IL6-INHIBITORS IN TREATMENT OF SARS COVID19

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The aim *of this study was to evaluate the clinical efficacy and safety of a two-dose approach in the administration of tocilizumab in patients with SARS COVID19*

Material and methods. *The study was carried out on the basis of the Odrex Medical House in 2000-2021. The total sample included 4,112 patients hospitalized in a specialized department with coronavirus pneumonia. Of this sample, 150 patients were prescribed tocilizumab at a dose of 8 mg/kg of patient weight, including 36 (24.0 %) cases when tocilizumab was administered in a two-dose regimen. In the case of a two-dose regimen, the second dose was administered no earlier than 24 hours after the first one.*

All patients were examined according to the current clinical protocols. The hemogram, the content of CRP, ferritin, interleukin-6 were assessed. All patients received dexamethasone intramuscularly at a dose of at least 6 mg per day. Statistical processing was carried out by methods of analysis of variance using the software Statistica 13.0.

Results. *After the use of tocilizumab, the patients had a decrease in body temperature and a decrease in the need for oxygen support. At the same time, the normalization of indicators of the activity of the systemic inflammatory response was observed.*

Mortality after the use of tocilizumab was 29.3 %; in all cases, the deaths had an extremely severe course of coronavirus infection and a significant comorbid background. There were no manifestations of anaphylaxis and cases of secondary infection after the appointment of tocilizumab.

Conclusions. *The use of tocilizumab could significantly improve the condition of patients with SARS COVID19. There were no signs of anaphylaxis and cases of secondary infection after the administration of tocilizumab. In the absence of a pronounced clinical effect within 24 hours after the first dose of tocilizumab in patients with severe SARS COVID19, it is advisable to re-administer the drug (two-dose regimen)*

Keywords: *COVID-19, IL-6 inhibitors, tocilizumab, respiratory failure, inflammation, monoclonal antibody, D-dimer, dexamethasone, mechanical ventilation*

1. Introduction

In December 2019, the first reports of COVID-19, a disease caused by the new severe acute respiratory syndrome of coronavirus ethology (SARS-CoV-2), were received from Wuhan (Hubei Province, China) [1]. Since then, the disease has become a global pandemic, with about 5 million deaths to date.

In severe and critical cases of Covid-19, which occur in 14 % and 5 % of patients, respectively, Covid-19-associated pneumonia could lead to acute respiratory distress syndrome [2, 3]. Respiratory failure is one of the leading causes of death in patients with Covid-19. In addition, there is a high risk of neurological and cardiac complications [4, 5].

One of the pathogenetically significant mechanisms of endothelial damage is the production of pleiotropic proinflammatory cytokines, in particular IL-6. COVID-19-associated systemic inflammation and respiratory failure have been shown to be associated with increased cytokine release. In this regard, drugs that reduce the production of cytokines have been used. These include, in addition to dexamethasone, specific IL-6 inhibitors, represented by monoclonal antibodies against the IL-6 receptor (sarilumab, tocilizumab) and against IL-6 itself (siltuximab). Current clinical guidelines for the treatment of COVID-19 recommend the use of IL-6 inhibitors in patients with severe systemic inflammatory reactions accompanied by respiratory failure [6].

In clinical trials involving hospitalized patients with COVID-19, tocilizumab, given in addition to standard care, including corticosteroid therapy, has been shown to reduce the risk of death within 28 days, as well as the duration of hospitalization. The risk of connection to a ventilator or death after 28 days of observation also decreased. Tocilizumab is a monoclonal antibody that reduces inflammation by blocking the interleukin-6 receptor and is approved for the treatment of systemic connective tissue diseases.

According to the EUA, the FDA is authorizing the emergency use of tocilizumab for the treatment of certain hospitalized patients with COVID-19. The data supporting this EUA are based on the results of 4 clinical trials,

including one randomized controlled open platform trial (Randomized Evaluation of COVID-19 Therapy - RECOVERY) and three randomized double-blind placebo-controlled trials (EMPACTA, COVACTA and REMDACTA). However, the most important scientific evidence for the potential benefit of tocilizumab comes from the RECOVERY and EMPACTA trials.

In the RECOVERY study, 4116 hospitalized patients with severe COVID-19 pneumonia were randomized to receive either tocilizumab in addition to usual treatment (2022 patients) or usual treatment alone (2094 patients). The primary endpoint was death at 28 days of follow-up, and the results of the primary analysis were statistically significant. The chance of death by day 28 was 30.7 % for patients treated with tocilizumab and 34.9 % for conventional care alone. The median time to hospital discharge was 19 days with tocilizumab and 28 days with conventional treatment.

