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ORIGINAL ARTICLE

# Interleukin 17 antagonist netakimab is effective and safe in the new coronavirus infection (COVID-19)

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**ABSTRACT. Background**: **Cytokine release syndrome is a serious complication of the new coronavirus infection (COVID-19). The aim of the study was to assess effectiveness and safety of the IL-17 antagonist nekatimab for its treatment. Methods**: **The retrospective study included COVID-19 patients with C-reactive protein levels >60 mg/L. Patients received either netakimab (group NET), IL-6 antagonist tocilizumab (group TOC) or no anti-cytokine treatment (group CON). Results**: **Forty-four patients were enrolled in the NET group, 27 patients in the TOC group, and 47 patients in the CON group. Mortality was lower in the NET group than in TOC and CON groups (2.3% vs. 14.8% and 31.9%; $p = 0.018$ and $p < 0.001$). NET group patients required intensive care unit admission (6.8% vs. 25.9% and 46.3%; $p = 0.025$ and $p < 0.001$) and mechanical ventilation (4.6% vs. 22.2% and 31.9%; $p = 0.022$ and $p = 0.002$) less frequently than patients of the TOC and CON groups. After 7-10 days of anti-cytokine drug administration, a reduction in lung lesion volume ($p = 0.016$) and an increase in the proportion of patients who did not need oxygen support ($p = 0.005$) or stayed in prone position ($p = 0.044$) was observed in the NET group only group; C-reactive protein levels were the same in the TOC and NET groups ($p = 0.136$) and lower in the CON group ($p < 0.001$ and $p = 0.005$). IL-6 levels decreased in the NET group ($p = 0.005$) and did not change in the TOC group ($p = 0.953$). There was no difference in the incidence of side effects between groups. Conclusion**: **The IL-17 antagonist netakimab is effective and safe in the treatment of cytokine release syndrome in COVID-19.**

**Key words:** COVID-19, cytokine release syndrome, interleukin 6, interleukin 17, tocilizumab, netakimab

## INTRODUCTION

The new coronavirus infection (COVID-19) has become a new challenge for humanity. The disease can be asymptomatic, mild, or have complications, among which the cytokine release syndrome is one of the most dangerous complications [1-3]. The main role in its development is played by different interleukins. Therefore, drugs that block their effects were proposed for the treatment of this complication. The use of interleukin (IL) 6 antagonist tozalizumab is the most studied to date [4–6]. Several experts have suggested that blocking the pathway of other interleukins, in particular IL-17, may be useful in the treatment of COVID-19 [7-10]. IL-17 is produced by Th17 cells and stimulates the formation of other cytokines, including IL-6 [9]. IL-17 antagonists are used in the treatment of axial spondyloarthritis and psoriasis [11]. To date, no studies have been published on their safety and efficacy in COVID-19, except for cases of COVID-19 in patients who received these drugs for axial spondyloarthritis or psoriasis [12-14]. Netakimab, a humanized monoclonal antibody against IL-17A, is one of the most recent drugs [11]. The aim of our study was to evaluate the effectiveness and safety of netakimab in the treatment of COVID-19 in comparison with the use of tocilizumab and with patients who did not receive anticytokine treatment.

**Abbreviations**

| | |
|---|---|
| COVID-19 | new coronavirus infection |
| CRP | C-reactive protein |
| IL | interleukin |

## MATERIALS AND METHODS

This was a retrospective study. All patients signed an informed consent for the use of off-label drugs. The study was approved by the local ethical committee.

### *Patients*

The study included patients admitted to the Clinic of internal diseases, gastroenterology and hepatology of

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Sechenov University with suspected COVID-19 in accordance with the guidelines of the World Health Organization [15] from April to July 2020 and had cytokine release syndrome. Unfortunately, there are no generally accepted criteria for cytokine release syndrome. According to Russian clinical guidelines [16], the indication for prescribing anticytokine drugs in COVID-19 was the C-reactive protein (CRP) level above 60 mg/L. Thus, the criteria for inclusion in the study were age over 18 years, laboratory-confirmed COVID-19 (a positive result of polymerase chain reaction on nasopharyngeal swab) or suspected COVID-19 (complex of clinical, radiological, and epidemiological data) [15, 16], the absence of pregnancy, the signing of informed consent to the administration of off-label drugs, and CRP level above 60 mg/L. Patients who used other anticytokine drugs (except tocilizumab and netakimab) were excluded.

