (p<0.001).

Table 2

Risks of treatment outcomes in patients with COVID-19 depending on the types of treatment used

	M32 (n=72)	MP (n=48)	T+M32 (n=48)	T+MP (n=52)	P
Intubation, %	49 (68.1)*	24 (50.0)	23 (47.9)	15 (28.8)	**<0.001**
Death, %	42 (58.3)*	20 (41.7)	23 (47.9)	15 (28.8)	**0.012**

Notes. * – the difference from the indicator for patients of T+MP group is statistically significant, p<0.05.

The multifactor logistic regression models were used for identification the risk factors of Intubation 2. The following risk factors were analyzed: treatment, age, sex, Intubation 1. During the selection of significant risk factors, three features were identified: treatment, sex, Intubation 1. A model based on these traits is adequate, AUC=0.9 (95 % CI 0.88-0.95), indicating a very strong association of factor traits with Intubation 2 risk. A model based on these traits is adequate, AUC=0.98 (95 % CI 0.96-0.99), indicating a very strong association of factor traits with Intubation 2 risk. Table 3 shows the results of the analysis.

There was established an increase (p<0.001) in the risk of Intubation 2 for patients on Intubation 1, OR=78.4 (95 % CI 23.4-262) compared with patients which were not on Intubation 1 (standardized by treatment and sex). There was also a lower risk of Intuation 2: for patients treated with MP (p=0.023, OR=0.22 (95 % CI 0.06-0.81)), for patients treated with T+M32 (p<0.001, OR=0.07 (95 % CI 0.02-0.27)), for patients treated with T+MP (p<0.001, OR=0.03 (95 % CI 0.01-0.11)) compared with patients treated with M32 (on adjusted by sex and Intubation 1). For men, the risk of Intubation 2 is higher (p=0.034, OR=2.3 (95 % CI 1.1-5.0)) compared to women on adjusted by the above indicators. Thus, when all risk factors are taken into account, the risk of intubation is higher in the treatment of M32 and MP than in the treatment of T+MP. The risk of Intubation 2 in the T+M32 group is not significantly different from that in the T+MP group.

Table 3

Risk analysis of the need for mechanical ventilation with intubation (Intubation 2) one week after treatment in the logistic regression model

Independent variables		Coefficients of model, b±m	The level of significance of the difference of the coefficient from 0, p	OR (95 % CI)
Treatment	M32	Reference		
	MP	-1.52±0.67	**0.023**	0.22 (0.06-0.81)
	T+M32	-2.71±0.71	**<0.001**	0.07 (0.02-0.27)
	T+MP	-3.64±0.72	**<0.001**	0.03 (0.01-0.11)
Intubation 1	No	Reference		
	Yes	4.36±0.62	**<0.001**	78.4 (23.4-262)
Sex	f	Reference		
	m	0.84±0.40	**0.034**	2.3 (1.1-5.0)

The method of constructing multifactor models of logistic regression with factor features: age, sex, Intubation 1, treatment was used to identify factors related to the risk of Death. The 2 features were identified when selecting significant risk factors: treatment and Intubation 1. A model based on these signs is adequate, AUC=0.93 (95 % CI 0.88-0.96). It indicates a very strong association of factor traits with the risk of Death. The results of the analysis are shown in Table 4.

There was an increase (p<0.001) risk of death for patients on Intubation 1, OR=147 (95 % CI 18-1180) compared with patients without Intubation 1 (adjusted by treatment, sex, procalcitonin, the number of erythrocytes, leukocytes, respiratory index PaO_2/FiO_2) (Table 5).

There was a higher risk of death of patients treated with M32 (p<0.001 OR=284 (95 % CI 19-4100) compared with patients treated with T+MP (adjusted by above signs). Patients treated with MP had a higher risk of death (p=0.002, OR=55 (95 % CI 4.3-700) compared with patients treated with T+MR (adjusted by above signs). Thus, taking into account all risk factors, of the risk of death in groups M32 and MR is higher than in the groups T+M32 and T+MP. The risk of death in the group T+M32 is not significantly different from that in the group T+MR. The therapy in groups T+M32 and T+MP was significantly effective only for intubated patients who were mechanically ventilated. For patients who were not on invasive ventilation and were not intubated, such combination therapy did not significantly affect the course of the disease.

