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Effect of tocilizumab on pulmonary gas exchange function in patients with severe COVID-19

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Abstract

Introduction. *COVID-19 causes cytokine storm and acute respiratory distress syndrome, which can lead to severe lung damage and multiple organ dysfunction. Early use of monoclonal antibodies has shown promising results in cytokine storm therapy, but the effects on lung gas exchange function have not yet been studied.*

Aim*. To evaluate the effect of tocilizumab on the dynamics of gas exchange parameters in patients with severe COVID-19.*

Material and methods. *The study included 26 patients in whom gas exchange parameters (PaO_2, $PaCO_2$, P/f ratio), blood oxygen saturation (saturation), respiration rate, duration and parameters of high-flow*

oxygen therapy and non-invasive mechanical ventilation, length of stay in intensive care unit and total hospital length of stay were assessed.

Results. *Tocilizumab significantly improved oxygenation on the third day (p=0.001) from* the time of drug administration.

Conclusion. *In the presented and analyzed cohort of patients with severe COVID-19 and cytokine storm, the normalization and significant increase of oxygenation parameters (PaO_2, p=0.001; P/f ratio, p=0.001) were observed within three days after a single-dose tocilizumab administration in a complex intensive therapy. No significant dynamics in the respiratory support parameters was revealed, nor an effect of this therapy on the duration of the respiratory support or the reduction in the aggressiveness of its parameters was observed within three days after tocilizumab administration (p>0.05).*

Keywords: coronavirus, COVID-19, inflammation, cytokine storm, respiratory distress syndrome, respiratory support

Conflict of interests Authors declare no conflict of interest

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ARDS, acute respiratory distress syndrome
CT, computed tomography
GCSH, glucocorticosteroid hormone
HFOT, high-flow oxygen therapy
ICU, intensive care unit
MLV, mechanical lung ventilation
COVID-19, Coronavirus disease 2019
NMLV, non-invasive mechanical lung ventilation
PCR, polymerase chain reaction
RS, respiratory support

RR, respiration rate

Introduction

The novel coronavirus infection COVID-19 pandemic has posed unprecedented challenges for the medical community around the world [1]. One of the most significant clinical features of the disease is the development of acute respiratory distress syndrome (ARDS), which can be caused by various factors, the most important of which is cytokine storm [2].

The term cytokine storm was coined in 1993 to describe the phenomenon of hypercytokinemia that develops as a result of graft-versus-host disease. Cytokine storm is a pathological state of the immune system that results from the release of excessive amounts of proinflammatory cytokines in response to infection [3]. In case of COVID-19, the cytokine storm is believed to contribute to the severe lung injury and multi-organ dysfunction seen in some patients. ARDS in patients with COVID-19 is also thought to be caused by dysregulation of the immune response to SARS-CoV-2 infection. The virus can directly damage lung cells and cause an inflammatory response, leading to an increased alveolar capillary membrane permeability and fluid accumulation in the lungs. This impairs gas exchange and can cause hypoxemia, leading to respiratory failure [4].

Diagnosis and treatment of cytokine storm and ARDS in patients with COVID-19 are decisive to reduce morbidity and mortality. Early intervention using targeted therapies, such as using monoclonal antibodies blocking the IL-6 receptors, has shown promise in the treatment of cytokine storm [5], but data on their effect on pulmonary gas exchange function are still lacking. Due to the lack of a convincing evidence base for the use of glucocorticosteroid hormones (GCSHs) at

the time of the study, patients in our study did not receive them as therapy, which is a distinctive feature of our study aimed at assessing the isolated use of tocilizumab.

Aim. To analyze the effect of intensive therapy using tocilizumab on the dynamics of gas exchange parameters in patients with severe cases of the new coronavirus infection COVID-19.

Material and methods

The study included 26 patients (15 men, 11 women) aged from 31 to 83 years (mean age 58±10 years) with severe and extremely severe COVID-19. All patients were treated in the Critical and Intensive Care Units (ICUs) of the infectious disease hospital facility at the N.V. Sklifosovsky Research Institute for Emergency Medicine from April 2020 to June 2020. The study was approved by the Local Ethics Committee.

The inclusion criteria for the study were as follows: patient age over 18 years; confirmed viral infection caused by the SARS-CoV-2 virus (positive polymerase chain reaction (PCR), computed tomography (CT) findings and clinical manifestations typical of viral pneumonia); the presence of community-acquired viral pneumonia; severe or extremely severe course of the disease; the need to use respiratory support (RS), in the form of high-flow oxygen therapy (HFOT) and/or non-invasive mechanical (mask) ventilation (NMLV).