### *Intervention*

Netakimab was administered once subcutaneously at a dose of 120 mg.

### *Controls*

There were two control groups. The first group consisted of patients who were administered tocilizumab once intravenously at a dose of 8 mg/kg. The second group included patients who did not receive anticytokine treatment.

The choice of the anticytokine drugs was determined by their availability in the Clinic. If these drugs were not available in the Clinic, anticytokine treatment was not performed and the patient was included in the control group without anticytokine treatment. Patients in all the groups also received antiviral, antibacterial, anticoagulant, and dexamethasone treatment according to indications and contraindications (Table S1).

### *Outcomes*

Survival or death of the patient was considered as the final outcome. Duration of hospitalization, total duration of the disease, the incidence of admission to intensive care unit and mechanical ventilation, and the change in the values of key biomarkers, chest CT, and respiratory function in 7-10 days after the administration of the anticytokine drug were considered as additional outcomes. The major side effects (cytopenia, secondary infections, thrombosis, increased transaminases, cholestasis) were also evaluated.

The volume of the affected lungs was determined by chest CT and included the sum of ground glass and consolidation volumes. Oxygen saturation was measured with a pulse oximeter. The value of the main biomarkers of the disease was evaluated at two points: the first point was 1-3 days before the administration of the anticytokine drug and the second point was 7-10 days after its administration.

After determining the average day of hospitalization following the administration of an anticytokine drug, this day of hospitalization $\pm 1$ day was used as point 1 for the group of patients who did not receive anticytokine drugs. The value of biomarkers 7-10 days after this point 1 was considered as point 2.

### *Statistics*

Results are presented as median [interquartile range]. The groups were compared using Mann–Whitney and Kruskal–Wallis tests for continuous data and chi-square test for categorical data. Wilcoxon test was used to assess the changes in continuous biomarkers. Survival was assessed using the Kaplan–Meier estimator and Cox's F-test. A $p \leq 0.050$ value was taken as the criterion for significance. Statistical calculations were performed using STATISTICA 10 (TIBCO Software, Palo Alto, CA).

## RESULTS

The study included 44 patients who received netakimab (group NET), 27 patients who received tocilizumab (group TOC), and 47 patients who did not receive anticytokine therapy (group CON) (*figure 1*). There was no significant difference among patient groups in age, gender distribution, body mass index, body temperature at admission, total duration of disease, symptoms of COVID-19, the incidence of comorbidities, and the frequency of the use of other drugs to treat COVID-19 (*tables 1 and S1*). Patients received antibiotics (100.0%), dexamethasone (89.8%), enoxaparin (83.1%), and hydroxychloroquine (67.8%) (*table S1*).

Patients who received tocilizumab stayed in hospital longer than those who did not receive anticytokine treatment. Patients who received netakimab were less likely to require intensive care unit admission or mechanical ventilation than patients from other groups. Among patients who underwent mechanical ventilation, the survival rate was 50% in NET group, 33.3% in TOC group, and 0.0% in CON group (*table 1*).

Patients who received tocilizumab had better survival rates than those who did not receive anticytokine treatment (85.2% vs. 68.1%; $p = 0.039$). Patients who received netakimab had better survival rates than those who did not receive anticytokine treatment or those who received tocilizumab (97.7% vs. 68.1% and 85.2%; $p < 0.001$ and $p = 0.018$) (*figure 2*).

There was no significant difference between patient groups in the value of most biomarkers tested before the administration of anticytokine drug (*table 2*).