Thus, different treatments had different effects on the primary endpoint of 28-day mortality. Mortality decreased most significantly with the simultaneous use of pulse therapy

Table 4

Analysis of the risk of death during treatment in the logistic regression model

Independent variables		Coefficients of model, b±m	The level of significance of the difference of the coefficient from 0, p	OR (95 % CI)
Treatment	M32	Reference		
	MP	-1.52±0.67	**0.023**	0.22 (0.06-0.81)
	T+M32	-2.71±0.71	**<0.001**	0.07 (0.02-0.27)
	T+MP	-3.64±0.72	**<0.001**	0.03 (0.01-0.11)
Intubation	No	Reference		
	Yes	4.36±0.62	**<0.001**	78.4 (23.4-262)
Sex	f	Reference		
	m	0.84±0.40	**0.034**	2.3 (1.1-5.0)

Note. The figures are shown for the seven-factor model (on adjusted by procalcitonin, leukocytes, erythrocytes, PaO_2/FiO_2).

Table 5

The risks of treatment outcomes of patients with severe COVID-19 depending on intubation before treatment, the absolute value (%)

Initial condition	The result of treatment	M32	MP	T+M32	T+MP	p
Intubated	Intubation 2	38 (100)	20 (83.3)	23 (74.2)	15 (51.7)	**<0.001**
	Death	38 (100)	20 (83.3)	22 (71.0)	14 (48.3)	**<0.001**
Non intubated	Intubation 2	11 (32.4)	4 (16.7)	0 (0)	0 (0)	**0.002**
	Death	4 (11.8)	0 (0)	1 (5.9)	1 (4.3)	0.311

with methylprednisolone and tocilizumab. Pulse therapy with methylprednisolone was more effective than therapy with the traditional dosage of methylprednisolone (32 mg/day). Connection of tocilizumab to therapy led to a decrease in mortality. It should be noted that these findings applied only to those patients who were intubated and required mechanical ventilation.

To interpret the data obtained, we considered it necessary to present the results of previously conducted studies of other authors regarding the effectiveness of glucocorticoids and tocilizumab in patients with severe COVID-19. Let's start with studies on the effectiveness of glucocorticoids. The course of the disease in our patients was accompanied by an increase in inflammatory markers: C-reactive protein, ferritin, IL-6. Numerous studies suggest a leading role of hyperinflammation in the pathogenesis of mortality in patients with COVID-19 [12], but there is no doubt that elevated serum concentrations of inflammatory and coagulation markers (including C-reactive protein, ferritin and D-dimer) and proinflammatory cytokines (IL-2R, IL-6, IL-10 and TNF-α) are associated with disease severity [13].

Glucocorticoids are one of the most effective drugs for treating the inflammatory syndrome in COVID-19. It should be noted that views on the appropriateness of using this class of medications have changed over the course of the COVID-19 epidemic. Previous meta-analyses have had rather conflicting results. Study of Bhimraj A. et al., 2020, did not recommend the use of corticosteroids [14]. Other studies found no benefit from corticosteroids and reported that corticosteroid treatment had no effect on the amount of lung damage caused by SARS-CoV-2 [13, 15, 16].

A cohort study of Yuan M. et al., 2020, that included 35 pairs of patients receiving and not receiving methylprednisolone at a dose of 40-50 mg/day showed no significant difference in treatment outcomes [17]. A study by Fadel R. et al., 2020 [18], showed that early administration of methylprednisolone at a dose of 0.5-1 mg/kg for 3 days increased the chance of a positive outcome, which included admission to an ICU, need for artificial ventilation or a lethal disease outcome.

Dexamethasone in the RECOVERY trial, 2020 [10], administered orally or intravenously at a dose of 6 mg/day for 10 days, reduced 28-day mortality compared with conventional treatment (mortality 21.6 % vs 24.6 %) among those who received either artificial ventilation or oxygen. Of interest, patients who did not receive oxygen at the time of randomization tended to have a higher mortality rate when receiving dexamethasone (17 % vs 13 %).