During hospitalization of patients, their condition severity was assessed using the NEWS and APACHE - II scores; the SOFA score was used to assess organ dysfunction. The chest CT was evaluated using a unified standard developed by US Center for Diagnostics and Telemedicine specialists during pandemic for classifying viral pneumonia by severity [6].

Patients with severe and extremely severe disease were admitted to the ICU, where, when signs of a cytokine storm appeared, they were administered tocilizumab as pathogenetic therapy, based on the temporary Guidelines (Version 5) of the Russian Federation Ministry of Health that were actually valid at the time of the study. Patients included in the study also received the full range of intensive care, including antiviral, antithrombotic, antibacterial, fluid therapy, and RS. The patients did not receive GCSH as therapy, which at that time had not yet been included in all international and national protocols and recommendations for the treatment of COVID -19.

The study included arterial blood sampling at three different time points: 30 minutes before tocilizumab administration (first study time point), 24 hours after it (second study time point) and on day 3 (third study time point). The following parameters were assessed: gas exchange parameters (PaO_2, $PaCO_2$, P/f ratio), blood oxygen saturation, respiration rate (RR), duration and parameters of HFOT and NMLV, length of stay in the ICU and total hospital length of stay. These parameters were used to evaluate the efficacy tocilizumab treatment.

To study the acid-base state and arterial blood gases, an “ABL 800” analyzer (RADIOMETER, Denmark) was used.

Statistical analysis of the data was performed using the Statistica 12 software package (StatSoft, Inc., USA). The normality of the quantitative characteristics distribution was checked using the Shapiro–Wilk method recommended for analysis where the number of study subjects was less than 50. Most of the data in the study did not correspond to a normal distribution, so nonparametric Mann–Whitney tests (M–W) were used to analyze quantitative characteristics. Quantitative data that did not correspond to a normal distribution are presented as median (Me), lower (Q1, 25%) and upper (Q3, 75%)

quartiles. For normally distributed variables, parametric statistical methods were used; these data are presented as the mean (Mean) and standard deviation (Std.Dev.). The χ^2 (Chi-square) test was used for comparison of intergroup qualitative characteristics, the Kendall concordance coefficient was used to comparison of intragroup characteristics. Comparisons of parameters within groups (dependent parameters) to look for differences between the study time points were carried out by the Wilcoxon test. Differences in values were considered statistically significant at a significance level of more than 95% ($p<0.05$).

Results

On admission the condition of patients included in the study was assessed as severe according to the NEWS score (6.7±1.5 points). According to the APACHE-II score, the mean risk of mortality was 40% (23.9±4.7 points). The mean SOFA score was high (10.9±3.0 points), indicating the development of Table 1 shows the distribution of patients with regard to the lung involvement severity according to the CT findings.

Table 1. The lung involvement severity based on chest computed tomography findings

Severity grading	Number of patients
CT-0	0
CT-1	1 (4%)
CT-2	7 (27%)
CT-3	11 (42%)
CT-4	7 (27%)

Note: Lung involvement severity grade: CT-0: no signs of viral pneumonia; CT-1: mild pneumonia with ground glass opacity areas, with less than 25% severity of pathological findings; CT-2: moderate pneumonia with 25–50% of the lungs being affected; CT-3: moderate pneumonia with 50–75% of the lungs being affected; CT-4: a severe form of pneumonia affecting >75% of the lungs.

The mean duration of respiratory support was 8.8±4.6 days. The mean length of ICU stay was 15.9±7.8 days, 22.6±9.0 days for total hospitalization.

The data, which were subsequently used to assess the dynamics of gas exchange and RS parameters, were recorded at three time points: 30 minutes before the tocilizumab administration (the first study time point), after 24 hours (the second study time point), and day 3 (the third study time point). Further, we made a comparative analysis of changes in the studied parameters between the study time points (between time points 1–2: before the drug administration – 24 hours after the administration; between time points 2–3: at 24 hours after the drug administration - on day 3 after its administration; between time points 1–3: before drug administration – on day 3 after its administration). The parameters and their pairwise comparisons are presented in Table. 2.