The following changes were observed 7-10 days after exposure to the anticytokine drug. There was a significant decrease in the volume of lung lesion according to chest CT data and in the activity of lactate dehydrogenase in the group of patients who received netakimab unlike patients of other groups. A significant increase in oxygen saturation was observed only in the groups of patients who received anticytokine drugs, and this increase was higher in the group of patients who received netakimab. A decrease in CRP, fibrinogen, creatinine level, and body temperature and an increase in lymphocyte and platelet count and alanine amino-

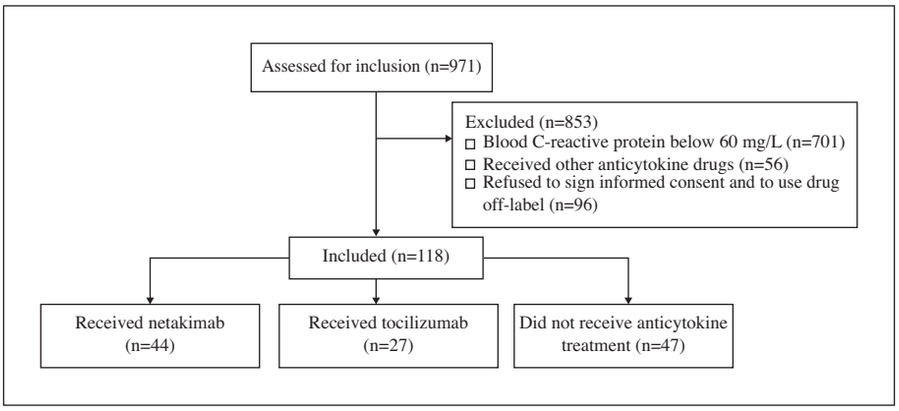


**Figure 1**
CONSORT 2010 Flow Diagram.

transferase activity were observed in all groups of patients. However, the decrease in CRP levels in the groups with anticytokine drugs was greater than in CON group, and there was no difference in the CRP levels between NET and TOC groups. The maximum decrease in the fibrinogen level was observed in the group of patients who received tocilizumab, and the maximum increase in oxygen saturation, lymphocyte, and platelet count was in the group of patients who received netakimab. There was no significant difference between the groups in body temperature, white blood cell and neutrophil count, creatinine level, and transferase activity 7-10 days after administration of anticytokine drugs. The level of D-dimer in blood was minimal in the group of patients who received netakimab. There was a significant decrease in blood IL 6 level in the group of patients who received netakimab, and no significant change was observed in the group of patients who received tocilizumab (*table 2*). Before the administration of anticytokine drugs, about 70% of patients in all the groups needed supplemental oxygen. After 7-10, half of these patients no longer needed it in the group of patients who received netakimab. There were no significant changes with regard to the group of patients who received tocilizumab. Multidirectional changes were observed in the group of patients who did not receive anticytokine drugs: a third of them needed mechanical ventilation, another third of them no longer needed supplemental oxygen, and the rest third of them remained without significant changes (*table 2*).

After 7-10 days following the administration of the anticytokine drug, the number of patients who needed to be in a prone position significantly decreased in the group of patients who received netakimab, increased among patients who did not receive anticytokine treatment, and did not significantly change in the group of patients who received tocilizumab (*table 2*). In patients who received anticytokine treatment, injection reactions and the development of cytopenias were not observed. There was no significant difference between patient groups in the incidence of hepatotoxicity, acute kidney injury, and extrapulmonary infection after administration of these drugs. Pulmonary embolism was significantly less common in patients who received netakimab (*table 3*).