When comparing data from previous studies with our results, it should be noted that in our study methylprednisolone at a daily dose of 32 mg had the least therapeutic effect compared with methylprednisolone pulse therapy and its combination with tocilizumab. The effect of methylprednisolone at a daily dose of 32 mg on patient mortality and the need for artificial ventilation was not significant. In other words, our data on standard-dose methylprednisolone therapy were rather a confirmation of the results of studies that suggested that glucocorticoids were not sufficiently effective in COVID-19.

Some studies justify the use of higher doses of glucocorticoids. In particular, if there is associated adrenal insufficiency, the glucocorticoid dose should be doubled [19, 20].

In our view, the work of Edalatifard M. et al., 2020, is very informative [21]. This study evaluated the effect of intravenous methylprednisolone at a daily dose of 250 mg for three days on the condition of patients with severe COVID-19. The data from the study showed that the use of methylprednisolone pulse therapy at the beginning of the early pulmonary phase of the disease significantly improved general condition and lung function, as assessed by oxygen saturation, dyspnea, heart rate, breathing rate, temperature and CRP and IL-6 levels. 94.1 % of patients treated with methylprednisolone pulse therapy recovered, with an average treatment duration of 11.8 days. In the group with conventional treatment, only 57.1 % of patients recovered, with an average duration of treatment of 16.4 days. Only 8.8 % of patients in the methylprednisolone pulse therapy group required non-invasive ventilation, whereas 32.1 % of patients in the conventional treatment group required it after

treatment. This study included patients with COVID-19 who did not necessitate invasive ventilation.

The efficacy of pulse therapy in our study was assessed by the number of patients requiring artificial ventilation, intubation and mortality, and it was higher than that of therapy with a standard dose of 32 mg/day of methylprednisolone. The effect of treatment with methylprednisolone alone at different doses was lower compared with combination therapy including tocilizumab. In assessing the effectiveness of methylprednisolone pulse therapy, it is worth noting that we did not obtain as significant results as those described in the Edalatifard M et al. study, 2020 [21]. The differences observed may be primarily due to differences in the severity of the initial patients' condition, small sample sizes, patients' age and differences in the dose of the medication. In the Edalatifard M. et al., 2020 study [21], patients did not require artificial ventilation. Patients with an initial saturation level below 75 % were not included in the study. In our study, there were no restrictions on the lower limit of saturation, some patients were on artificial ventilation even before the methylprednisolone pulse therapy. The contingent of patients in our study was significantly more severe.

Almost from the beginning of the COVID-19 epidemic, there have been reports of significant efficacy of tocilizumab in the treatment of severe forms of the disease. Tocilizumab is the drug of choice in the case of hyperinflammation development related to cytokine storm syndrome [22]. Early studies of tocilizumab demonstrated significant clinical efficacy [23]. An institutional cohort study at the University of Michigan of patients with COVID-19 who were on artificial ventilation showed a significant positive effect of tocilizumab. Mortality on therapy with tocilizumab was almost halved, despite an increase in infectious complications [24].

In the study by Toniati et al., 2020 [25], 65 % of patients who received tocilizumab on a background of COVID-19 had non-invasive ventilation suspended due to improvement in patients' general condition. Respiratory function deteriorated in 23 % (23 patients), of whom 20 % (20 patients) died.

The study by Guaraldi G. et al., 2020 [26], compared 179 patients treated with tocilizumab and 365 patients treated with conventional therapy at three Italian treatment centers. The use of tocilizumab was associated with a lower risk of artificial ventilation or death.

In the study by Capra R. et al., 2020 [27], tocilizumab treatment (62 patients) was associated with improved survival and a favorable clinical course compared with standard treatment (23 patients).

Data from a meta-analysis by Richier Q, et al., 2021 [28], showed a reduction in the risk of invasive mechanical ventilation in patients treated with tocilizumab and an improvement in survival in these patients. It was concluded that the use of tocilizumab can reduce the time of hospitalization of patients with severe forms of COVID-19.

It is important to note the adverse reactions of tocilizumab. These are infectious complications, including urinary tract infections, bacterial arthritis, generalized suppurative peritonitis, fistulas, abscesses, sepsis, cellulitis, herpes zoster, gastroenteritis, diverticulitis, gastrointestinal perforation, increased blood pressure, headache, rash, anaphylactic reactions[29]. The authors state that despite the fact that tocilizumab is recommended by clinical guidelines, the current data on its effectiveness are obtained mainly from retrospective clinical trials with a relatively small cohort, most of which lack a control group. Therefore, it is premature to recommend tocilizumab for widespread use. Further research on its effectiveness is needed [29].