Table 2. Pairwise comparisons of the studied parameters

30 minutes before tocilizumab administration – 24 hours after administration			
Parameters	30 minutes before administration	24 hour after administration	p
PaO_2, mm Hg	60.0 (57.0;61.0)	60.5 (58.0;63.0)	0.051
$PaCO_2$, mm Hg	30.0 (29.0;31.0)	31.0 (30.0;32.0)	**0.016**
P/f ratio	285.0 (271.0;290.0)	287.5 (276.0;300.0)	0.092
SpO_2 when breathing atmospheric air, %	88.0 (83.0;91.0)	87.5 (85.0;90.0)	0.472
SpO_2 at RS, %	97.0 (94.0;98.0)	98.0 (97.0;99.0)	0.285
RR /min	20.0 (19.0;22.0)	20.0 (18.0;21.0)	0.112
Flow, L/min	45.0 (35.0;50.0)	45.0 (35.0;55.0)	0.325 _
FiO_2, %	55.0 (45.0;72.0)	57.0 (50.0;70.0)	0.273
Support pressure, cm H_2O	11.0 (8.0;14.0)	10.0 (7.0;13.0)	0.584
PEEP, cm H_2O	7.5 (5.0;8.0)	7.0 (5.0;8.0)	0.655
FiO_2, %	50.0 (50.0;50.0)	50.0 (50.0;55.0)	0.079
24 hours after tocilizumab administration – 3rd day after administration			
Parameters	24 hours after administration	Day 3 after administration	p
PaO_2, mm Hg	60.5 (58.0;63.0)	64.5 (60.0;70.0)	**0.001**
$PaCO_2$, mm Hg_	31.0 (30.0;32.0)	30.0 (30.0;31.0)	0.433
P/f ratio	287.5 (276.0;300.0)	311.0 (300.0;333.0)	**0.001**
SpO_2 when breathing atmospheric air, %	87.5 (85.0;90.0)	89.0 (85.0;90.0)	0.306
SpO_2 at RS, %	98.0 (97.0;99.0)	98.0 (96.0;99.0)	0.234
RR /min	20.0 (18.0;21.0)	20.0 (18.0;21.0)	1,000
Flow, L/min	45.0 (35.0;55.0)	45.0 (35.0;50.0)	0.500
FiO_2, %	57.0 (50.0;70.0)	60.0 (45.0;65.0)	0.480

Support pressure, cm H_2O	10.0 (7.0;13.0)	9.0 (8.0;12.0)	0.678
PEEP, cm H_2O	7.0 (5.0;8.0)	8.0 (5.0;8.0)	0.575
FiO_2, %	50.0 (50.0;55.0)	50.0 (45.0;50.0)	0.103
30 minutes before tocilizumab administration – 3rd day after administration			
Parameters	30 minutes before administration	Day 3 after administration	P
PaO_2, mm Hg	60.0 (57.0;61.0)	64.5 (60.0;70.0)	**0.001**
$PaCO_2$, mm Hg	30.0 (29.0;31.0)	30.0 (30.0;31.0)	0.237
P/f ratio	285.0 (271.0;290.0)	311.0 (300.0;333.0)	**0.001**
SpO_2, when breathing atmospheric air, %	88.0 (83.0;91.0)	89.0 (85.0;90.0)	0.896
SpO_2 at RS, %	97.0 (94.0;98.0)	98.0 (96.0;99.0)	0.051
RR /min	20.0 (19.0;22.0)	20.0 (18.0;21.0)	0.098
Flow, L/min	45.0 (35.0;50.0)	45.0 (35.0;50.0)	1,000
FiO_2, %	55.0 (45.0;72.0)	60.0 (45.0;65.0)	0.477
Support pressure, cm H_2O	11.0 (8.0;14.0)	9.0 (8.0;12.0)	0.407
PEEP, cm H_2O	7.5 (5.0;8.0)	8.0 (5.0;8.0)	0.541
FiO_2, %	50.0 (50.0;50.0)	50.0 (45.0;50.0)	0.721

Notes: Data are presented as median and interquartile range Me (Q1;Q3);
PaO_2, partial pressure of oxygen, $PaCO_2$; partial pressure of carbon dioxide; SpO_2, oxygen saturation of hemoglobin; RR, respiration rate; FiO_2, fraction of oxygen in the inhaled mixture; PEEP, positive end-expiratory pressure

No significant differences were observed in the parameter values between the 1st and 2nd study time points. However, between the 2nd and 3rd time points, significant differences appeared in the parameters related to oxygenation (PaO_2 and P/f ratio). At 24 hours after tocilizumab administration, the median PaO_2 was 60.5 mm Hg and statistically significantly increased to 64.5 mm Hg on day 3 (p=0.001). Similarly, the median P/f ratio increased from 287.5 to 311.0 on day 3 after the drug administration (p=0.001). In addition, significant differences were found between the 1st and 3rd study time points: the median PaO_2 increased from 60.0 mm Hg before the tocilizumab administration up to 64.5 mm Hg on day 3 (p=0.001), and the median P/f ratio increased from 285.0 to 311.0 on day 3 after the drug administration (p=0.001). Figures 1, 2, 3 display the dynamics of gas exchange parameters.