**Table 1**
Main characteristics of patients by groups

| | **Group NET (n = 44)** | **Group TOC (n = 27)** | **Group CON (n = 47)** | ***p*, NET vs. TOC** | ***p*, NET vs. CON** | ***p*, TOC vs. CON** |
|---|---|---|---|---|---|---|
| Age, years | 58[51-67] | 59[45-66] | 62[54-70] | 0.929 | 0.068 | 0.100 |
| Male/Female | 29/15 | 14/13 | 23/24 | 0.239 | 0.102 | 0.809 |
| Body temperature at admission, $^0$C | 37.7[37.3-38.0] | 38.0[37.5-38.5] | 37.8[37.4-38.3] | 0.129 | 0.565 | 0.152 |
| Body mass index, kg/m$^2$ | 32.6[30.3-37.9] | 30.5[24.9-32.7] | 30.0[26.4-33.3] | 0.133 | 0.068 | 0.824 |
| Length of hospital stay, days | 17[14-22] | 20[17-25] | 16[13-21] | 0.080 | 0.371 | *0.019* |
| Total duration of disease, days | 23[20-29] | 27[22-31] | 23[20-29] | 0.154 | 0.924 | 0.081 |
| Death | 1 (2.3%) | 4 (14.8%) | 15 (31.9%) | *0.018* | *<0.001* | *0.039* |
| Admission to intensive care unit | 3 (6.8%) | 7 (25.9%) | 22 (46.8%) | *0.025* | *<0.001* | 0.077 |
| Staying in intensive care unit, days | 12[1-20] | 8[3-12] | 5[3-12] | 0.732 | 0.770 | 0.508 |
| The need for mechanical ventilation | 2 (4.6%) | 6 (22.2%) | 15 (31.9%) | *0.022* | *0.001* | 0.373 |
| Ventilated survivors | 1 (2.3%) | 2 (7.4%) | 0 (0.0%) | 0.297 | 0.299 | 0.057 |

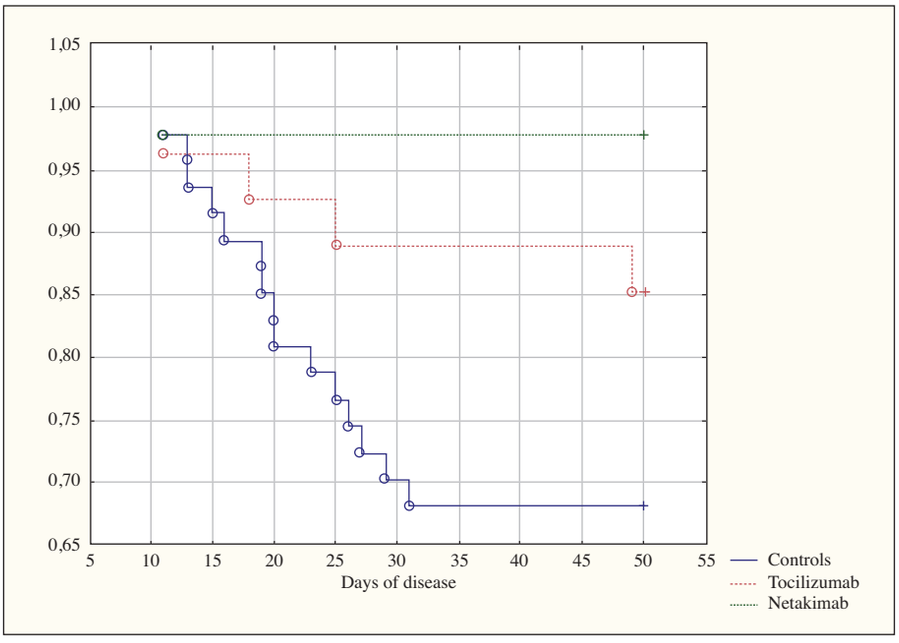


**Figure 2**
Survival curves for patients with COVID-19 and cytokine release syndrome who did not receive anticytokine treatment (Control group), received tocilizumab (Tocilizumab group), and received netakimab (Netakimab group).

## DISCUSSION

The pathogenesis of COVID-19 is complex and still not fully understood. It can be a systemic disease accompanied by massive cytokine release, which is called cytokine release syndrome, cytokine storm, or hyperinflammatory syndrome [1-3]. It is believed that IL-6 has primary importance in its development. So, it was natural that antagonists of this cytokine were proposed for its treatment. They have shown beneficial effects in a number of low-quality studies [4-6]. Recently, a large multicenter study was published that did not reveal a significant difference in the mortality of patients who received and did not receive tocilizumab [17]. However, unlike our study, patients did not receive antibiotics and only 10% of them received dexamethasone in that study and these could lead to this result. New studies are needed with the use of more complex treatment and, especially, with the use of glucocorticoids.