A study by Lorenzo M Canziani et al., 2020 [30], investigated the effect of tocilizumab on the risk of death. The use of tocilizumab in COVID-19 was associated with a lower probability of a need for artificial ventilation (hazard ratio 0.36, 95 % confidence interval 0.16-0.83; P=0.017), but not with the lower risk of thrombosis, bleeding or infection. The use of tocilizumab had no effect on the 30-day mortality of patients. Among secondary outcomes, there was less use of artificial ventilation in the group using tocilizumab.

The large COVACTA trial, 2020 [31], reported that the use of tocilizumab showed no superiority of the medication over placebo in the primary endpoint of the trial.

The authors of the systematic review, Cortegiani A. et al., 2021 [8] believe that there is insufficient evidence to recommend the use of tocilizumab in the treatment of patients with COVID-19. Its use should be considered experimental, requiring ethical approval and oversight of clinical trials.

However, the World Health Organization in 2022 added tocilizumab to the list of prequalified drugs for the treatment of COVID-19. Tocilizumab was recommended for use only in patients with severe or critical COVID-19 [32].

We are probably not entitled to compare our efficacy data for tocilizumab with the above-mentioned studies, as we have not studied the effects of tocilizumab alone.

It is conceivable that the side effects of tocilizumab therapy would be reduced if it were combined with glucocorticoids. There are studies assessing the effects of such a combination.

Herrero S. et al., 2020 [33] compared mortality among those taking a combination of methylprednisolone and tocilizumab and those taking tocilizumab without steroids. It was found that the combination of medications was more effective.

In a study by Ramiro S et al., 2020 [34] patients with COVID-19 and hyperinflammatory syndrome received high-dose methylprednisolone intravenously for 5 consecutive days (250 mg on day 1 and then 80 mg on days 2-5). If respiratory status did not improve, tocilizumab (8 mg/kg, single infusion) was administered. It was noted that this strategy accelerated respiratory recovery, reduced mortality and the probability of artificial ventilation in cytokine storm syndrome associated with COVID-19.

In another observational cohort study conducted in the Netherlands, 2020 [35], patients were treated with methylprednisolone at doses higher than the average for 5-7 days, followed by tocilizumab administration in patients who did not show clinical improvement. The authors of the study retrospectively compared these results with those of patients receiving standard treatment alone. Patients in the steroid-tocilizumab combination group did better than the control group who did not receive this therapy. They were less likely to die and less likely to need artificial ventilation. The authors of the study believe that corticosteroids and IL-6 inhibitors will be harmful if used too early and ineffective if used too late.

To summarize the above, there is still no clear consensus on the appropriateness and dosages of tocilizumab, glucocorticoids and their combination for the treatment of patients with COVID-19. In our study, methylprednisolone therapy, either alone or in combination with tocilizumab, had a positive clinical effect in patients with a severe form of COVID-19 and hyperinflammatory syndrome. In other words, our data are a confirmation of those studies that showed a positive effect of tocilizumab and its combination with glucocorticoids.

Limitations. There were some limitations to this study. First, this was a two-center retrospective study with a small sample size and some loss of clinical data, which had selection bias, confounding bias, and some other shortcomings. In addition, varying clinical experience among treating physicians may also have led to differences in treatment outcomes. This study did not have external validation, to confirm the results, similar studies should be conducted on a larger number of study patients, studies should collect data from several other centers. It would be better if such studies were randomized and the patients studied belonged to different races. There may be many confounding factors between study groups that cannot be accounted for, and randomized controlled trials adjusted for such data are needed. Tracheal intubation was performed based on the decision of the individual physician. Observational studies using strict intubation criteria are required. Associated infectious complications are likely an important factor influencing mortality. Study designs targeting the investigation of infectious complications and mortality associated with glucocorticoid pulse therapy and tocilizumab are needed. Our results may reflect the influence of more than just steroids and tocilizumab, because other medications (antibiotics, anticoagulants, antivirals, fluids) were used during treatment.