The EMPACTA study of 389 hospitalized patients with COVID-19 pneumonia assessed the need for mechanical ventilation or death at 28 days of follow-up as the primary endpoint. Patients treated with tocilizumab experienced less progression to the need for mechanical ventilation or death compared to those treated with placebo, and the results of the primary analysis were statistically significant. The proportion of patients who required mechanical ventilation or died by day 28 was 12.0 % with tocilizumab and 19.3 % with placebo.

In the COVACTA study of 452 hospitalized patients with severe COVID-19 pneumonia, the primary endpoint was clinical status at 28 days of follow-up, assessed on an ordinal scale of 7 categories. Although there was no statistically significant difference between treatment groups, the COVACTA study contributed to the evaluation of the drug's safety when used to treat COVID-19.

In the REMDACTA study, 649 hospitalized patients with severe COVID-19 pneumonia were randomized to receive tocilizumab plus remdesivir (430 patients) or placebo plus remdesivir (210 patients). The primary endpoint was time to hospital discharge or readiness to discharge after 28 days of follow-up. Although there were no statistically significant differences between treatment groups in terms of time to hospital discharge or "ready to discharge" at 28 days of follow-up, the REMDACTA study contributed to assessing the safety of tocilizumab. Its side effects seen in COVID-19 studies include constipation, anxiety, diarrhea, insomnia, hypertension, and nausea.

At the same time, it remains unclear how drugs of this class work in the long run. In addition, their use in patients with chronic liver disease, erosive ulcerative mucosal lesions of various gastrointestinal tract, severe bacterial, fungal or non-SARS-CoV-2 viral infection, immunodeficiency, thrombocytopenia and individual intolerance [7, 8]. Corticosteroid coverings are recommended to reduce the risk of adverse effects from IL6 inhibitors [9].

At present, only tocilizumab is registered in Ukraine out of all the above-mentioned IL6 inhibitor drugs. Not all clinical centers have experience of its use, which is due to the significant cost of the drug. The question of the optimal dose of the drug, in particular the feasibility of prescribing its second dose, remains controversial.

The aim of this study was to evaluate the clinical efficacy and safety of a two-dose approach in the administration of tocilizumab in patients with SARS COVID19

2. Material and methods

The study was carried out based on the Odrex Medical House in 2000–2021. The total sample included 4,112 patients hospitalized in a specialized department with coronavirus pneumonia. Of this sample, 150 patients were prescribed tocilizumab at a dose of 8 mg/kg of patient weight, including 36 (24.0 %) cases when tocilizumab was administered in a two-dose regimen. In the case of a two-dose regimen, the second dose was administered no earlier than 24 hours after the first one.

Ethical approval. The study was approved by the Committee on Bioethics of the LLC "House of Medicine" on September 17, 2020 protocol No. 33., informed consent was obtained from all study participants.

Study was in line with the Declaration of Helsinki.

All patients were examined according to the current clinical protocols. The hemogram, the content of CRP, ferritin, interleukin-6 were assessed. All patients received dexamethasone intramuscularly at a dose of at least 6 mg per day.

Statistical processing was carried out by methods of analysis of variance using the software Statistica 13.0 [10]. The Kolmogorov-Smirnov test was used to check the normality of the distribution of variables. The Wilcoxon test and the Mann-Whitney test were used to compare the mean values. The difference between the mean values in the groups was confirmed by nonparametric analysis of variance (p<0.05).

3. Results

The mean age of patients with SARS COVID19 was 58.3±1.1 years, and candidates for tocilizumab were 47.9±1.3 years. The gender composition of the sample was in equilibrium (46.0 % – women, 54.0 % – men). At the time of admission, all patients had a confirmed coronavirus infection with a pronounced systemic inflammatory response. A severe course was registered in 134 (89.3 %) patients, a course of moderate severity with a tendency to aggravate the phenomena of "cytokine storm" – in 16 (10.7 %) patients.

Patients with SARS COVID19 of moderate severity had fever (body temperature more than 38.0 °C), hypoxemia (SpO2 <95 %), severe shortness of breath (respiratory rate> 22 / min), increased serum CRP> 10 mg/l. Changes in the lungs at CT are characteristic, typical for a viral lesion (the volume of the lesion is minimal or medium, the phenomenon of "frosted glass" with or without signs of consolidation). Patients with severe SARS COVID19 have hyperpyrexia (≥39 °C), severe dyspnea (respiratory rate ≥30 / min), severe hypoxemia (SpO2 ≤ 93 %), changes in the level of consciousness in the form of stunning or agitation, unstable hemodynamics (BP <90 mm Hg or BP diast. <60 mm Hg), decreased urine output less than 20 ml / hour. In patients with severe course, there were marked changes in the lungs on CT, typical for viral lesions, with a significant or subtotal lesion volume. These changes were accompanied by

lactic acidosis (arterial blood lactate> 2 mmol / L), which corresponds to qSOFA> 2 points.