It was found that the pathway of Th17 cells is activated and blood IL-17 level is increased in cytokine release syndrome in COVID-19 [7-10]. This pathway is extensively studied in psoriasis and axial spondyloarthritis, and a group of monoclonal antibodies has been proposed for its blockade [11].

IL-17 has a complex proinflammatory effect. It enhances the formation of IL-6 and other cytokines. In this regard, the idea arose to use blockers of IL-17 pathway in the treatment of COVID-19 [7-10]. However, we did not find any published studies describing the effect of monoclonal antibodies that block the IL-17 pathway on the course of COVID-19. Thus, our work will be the first, and this is its strong point.

In our study, we used netakimab, which represents the latest generation of monoclonal antibodies against IL-17 [11]. The comparison was with patients who received tocilizumab, the most studied monoclonal antibody that blocks the effect of IL-6, and with patients who did not receive anticytokine treatment.

Unfortunately, there is no generally accepted criterion for diagnosis of cytokine release syndrome. Perhaps the ideal would be the level of pro-inflammatory cytokines, in particular IL-6, but these tests are expensive and are not yet available in most clinics. We used CRP as a biomarker for the development of this syndrome because it is the main biomarker of inflammation and can be easily determined in all clinics of the world.

As previously reported, taking tocilizumab led to a significant reduction in mortality in COVID-19 in our study, but the reduction in mortality after taking netakimab was greater. Tocilizumab and netakimab showed the same effect in reducing the level of inflammatory markers in COVID-19, in particular CRP, and this decrease was more significant than in patients who did not received anticytokine treatment.

IL-6 level did not change significantly in the tocilizumab group, but it decreased remarkably in the netakimab group. This is easily explained since tocilizumab blocks the effects of IL-6, not its formation, while netakimab blocks the effects of IL-17, one of which is the formation of IL-6. Most likely, the formation of IL-17 is an earlier step in the pathogenesis of cytokine release syndrome than the formation of IL-6, and blocking the IL-17 pathway gives a better effect than blocking the IL-6 pathway. Unfortunately, the level of IL-6 was studied only in one patient who did not receive anticytokine drugs, and this did not allow comparing the change in its level with the group of these patients.

Respiratory function changed differently in different groups during the first week after the administration of the anticytokine drug. The divergent change was observed in the group that did not receive anticytokine

**Table 2**

Change in the values of the main biomarkers 7-10 days after the administration of anticytokine drugs. Point 1 was 1-3 days before administration of these drugs or equivalent days in CON group. Point 2 was 7-10 days after the administration of these drugs or equivalent days in CON group.