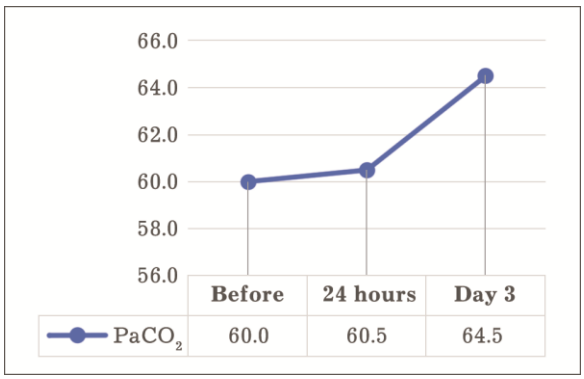

Fig. 1. Dynamics of median PaO_2

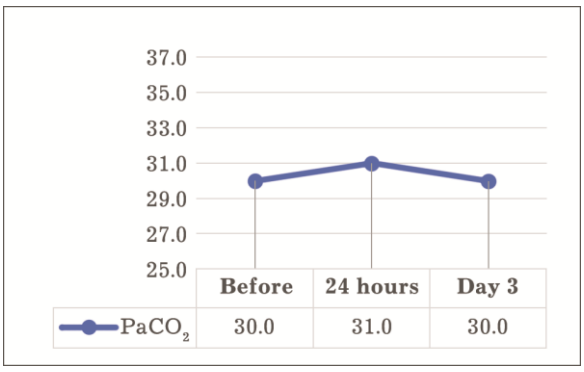

Fig.2. Dynamics of median $PaCO_2$

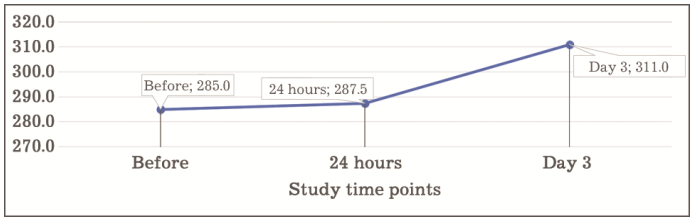

Fig. 3. Dynamics of median P/f ratio

There were no significant changes in respiratory support parameters. At 24 hours after administering the pathogenetic therapy with tocilizumab, each patient underwent a chest CT scanning to assess the dynamics of the lung involvement extent. The CT results demonstrated positive dynamics in 12 patients (46%), no changes in 8 (31%) patients, and negative dynamics in 6 (23%).

The severity of patients assessed by the NEWS score was at mean 5.9±1.0 points (p=0.022) at 24 hours after the drug administration, and 4.5±0.9 points (p=0.001) on day 3 after the drug administration. The mean SOFA score decreased to 8.6±2.6 points after 24 hours (p=0.003), and to 5.9±2.4 points on days 3 (p=0.001). Thus, the use of tocilizumab in the respiratory distress syndrome development leads both to an improvement in gas exchange, and also to an improvement in the general condition of patients, as evidenced by a statistically significant decrease in patient severity assessed by the NEWS score, as well as a decrease in the manifestation of organ dysfunction by SOFA score as early as at 24 hours after drug administration.

At the time hospital admission of patients who needed the use of anti–interleukin-6 receptor monoclonal antibodies, blocking the IL-6, the

mortality risk scored by APACHE-II was 15.8% in 8 patients, 21.3% in 11 patients, and 75% in 7 patients. In the presented study, there were no deaths, nor were there any cases of placing a patient on mechanical lung ventilation (MLV). This finding should be interpreted as follows: the use of tocilizumab resulted in a significant improvement in disease outcomes compared with the predicted outcome.

Discussion of results

The data obtained indicate a statistically significant improvement in oxygenation parameters at 72 hours after the tocilizumab administration suggesting a beneficial effect of the drug on the lung oxygenation function, which is associated with the drug effect on the course of cytokine storm and lung parenchyma.

The main factor in the COVID-19 development is a cytokine storm, a condition that includes an excessive production of cytokines, including IL-6, and is common in rheumatology, transplantation, and hematology-oncology. Early clinical and laboratory results of COVID-19 showed significant similarities to classic cytokine storm. Disease severity, especially the lung involvement, and outcome were associated with the severity of the cytokine storm. As a result, tocilizumab, an IL-6 receptor blocker, has been proposed as a possible treatment option [5].