Conclusions

1. The combination of tocilizumab with methyl-prednisolone pulse therapy may improve the 28-day mortality in patients with severe COVID-19.

2. The therapeutic effect of tocilizumab was primarily seen in intubated patients.

3. The safety and efficacy of tocilizumab in combination with steroid pulse therapy need to be demonstrated using RCTs or big data analysis.

Source of funding – government funding.

References

1. Order of the Ministry of Health of Ukraine dated January 30, 2024 No. 154 “On Amendments to the Order of the Ministry of Health of Ukraine dated May 18, 2022 No. 831”. *Official website of the Ministry of Health of Ukraine*. https://moz.gov.ua/article/ministry-mandates/nakaz-moz-ukraini-vid-30012024--154-pro-vnesennja-zmin-do-nakazu-ministerstva-ohoroni-zdorovja-ukraini [in Ukrainian].

2. Quirch, M., Lee, J., & Rehman, S. (2020). Hazards of the cytokine storm and cytokine-targeted therapy in patients with COVID-19. *Journal of medical Internet research*, *22*(8), e20193.

3. Michelozzi, P., de’Donato, F., Scortichini, M., De Sario, M., Noccioli, F., Rossi, P., & Davoli, M. (2020). Mortality impacts of the coronavirus disease (COVID-19) outbreak by sex and age: rapid mortality surveillance system, Italy, 1 February to 18 April 2020. *Eurosurveillance*, *25*(19), 2000620.

4. Klopfenstein, T., Gendrin, V., Kadiane-Oussou, N. D. J., Conrozier, T., Zayet, S., & HNF Hospital Tocilizumab Multidisciplinary Team. (2022). Tocilizumab in COVID-19 pneumonia: Practical proposals based on a narrative review of randomised trials. *Reviews in medical virology*, *32*(1), e2239.

5. Li, G., Hilgenfeld, R., Whitley, R., & De Clercq, E. (2023). Therapeutic strategies for COVID-19: progress and lessons learned. *Nature Reviews Drug Discovery*, *22*(6), 449-475.

6. Aletaha, D., Kerschbaumer, A., Kastrati, K., Dejaco, C., Dougados, M., McInnes, I. B., ... & Smolen, J. S. (2023). Consensus statement on blocking interleukin-6 receptor and interleukin-6 in inflammatory conditions: an update. *Annals of the rheumatic diseases*, *82*(6), 773-787.

7. Rosas, I. O., Bräu, N., Waters, M., Go, R. C., Hunter, B. D., Bhagani, S., ... & Malhotra, A. (2021). Tocilizumab in hospitalized

patients with severe Covid-19 pneumonia. *New England Journal of Medicine*, *384*(16), 1503-1516.

8. Cortegiani, A., Ippolito, M., Greco, M., Granone, V., Protti, A., Gregoretti, C., ... & Cecconi, M. (2021). Rationale and evidence on the use of tocilizumab in COVID-19: a systematic review. *Pulmonology*, *27*(1), 52-66.

9. National Institutes of Health. (2023). COVID-19 treatment guidelines panel: Coronavirus diseases 2019 (COVID-19) treatment guidelines.

10. RECOVERY Collaborative Group. (2021). Dexamethasone in hospitalized patients with Covid-19. *New England Journal of Medicine*, *384*(8), 693-704.

11. Okano, H., Sakurai, R., & Yamazaki, T. (2023). Steroid Pulse Therapy as a Treatment for Patients With COVID-19 Pneumonia at an Intensive Care Unit: A Single-Center Retrospective Observational Study. *Cureus*, *15*(3).

12. Channappanavar, R., & Perlman, S. (2017, July). Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. In *Seminars in immunopathology* (Vol. 39, pp. 529-539). Springer Berlin Heidelberg.

13. Chen, G., Wu, D. I., Guo, W., Cao, Y., Huang, D., Wang, H., ... & Ning, Q. (2020). Clinical and immunological features of severe and moderate coronavirus disease 2019. *The Journal of clinical investigation*, *130*(5), 2620-2629.