| **Group** | **Group NET (n = 44)** | | | **Group TOC (n = 27)** | | | **Group CON (n = 47)** | | | ***p****** | ***p*, NET vs. TOC** | ***p*, NET vs. CON** | ***p*, TOC vs. CON** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Point | 1 | 2 | *p*** | 1 | 2 | *p*** | 1 | 2 | *p*** | 1 | 2**** | 2**** | 2**** |
| Lung lesion volume, % | 44[33-63] | 38[30-50] | *0.016* | 50[44-63] | 50[38-63] | 0.641 | 44[35-63] | 38[28-61] | 0.056 | 0.271 | *0.003* | 0.492 | *0.031* |
| C-reactive protein, mg/L | 113[80-210] | 5[2-12] | *<0.001* | 146[93-214] | 3[2-9] | *<0.001* | 138[103-169] | 14[4-49] | *<0.001* | 0.491 | 0.136 | *0.005* | *<0.001* |
| Oxygen saturation, % | 91[88-93] | 95[93-97] | *<0.001* | 90[82-92] | 92[85-95] | *0.004* | 91[85-94] | 94[74-97] | 0.764 | 0.175 | *0.003* | 0.071 | 0.563 |
| Body temperature, $^0$C | 37.4[36.9-38.4] | 36.6[36.5-36.7] | *<0.001* | 37.4[36.7-37.8] | 36.6[36.5-36.8] | *<0.001* | 37.5[36.7-38.0] | 36.6[36.4-36.7] | *<0.001* | 0.666 | 0.804 | 0.455 | 0.305 |
| Fibrinogen, g/L | 7.0[6.7-8.4] | 4.1[3.5-4.8] | *<0.001* | 7.2[5.6-9.0] | 3.0[2.3-3.7] | *<0.001* | 7.3[5.6-8.4] | 4.4[3.2-6.0] | *<0.001* | 0.960 | *<0.001* | 0.491 | *<0.001* |
| D-dimer, mg/L* | 0.9[0.8-1.2] | 0.8[0.6-1.1] | 0.753 | 1.0[0.6-1.2] | 1.4[1.0-4.7] | 0.715 | 1.0[0.6-2.4] | 1.9[1.1-2.2] | 0.180 | 0.740 | 0.075 | *0.004* | 0.710 |
| White blood cells, $10^9$/L | 6.1[4.3-8.5] | 8.8[7.0-11.3] | *<0.001* | 7.8[4.9-12.0] | 8.9[6.4-12.6] | 0.381 | 7.0[5.6-8.4] | 11.1[7.0-14.1] | *<0.001* | 0.092 | 0.718 | 0.245 | 0.293 |
| Neutrophils, $10^9$/L | 4.3[2.7-6.6] | 6.5[4.4-9.1] | *0.001* | 6.6[4.8-9.1] | 5.9[4.5-10.3] | 0.866 | 5.5[4.2-8.0] | 7.7[4.2-11.8] | *0.001* | 0.040 | 0.915 | 0.290 | 0.391 |
| Lymphocytes, $10^9$/L | 0.9[0.6-1.3] | 1.7[1.2-2.4] | *<0.001* | 0.9[0.6-1.2] | 1.2[0.7-1.8] | *0.032* | 0.8[0.6-1.1] | 1.4[0.7-2.0] | *<0.001* | 0.715 | *0.003* | *0.037* | 0.400 |
| Platelets, $10^9$/L | 205[106-261] | 354[283-404] | *<0.001* | 195[174-267] | 273[207-364] | *0.012* | 230[189-268] | 283[206-439] | *0.005* | 0.664 | *0.003* | 0.057 | 0.451 |
| Creatinine, µmol/L | 99[83-122] | 88[81-97] | *0.003* | 88[77-104] | 85[70-91] | *0.026* | 87[81-108] | 82[71-97] | *0.009* | 0.167 | 0.060 | 0.108 | 0.657 |
| ALT, U/L | 34[23-63] | 63[34-109] | *<0.001* | 31[25-44] | 71[39-136] | *<0.001* | 36[24-60] | 56[34-84] | *0.014* | 0.593 | 0.347 | 0.190 | 0.054 |
| AST, U/L | 38[29-51] | 36[24-46] | 0.071 | 39[26-54] | 35[24-48] | 0.563 | 46[29-71] | 56[34-84] | *0.001* | 0.278 | 0.915 | 0.965 | 0.827 |
| LDH, U/L | 658[504-838] | 492[396-593] | *<0.001* | 779[539-939] | 633[518-1020] | 0.426 | 673[500-907] | 492[354-868] | 0.081 | 0.474 | *0.003* | 0.596 | 0.052 |
| Interleukin 6, pg/ml* | 89[59-120] | 6[0-14] | *0.005* | 70[41-111] | 81[47-148] | 0.953 | - | - | - | 0,262 | *0,002* | - | - |
| Supplemental oxygen | 31 (70.5%) | 16 (36.4%) | *0.001* | 18 (66.7%) | 16 (59.3%) | 0.573 | 33 (70.2%) | 13 (27.7%) | *<0.001* | 0,939 | 0.060 | 0.373 | *0.007* |
| Mechanical ventilation | 0 (0.0%) | 2 (4.6%) | 0.153 | 0 (0.0%) | 3 (11.1%) | 0.075 | 0 (0.0%) | 11 (23.4%) | *<0.001* | | 0.294 | *0.010* | 0.194 |
| No respiratory support | 13 (29.6%) | 26 (59.1%) | *0.005* | 9 (33.3%) | 8 (29.6%) | 0.770 | 14 (29.8%) | 23 (48.9%) | 0.057 | | *0.016* | 0.332 | 0.105 |
| Prone position | 8 (18.2%) | 2 (4.6%) | *0.044* | 5 (18.5%) | 3 (11.1%) | 0.444 | 5 (10.6%) | 14 (29.8%) | *0.021* | 0.525 | 0.294 | *<0.002* | 0.066 |

ALT: Alanine aminotransferase; AST: Asparagin aminotransferase; LDH: Lactate dehydrogenase. *: Interleukin 6 and D-dimer were not tested in all included patients. **: Difference between points 1 and 2. ***: Difference between all the groups at point 1. ****: Difference between certain groups at point 2.

