

Effective therapy regimens for COVID-19 pneumonia in critically ill patients with the development of the cytokine storm syndrome.

In the pathogenesis of ARDS due to COVID-19, the main role is played by the excessive response of the immune system with the rapidly developing severe life-threatening cytokine release syndrome (cytokine storm). The cytokine release syndrome poses the threat of the onset and progression of ARDS. It is extremely important to diagnose the cytokine storm in the early stages of its development.

The cytokine storm, usually leads to the development of ARDS in almost half of patients with COVID-19, to the multiple organ failure and can cause the death of a patient.

Clinically, the cytokine storm can manifest itself as persistent febrile fever refractory to antimicrobial therapy, ARDS, splenomegaly, edematous, hemorrhagic syndromes, hepatomegaly, jaundice, symptoms of central nervous system damage (excitability, convulsions, meningeal signs, depression of consciousness), non-specific skin rash.

Early laboratory signs of the cytokine storm are serum ferritin levels  $> 600$  ng/mL or a combination of two of the following: a decrease in platelet counts  $\leq 180 \times 10^9/L$ , white blood cells  $\leq 3.0 \times 10^9/L$ , lymphopenia or a rapid decrease in the number of platelets and/or leukocytes (during a day) more than twice against the background of continued high inflammatory activity, increased activity of AST, serum triglycerides  $> 156$  mg/dL; decrease in blood fibrinogen  $\leq 360$  mg/dL.

For the treatment of the cytokine storm with COVID-19, IL-6 inhibitors are used – the Tocilizumab and Sarilumab drugs (monoclonal antibodies to the IL-6 receptor).

Indications for the administration of IL-6 receptor inhibitors are a combination of data of thoracic computed tomography (CT) (a significant pulmonary parenchyma lesion of more than 50% (CT 3-4)

c with 2 and more signs):

- decrease in  $SpO_2$ ;
- CRP  $> 60$  mg/L or a 3-fold increase in CRP levels on 8th-14th days of illness;
- fever  $> 38$  °C for 5 days;
- leukocyte count  $< 3.0 \times 10^9/L$ ;
- absolute lymphocyte count  $< 1 \times 10^9/L$ ;
- blood ferritin level  $> 500$  ng/mL;
- IL-6 level  $> 40$  pg/mL.

Contraindications for the administration of genetically engineered biological drugs (GEBD):

- Sepsis confirmed by pathogens other than COVID-19;
- Hypersensitivity to any component of the drug;
- Viral hepatitis B;
- Concomitant diseases associated, according to the clinical decision, with an unfavorable prognosis;
- Immunosuppressive therapy for organ transplantation;
- Neutropenia  $< 0.5 \times 10^9/L$ ;
- Increased activity of AST or ALT of more than 5 norms;
- Platelet deficiency  $< 50 \times 10^9/L$ .

In pregnancy, the use of GEBD is undesirable.

During the therapy with IL-6 inhibitors, one should remember serious adverse events

- Infectious diseases: bacterial pneumonia, phlegmon, infections caused by *Herpes zoster*, etc.
- Increased activity of hepatic transaminases.
- Rash, itching, urticaria.
- High blood pressure.
- Leukopenia, neutropenia, platelet deficiency
- Increased lipid metabolism (total cholesterol, triglycerides, HDL, LDL). [1]

Given the long list of contraindications for the use of IL-6 inhibitors and the fact that the age of patients with severe COVID-19 is mainly over 60 years, they are people who have mainly severe concomitant pathologies (arterial hypertension, chronic heart failure, diabetes mellitus, cancers, liver diseases, COPD and others),

the main indicator of the administration of IL-6 inhibitors to the patients becomes very important. We associate the increase in C-reactive protein in the blood with the development of endotheliitis and pulmonary vascular microthrombosis. Near vascular edema in the interstitial tissue may develop, as a result, edema forms in the near alveolar zone. In case of edema in the near alveolar zone, exudate enters the alveolus, as a result of which the C-reactive protein in the blood increases and thoracic CT scans show frosted-glass image. The C-reactive protein is the main marker of disease severity and a prognostic marker of patient death. [2,3] Moreover, taking into account the experience of colleagues from Spain, who have carried out a multicenter cohort study, the effective use of IL-6 inhibitors was noted at  $\text{CRP} > 150 \text{ mg/L}$ , but at  $\text{CRP} \leq 150 \text{ mg/L}$  any significant effect of treatment using these drugs was not observed. [4]

It becomes important to prevent an increase in  $\text{CRP} > 150 \text{ mg/L}$  in the blood of patients. In our opinion, the most effective method is to use glucocorticoids in small doses. Recently, the World Health Organization supported the highly effective use of dexamethasone for critically ill patients with COVID-19 based on data from British scientists in the regimen of 6 mg 1 time a day for 10 days. [5]

The use of methylprednisolone in small doses in India is also showing high efficiency in the treatment of patients in critical condition in the regimen of 30 mg 2 times a day. [6] Italian scientists also confirm the high efficiency of the use of prolonged low doses of methylprednisolone in severe forms of COVID-19 pneumonia, which allows reducing the number of patients admitted to ICU. [7, 11]

One of the mechanisms of the possible development of a high systemic immune response may be a high growth of neutrophils and an increase in the D-dimer in the blood (the development of systemic microthrombosis), which leads to the development of the cytokine storm syndrome. In this case, endothelial dysfunction develops. The use of low doses of methylprednisolone is likely to increase the survival of patients with severe COVID-19 pneumonia [8]