14. Bhimraj, A., Morgan, R. L., Shumaker, A. H., Lavergne, V., Baden, L., Cheng, V. C. C., ... & Falck-Ytter, Y. (2020). Infectious Diseases Society of America Guidelines on the treatment and management of patients with coronavirus disease 2019 (COVID-19). *Clinical Infectious Diseases*, ciaa478.

15. Shi, Y., Wang, Y., Shao, C., Huang, J., Gan, J., Huang, X., ... & Melino, G. (2020). COVID-19 infection: the perspectives on immune responses. *Cell Death & Differentiation*, *27*(5), 1451-1454.

16. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... & Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The lancet*, *395*(10223), 497-506.

17. Yuan, M., Xu, X., Xia, D., Tao, Z., Yin, W., Tan, W., ... & Song, C. (2020). Effects of corticosteroid treatment for non-severe COVID-19 pneumonia: a propensity score-based analysis. *Shock*, *54*(5), 638-643.

18. Fadel, R., Morrison, A. R., Vahia, A., Smith, Z. R., Chaudhry, Z., Bhargava, P., ... & Ramesh, M. S. (2020). Early short-course corticosteroids in hospitalized patients with COVID-19. *Clinical Infectious Diseases*, *71*(16), 2114-2120.

19. Almeida, M. Q., & Mendonca, B. B. (2020). Adrenal insufficiency and glucocorticoid use during the COVID-19 pandemic. *Clinics*, *75*, e2022.

20. Arlt, W., Baldeweg, S. E., Pearce, S. H., & Simpson, H. L. (2020). Endocrinology in the time of COVID-19: Management of adrenal insufficiency. *European Journal of Endocrinology*, *183*(1), G25-G32.

21. Edalatifard, M., Akhtari, M., Salehi, M., Naderi, Z., Jamshidi, A., Mostafaei, S., ... & Rostamian, A. (2020). Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. *European Respiratory Journal*, *56*(6).

22. Luo, P., Liu, Y., Qiu, L., Liu, X., Liu, D., & Li, J. (2020). Tocilizumab treatment in COVID-19: a single center experience. *Journal of medical virology*, *92*(7), 814-818.

23. Canziani, L. M., Trovati, S., Brunetta, E., Testa, A., De Santis, M., Bombardieri, E., ... & Selmi, C. (2020). Interleukin-6 receptor blocking with intravenous tocilizumab in COVID-19 severe acute respiratory distress syndrome: A retrospective case-control survival analysis of 128 patients. *Journal of autoimmunity*, *114*, 102511.

24. Somers, E. C., Eschenauer, G. A., Troost, J. P., Golob, J. L., Gandhi, T. N., Wang, L., ... & Pogue, J. M. (2021). Tocilizumab for treatment of mechanically ventilated patients with COVID-19. *Clinical Infectious Diseases*, *73*(2), e445-e454.

25. Toniati, P., Piva, S., Cattalini, M., Garrafa, E., Regola, F., Castelli, F., ... & Latronico, N. (2020). Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. *Autoimmunity reviews*, *19*(7), 102568.

26. Guaraldi, G., Meschiari, M., Cozzi-Lepri, A., Milic, J., Tonelli, R., Menozzi, M., ... & Mussini, C. (2020). Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *The Lancet Rheumatology*, *2*(8), e474-e484.

27. Capra, R., De Rossi, N., Mattioli, F., Romanelli, G., Scarpazza, C., Sormani, M. P., & Cossi, S. (2020). Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. *European journal of internal medicine*, *76*, 31-35.

28. Richier, Q., Plaçais, L., Lacombe, K., & Hermine, O. (2021). COVID-19: encore une place pour le tocilizumab? *La Revue de médecine interne*, *42*(2), 73-78.

30. Canziani, L. M., Trovati, S., Brunetta, E., Testa, A., De Santis, M., Bombardieri, E., ... & Selmi, C. (2020). Interleukin-6 receptor blocking with intravenous tocilizumab in COVID-19 severe acute respiratory distress syndrome: A retrospective case-control survival analysis of 128 patients. *Journal of autoimmunity*, *114*, 102511.

31. Rosas, I. O., Bräu, N., Waters, M., Go, R. C., Hunter, B. D., Bhagani, S., ... & Malhotra, A. (2021). Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. *New England Journal of Medicine*, *384*(16), 1503-1516.