**Table 3**
Complications of COVID-19 and of its treatment in patients who received netakimab (group NET), who received tocilizumab (group TOC), and who did not receive anticytokine drugs (group CON).

| Complication | Group NET (n = 44) | Group TOC (n = 27) | Group CON (n = 47) | *p*, NET vs. TOC | *p*, NET vs. CON | *p*, TOC vs. CON |
|---|---|---|---|---|---|---|
| Pulmonary embolism | 1 | 3 | 8 | 0.117 | *0.019* | 0.492 |
| Acute kidney injury | 3 | 4 | 3 | 0.273 | 0.933 | 0.233 |
| Extrapulmonary infection | 0 | 2** | 0 | 0.067 | - | 0.059 |
| ALT > ULN | 27 | 16 | 31 | 0.860 | 0.565 | 0.649 |
| ALT > 3 ULN | 8 | 10 | 12 | 0.076 | 0.398 | 0.298 |
| ALT > 10 ULN | 1 | 2 | 6 | 0.297 | 0.061 | 0.474 |
| Cholestasis* | 2 | 1 | 0 | 0.864 | 0.139 | 0.192 |

ALT: Alanine aminotransferase; ULN: Upper limit of normal. *: Increased activity of gamma-glutamate transferase and alkaline phosphatase. **: Uncomplicated urinary infection.

drugs: respiratory function improved in some patients and they no longer needed supplemental oxygen, and, on the contrary, it worsened in the others: they needed mechanical ventilation and a transfer to a prone position. Stabilization of the respiratory function was in most patients who received tocilizumab. In the netakimab group, there was mainly an improvement in the respiratory function, which was manifested by an increase in the proportion of patients who did not need supplemental oxygen and a decrease in the number of patients who needed to be in a prone position. The netakimab group was the only one in which there was a significant reduction in lung lesion volume on chest CT data. This may serve as evidence that the blockade of the IL-17 effect by netakibam has a more complex effect, and it affects not only the inflammatory response, but also directly the pathologic processes in the lungs.

There was an insignificant increase in the level of D-dimer, the main hemostasis activation marker, in the groups with tocilizumab and without anticytokine treatment, which was not observed in the netakimab group. Nevertheless, 7-10 days after administration of the drug, the level of this biomarker in the netakimab group was significantly lower than in the control group, which was also accompanied by a decrease in the incidence of pulmonary thromboembolism. It is likely that the blockade of the IL-17 pathway also results in the blockade of pathological activation of the hemostasis system, the consequences of which as pulmonary embolism, myocardial infarction, and ischemic strokes make a large contribution to the mortality of patients with COVID-19. Netakimab can also improve the survival of these patients owing to this complex effect.

The administration of netakimab and tocilizumab was not accompanied by the development of injection reactions and any significant complications. The weak point of our study is its retrospective and nonrandomized nature. Although the study groups did not differ in the main baseline parameters, selection biases cannot be excluded. A prospective randomized trial is needed to verify our results.

## CONCLUSION

In conclusion, blockade of the effects of IL-17 with netakimab in patients with cytokine release syndrome in COVID-19 has shown to be an effective and safe method of its treatment.

## CONFLICTS OF INTEREST

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## *Annexe A*

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1684/ecn.2021.0463.

## *Annexe B*

## [[(Annexe A)}]Supplementary data

Table S1

Symptoms, comorbidities, and used drugs in patients who received netakimab (NET group) and tocilizumab (TOC group) and who did not receive anticytokine treatment (CON group).