During the early stages of the COVID-19 pandemic, the use of tocilizumab to manage cytokine storm in patients was not formally approved. However, despite this, the drug was included in the international and national protocols for the COVID-19 treatment, including the temporary Guidelines of the Russian Federation Ministry of Health. At the time of this study, tocilizumab had already been recommended for use in patients with cytokine storm, and its clinical efficacy had been demonstrated in the studies conducted [7]. Therefore, it

were unethical to conduct a study in which the patients with cytokine storm who had no contraindications to these drugs would not have been administered monoclonal antibodies that block IL-6 receptors. On the other hand, the evidence base in favor of the use of GCSH was still limited, and the valid at that time temporary Guidelines (Version 5) of the Russian Federation Ministry of Health for the treatment of COVID-19 did not specifically mention the clinical use of this treatment option. Later, the efficacy of GCSH was confirmed by convincing data that was included in all international and national guidelines for the treatment of COVID-19 [8]. For ethical reasons, the design of this study cannot be replicated, making it unique.

The main result of the study was the significant improvement in the lung oxygenation function achieved with the use of tocilizumab. By day 3 after the drug administration, the PaO_2 level had statistically significantly increased and normalized, along with a statistically significant increase and normalization of the P/f ratio. This improvement in oxygenation parameters was attributed to the effect of tocilizumab on the cytokine storm and lung parenchyma, which is supported by various studies, including multicenter studies, which showed the clinical efficacy of tocilizumab. They showed that tocilizumab therapy improved survival of patients with both non-invasive and invasive mechanical ventilation, increased the likelihood of discharge from hospital within 28 days of the illness onset, reduced the risk of disease progression requiring patient's transfer from non-invasive to invasive mechanical ventilation, and reduced the mortality risk [9]. Thus, the timely use of the anti–IL-6 receptor monoclonal antibodies, in particular tocilizumab, an IL-6 inhibitor, may be one of the few, if not the only, therapeutic option that can improve the course of the disease.

There is also evidence in the literature that tocilizumab may not reduce the incidence of tracheal intubation and mortality in patients with COVID -19, and these results should be carefully analyzed [10]. The use of anti–IL-6 receptor monoclonal antibodies, such as tocilizumab that blocks IL-6 is contraindicated in the presence of bacterial inflammation, as this can lead to the development of sepsis and death [11]. It is important to note that bacterial infections, both hospital-acquired and community-acquired, are common in ICU patients with COVID-19. In addition, the pharmacodynamic effects of tocilizumab and other IL-6 blocking drugs may last for 2–4 weeks [12], and even if the drug is administered to a patient without bacterial inflammation, bacterial complications may develop days or weeks later while the drug is still active. This increases the risk of sepsis and death.

In the present study, there were no cases of sepsis or deaths in the COVID-19 patients who were treated for cytokine storm by using the anti–IL-6 receptor monoclonal antibodies blocking the IL-6. These relatively favorable outcomes may be partially accounted for the disease-causing viral strain. As the study was conducted during the first wave of the COVID-19 pandemic, the causative agent was most likely the Wuhan coronavirus strain. If the study had been conducted at a later time when the delta strain was common, the outcomes could have been worse.

Although many studies, including multicenter studies, have investigated the efficacy of tocilizumab therapy, most of them have focused on the clinical efficacy. We were unable to find studies that would have examined the effect of tocilizumab on the gas exchange function of the lungs, and which would have presented data on the dynamics of gas exchange parameters in patients with COVID-19 and the cytokine storm development. Therefore, we emphasize this as the novelty

of this study, which was conducted at the initial stage of using the drug in patients of this group.

The limitations of the presented study are the small sample size, the design of a retrospective cohort study without a control group performed in a single center, and the lack of the analysis of the patient age heterogeneity, taking into account data on the critical impact of age and comorbidity on the course and outcomes of severe forms of COVID-19.

Conclusions

1. The use of tocilizumab in patients with severe course of the new coronavirus infection COVID-19 and cytokine storm promotes the normalization and a statistically significant increase in oxygenation parameters (PaO_2, p=0.001; P/f ratio, p=0.001) within 3 days after the drug administration.

2. When using tocilizumab in patients with severe course of the new coronavirus infection COVID-19 and cytokine storm, no effect was found on the duration of the respiratory support or the reduction of the aggressiveness of its parameters for three days (p>0.05).

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