32. Flisiak, R., Flisiak-Jackiewicz, M., Rzymski, P., & Zarębska-Michaluk, D. (2023). Tocilizumab for the Treatment of COVID-19. *Expert Review of Anti-infective Therapy*, *21*(8), 791-797.

33. Herrero, F. S., Gimeno, F. P., García, P. O., Gómez, C. F., Mochón, M. O., & Deltoro, M. G. (2021). Methylprednisolone added to tocilizumab reduces mortality in SARS-CoV-2 pneumonia: an observational study. *Journal of internal medicine*, *289*(2), 259.

34. Ramiro, S., Mostard, R. L., Magro-Checa, C., van Dongen, C. M., Dormans, T., Buijs, J., ... & Landewé, R. B. (2020). Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study. *Annals of the rheumatic diseases*, *79*(9), 1143-1151.

35. Winthrop, K. L., & Mariette, X. (2020). To immunosuppress: whom, when and how? That is the question with COVID-19. *Annals of the rheumatic diseases*, *79*(9), 1129-1131.

ПОРІВНЯННЯ ЕФЕКТИВНОСТІ МЕТИЛПРЕДНІЗОЛОНУ ТА ТОЦИЛІЗУМАБУ У ПАЦІЄНТІВ З ТЯЖКОЮ ФОРМОЮ COVID-19

О. В. Олійник

Національний медичний університет ім. О. О. Богомольця, Жешувський університет (Польща)

РЕЗЮМЕ. Останнім часом спостерігається деяке зростання захворюваності на COVID-19. Лікування пацієнтів із тяжкою формою коронавірусної інфекції є серйозною медичною проблемою.

Метою цього дослідження було порівняння ефективності стандартної та пульс-терапії метилпреднізолоном у поєднанні з тоцилізумабом або без нього пацієнтів із тяжкою формою COVID-19.

Пацієнти і методи. *У ретроспективному дослідженні було проаналізовано медичні карти 220 пацієнтів із тяжким ступенем COVID-19. Хворі були розподілені на чотири групи: ті, що отримували метилпреднізолон щоденно в дозі 32 мг ентерально; особи, які отримували пульс-терапію метилпреднізолоном (500 мг на добу внутрішньовенно протягом трьох днів з подальшим переходом на 32 мг метилпреднізолону на добу); пацієнти, які отримували разову дозу 400 мг тоцилізумабу у поєднанні з 32 мг метилпреднізолону щодня; хворі, які отримали разову дозу 400 мг тоцилізумабу у поєднанні з пульс-терапією метилпреднізолоном. Наприкінці терапії аналізували 28-денну смертність і кількість інтубацій у кожній групі через тиждень після закінчення терапії.*

Результати. *Пацієнти, які отримували комбінацію тоцилізумабу та пульс-терапії метилпреднізолоном, мали найнижчий ризик смерті (p<0,001), OR=0,03 (95 % ДІ 0,01-0,16), порівняно з хворими, які отримували лише 32 мг метилпреднізолону.*

Висновки. *Пульсотерапія метилпреднізолоном ефективніша за терапію метилпреднізолоном у добовій дозі 32 мг. Комбінація метилпреднізолону і тоцилізумабу більш ефективна, ніж ізольоване введення метилпреднізолону. Найбільший терапевтичний ефект мала комбінація тоцилізумабу з пульс-терапією метилпреднізолоном.*

Ключові слова: *COVID-19, метилпреднізолон, тоцилізумаб.*

Інформація про автора:

Олійник Олександр Валентинович – д. мед. наук, професор, професор кафедр анестезіології та інтенсивної терапії Національного медичного університету ім. О. О. Богомольця і Жешувського університету, Польща; e-mail: Alexanderoliynyk8@gmail.com

ORCID: 0000-0003-2886-7741.

Information about the author:

Oliynyk O. V. – MD, Professor, Professor of the Department of Anesthesiology and Intensive Care of the O. O. Bogomolets National Medical University, Rzeszow University, Poland; e-mail: Alexanderoliynyk8@gmail.com

ORCID: 0000-0003-2886-7741.

Конфлікт інтересів: немає.

Author has no conflict of interest to declare.

Отримано 15.05.2024 р.