The patients' BMI averaged 29.9 ± 1.3 kg/m^2, i.e., in the structure of the diseased there were many overweight persons.

The level of interleukin-6 in patients at the time of inclusion in the study averaged 19.9 ± 0.9 pg / ml, which significantly exceeds the reference values. Further analysis showed the efficacy of tocilizumab in both single-dose and double-dose administration (Table 1).

Table 1

The results of treatment with different regimens of tocilizumab use

Indices	One dose mode		Two dose mode	
	Before treatment	After treatment	Before treatment	After treatment
CRP (0–1 mg/l)	28.4 ± 0.7	4.3 ± 0.3	34.2 ± 1.4	3.9 ± 0.3
Ferritin (20–250 mcg/l males, 10–120 µg/l females)	1446 ± 48	312 ± 12	1638 ± 97	245 ± 18
Interleukin-6 (0–7 pg/ml)	18.8 ± 1.1	6.3 ± 0.3	22.3 ± 1.7	5.9 ± 0.5

After the use of tocilizumab, the patients had a decrease in body temperature and a decrease in the need for oxygen support. At the same time, the normalization of indicators of the activity of the systemic inflammatory response was observed.

Mortality after the use of tocilizumab was 29.3 %; in all cases, the deaths had an extremely severe course of coronavirus infection and a significant comorbid background. There were no manifestations of anaphylaxis and cases of secondary infection after the appointment of tocilizumab.

4. Discussion

Indications for the administration of tocilizumab are interstitial pneumonia with acute respiratory failure, progressive respiratory failure, the need to connect to non-invasive or invasive ventilation, the presence of extrapulmonary organ lesions. Elevated C-reactive protein, D-dimer, and ferritin levels correlate with elevated IL-6 levels and poor outcomes in patients with severe COVID-19 infection

Tocilizumab is recommended for use in addition to corticosteroid therapy in patients with rapid respiratory decompensation. These are patients undergoing invasive mechanical ventilation for no more than 24 hours; patients with rapidly increasing oxygen requirements requiring non-invasive mechanical ventilation or high-flow oxygen, and in whom the level of C-reactive protein is 5 times higher than the upper reference value.

With the progression of the disease, tocilizumab is prescribed no earlier than 7 days from the onset of clinical symptoms or considering X-ray changes (in some patients, clinical signs of the initial period are absent). The recommended dose of tocilizumab is 8 mg/kg as a single intravenous infusion. The total dose should not exceed 800 mg. Tocilizumab should be diluted in 100 ml of 0.9 % sodium chloride and administered over an hour.

The national clinical protocol does not recommend the administration of a second dose; however, most modern studies believe that the use of a second dose after 24 hours in the absence of a sufficient response to the introduction of the first is justified [1, 3, 5].

Since tocilizumab inhibits the production of C-reactive protein, a decrease in its level should not be used as a sign of clinical improvement. Contraindications to the administration of tocilizumab: AST / ALT> 5 times higher than normal; the number of neutrophils <50,000; sepsis not caused by SARS-CoV-2; increased level of procalcitonin (more than 2 times); the presence of comorbid conditions that can lead to a negative prognosis, complicated diverticulitis, pyoderma, a negative response to immunosuppressive therapy. The use of tocilizumab outside of a hospital setting is unacceptable.

Tocilizumab, an interleukin (IL-6) receptor antagonist, reduces the need for mechanical ventilation, reduces the risk of death in hospitalized patients with COVID-19, without increasing serious adverse events.

Tocilizumab should be used in hospitalized patients with SARS-CoV-2 with a moderate to severe course. Patients taking tocilizumab should be monitored for adverse reactions, including hepatotoxicity, thrombocytopenia, neutropenia, and late secondary infections.

Research limitations. Group mortality was strongly influenced by comorbidity, patient weight, and age. These facts were not considered in the present study, which is a limitation of this study.

Prospects for further research. The prospect of further research is to identify the relationship between indicators of inflammation, mortality in patients, depending on comorbidities, patient weight, age and other factors. This will allow to personalize the tactics of treatment with tocilizumab depending on the characteristics of the patient and improve treatment outcomes.

5. Conclusions

1. The use of tocilizumab could significantly improve the condition of patients with SARS COVID19

2. Mortality after the use of tocilizumab was 29.3 %, in all cases the deaths had an extremely severe course of coronavirus infection and a significant comorbid background.

3. There were no signs of anaphylaxis and cases of secondary infection after the administration of tocilizumab.

4. In the absence of a pronounced clinical effect within 24 hours after the first dose of tocilizumab in patients with severe SARS COVID19, it is advisable to re-administer the drug (two-dose regimen).

Conflict of interests

The authors declare that they have no conflicts of interest.

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