In our health care institution, patients requiring oxygen support are orally administered 40 mg of famotidine 2 times a day. Preventive anti-inflammatory therapy is also used. It is prescribed in the presence of 2 or more signs: a decrease in  $\text{SpO}_2 < 93\%$  when breathing air,  $\text{CRP} > 60 \text{ mg/L}$  or an increase in CRP level 3 times or more on the 8th-14th days of illness, fever  $> 38.5^\circ\text{C}$  for 5 days, leukocyte count  $< 3.0\text{-}3.5 \times 10^9/\text{L}$ , lymphocyte count  $< 1 \times 10^9/\text{L}$ , and/or  $< 15\%$ . Prednisolone (methylprednisolone) is administered according to the scheme: 120 mg - 1st day, 90 mg - 2nd day, 90 mg - 3rd day, 60 mg - 4th day, 60 mg - 5th day, 30 mg - 6th day or 6 mg of dexamethasone 1 time a day. In addition, Enoxaparin sodium is administered subcutaneously: 6,000 IU (60 mg) 2 times/day or 8,000 IU (80 mg) 2 times/day (the dose is determined based on the weight of the patient), and antibiotic therapy according to the scheme.

Having used these treatment regimens for critically ill patients with COVID-19 pneumonia, the level of IL-6 in the blood  $> 40 \text{ pg/mL}$  practically does not rise in patients, except for the group of patients where the level of procalcitonin is  $\geq 0.5 \text{ } \mu\text{g/L}$ . An increase in procalcitonin indicates the addition of a bacterial infection, and this is due to an increase in IL-6 in the blood  $> 40 \text{ pg/mL}$ .

However, an interesting study proves that IL-6 levels in patients with the hyperinflammatory phenotype of ARDS are 10- to 200-fold higher than levels in patients with severe COVID-19 see table [9]

For example, a recent postmortem report of patients with COVID-19 ARDS identified severe vascular injury, including alveolar microthrombi that were 9 times more prevalent than found in postmortem studies of patients with influenza ARDS. [10]

Conclusions: The main reason for the development of severe pneumonia in patients with COVID-19 is apparently injury of the endothelium by the virus and the immune system, which leads to the development of massive microthrombosis. We believe that it is very important to prescribe anticoagulants to COVID-19 patients as early as possible and to administer prolonged low doses of glucocorticoids at certain indicators.

These treatment regimens are expected to reduce the mortality caused by COVID-19.

Perhaps it is necessary to be very careful about the administration of IL-6 inhibitors. We assume that the main indicators for the administration of IL-6 inhibitors are the following indicators: CRP > 150 mg/L, IL-6 in the blood > 40 pg/mL, procalcitonin < 0.5 µg/L. To confirm our hypotheses, a large-scale study is required.

## From: Is a “Cytokine Storm” Relevant to COVID-19?

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**Table. Plasma Levels of Interleukin-6 Reported in COVID-19 Compared With Levels Previously Reported in ARDS<sup>a</sup>**

COVID-19	Total population		Severe disease		Measurement platform
	No.	IL-6 levels, pg/mL	No.	IL-6 levels, pg/mL	
Zhou et al <sup>1</sup>	191	7 (5-11)	54 <sup>b</sup>	11 (8-14)	CL
Wu et al <sup>1</sup>	123	7 (6-9)	84 <sup>c</sup>	7 (6-11)	CL
Mo et al <sup>1</sup>	155	45 (17-96)	85 <sup>d</sup>	64 (31-165)	CL
Qin et al <sup>2</sup>	452	21 (6-47)	286 <sup>e</sup>	25 (10-55)	CL
Cummings et al <sup>6</sup>	NR	NR	237 <sup>f</sup>	26 (11-69)	CL
ARDS	Hypoinflammatory		Hyperinflammatory		Measurement platform
	No.	IL-6 levels, pg/mL	No.	IL-6 levels, pg/mL	
ALVEOLI <sup>7</sup>	521	238 (94-741) <sup>g</sup>	386	154 (67-344)	ELISA
FACTT <sup>8</sup>	884	130 (46-411) <sup>g</sup>	638	86 (34-216)	ELISA
SAILS <sup>9</sup>	720	443 (173-1513) <sup>g</sup>	451	282 (115-600)	ELISA

Abbreviations: ALVEOLI, Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury; ARDS, acute respiratory distress syndrome; CL, clinical laboratory; CLIA, chemiluminescent immunoassay; ELISA, enzyme-linked immunosorbent assay; FACTT, Fluids And Catheters Treatment Trial; ICU, intensive care unit; IL-6, interleukin-6; NR, not reported; SAILS, Statins for Acutely Injured Lungs From Sepsis.

<sup>a</sup> Presented values are the medians with interquartile ranges. The top segment of the Table reports data from selected COVID-19 cohorts (n > 100) and their corresponding severe subgroups. The bottom segment reports data from 3 National Heart, Lung, and Blood Institute ARDS network randomized clinical trials. Values are reported for the total cohorts and in subgroups stratified by ARDS phenotypes (hypoinflammatory and hyperinflammatory). The mean (SD) IL-6 levels for the ARDS trials were as follows: ALVEOLI, 2051 (8208) pg/mL; FACTT, 1048 (3348) pg/mL; and SAILS, 2363 (10 940) pg/mL.

<sup>b</sup> Nonsurvivors.

<sup>c</sup> ARDS.

<sup>d</sup> Refractory hypoxemia.

<sup>e</sup> Acute hypoxemic respiratory failure.

<sup>f</sup> Requiring ICU admission.

Table Title:

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