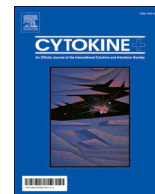




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## Short communication

## Anti-IL-17 monoclonal antibodies in hospitalized patients with severe COVID-19: A pilot study



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## ARTICLE INFO

## Keywords:

COVID-19  
Cytokine storm  
IL-17  
Netakimab  
Therapeutics

## ABSTRACT

**Background:** One of the main pathophysiological mechanisms underlying the severe course of COVID-19 is the hyper-inflammatory syndrome associated with progressive damage of lung tissue and multi-organ dysfunction. IL-17 has been suggested to be involved in hyper-inflammatory syndrome.

**Objective:** To evaluate the efficacy and safety of the IL-17 inhibitor netakimab in patients with severe COVID-19. Study design.

In our retrospective case-control study we evaluated the efficacy of netakimab in hospitalized patients with severe COVID-19 outside the intensive care unit (ICU). Patients in the experimental group were treated with standard of care therapy and netakimab at a dose of 120 mg subcutaneously.

**Results:** 171 patients with severe COVID-19 were enrolled in our study, and 88 of them received netakimab. On the 3 day of therapy, body temperature, SpO<sub>2</sub>/FiO<sub>2</sub>, NEWS2 score, and CRP improved significantly in the netakimab group compared to the control group. Other clinical outcomes such as transfer to ICU (11.4% vs 9.6%), need for mechanical ventilation (10.2% vs 9.6%), 28-day mortality (10.2% vs 8.4%), did not differ between the groups.

**Conclusion:** In hospitalized patients with severe COVID-19, anti-IL-17 therapy might mitigate the inflammatory response and improve oxygenation, but do not affect the need for mechanical ventilation and mortality.

## 1. Introduction

One of the main pathophysiological mechanisms underlying the severe course of COVID-19 is the hyper-inflammatory syndrome (analogous to cytokine storm) associated with progressive damage of lung tissue, the development of acute respiratory distress syndrome (ARDS), and multi-organ dysfunction [1]. In order to influence this pathogenetic mechanism, targeted cytokine inhibitors are used that block IL-6 (tocilizumab, sarilumab), IL-1 (anakinra, canakinumab), as well as inhibitors of JAK kinases (baricitinib, ruxolitinib) [2]. Given the controversial efficacy results and shortage of these drugs during the current pandemic, the search for additional drugs with an anticytokine effect for the treatment of patients with severe COVID-19 is relevant.

In a recently published study by Parackova et al., activation of the

Th17 pathway was shown in patients with COVID-19 [3]. Xu et al. demonstrated an increase in the number of CCR4+CCR6+ Th17-lymphocytes in the peripheral blood in patients with severe COVID-19 [4]. One of the main cytokines produced by Th17-lymphocytes is IL-17. It is known that the overproduction of IL-17 stimulates the T-cell response and increases the production of other inflammatory mediators – IL-1 $\beta$ , IL-6, TNF $\alpha$ , growth factors (G-CSF, GM-CSF), and various chemokines [5]. The activation of Th17-lymphocytes and the production of IL-17 increases the recruitment of neutrophils and prevents their apoptosis, which ultimately increases the damage to the lung parenchyma, and contributes to the development of pulmonary edema [5,6]. In addition, IL-17 has been suggested to be involved in the development of endothelial dysfunction and thrombophilia in COVID-19 [7]. These factors gave rise to a number of researchers to consider IL-17 as a

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<https://doi.org/10.1016/j.cyto.2021.155627>

Received 23 February 2021; Received in revised form 30 May 2021; Accepted 12 June 2021

Available online 3 July 2021

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potential therapeutic target for the use of appropriate cytokine inhibitors in COVID-19 [5,8,9].

The objective of our study was to evaluate the efficacy and safety of the IL-17 inhibitor netakimab in patients with severe COVID-19.

## 2. Methods

This retrospective case-control study was conducted in COVID-19 care units of a university-affiliated hospital (Sechenov Moscow Medical University) between April 8 and November 12, 2020. The study was approved by the University ethics committee (approval number 16–20) and exempted from written informed consent.

Eligible patients were hospitalized subjects aged over 18 years, with a confirmed diagnosis of COVID-19, bilateral pneumonia,  $SpO_2 \leq 92\%$ , and the presence of at least one of the following criteria: fever  $>38^\circ C$  for  $\geq 3$  days, CRP  $\geq 40$  mg/L, leukocytes  $\leq 3.0 \times 10^9/L$ , lymphocytes  $\leq 0.8 \times 10^9/L$ . Patients were excluded if they were hospitalized in the intensive care unit (ICU), treated with other targeted cytokine inhibitors, had clinical and laboratory signs of active bacterial infection, and pregnancy.

All patients were divided into two groups: experimental and control groups. Controls were matched to patients in the experimental group by age, levels of C-reactive protein,  $SpO_2/FiO_2$  ratio, and NEWS2 score. Patients in both study groups received standard of care (SOC) therapy (hydroxychloroquine, azithromycin, low-molecular-weight heparins, corticosteroids). In the experimental group, in addition to SOC therapy, patients also received netakimab (Efleira®, Biocad) – a recombinant humanized monoclonal antibody that binds IL-17 (officially indicated for adults with moderate-to-severe plaque psoriasis, active psoriatic arthritis, and active ankylosing spondylitis). Netakimab was administered subcutaneously at a single dose of 120 mg.

Clinical and laboratory data were recorded at baseline and at day 3. WHO 7-point ordinal scale at day 3 was utilized for efficacy evaluation. We also analyzed the length of hospitalization and outcome of the disease, such as transfer to ICU, need for non-invasive ventilation (NIV) and invasive mechanical ventilation (IMV), and all-cause 28-day mortality. Discharge criteria were defined as clinical recovery – i.e., normalization of pyrexia, relief of cough, respiratory rate  $\leq 24$  breaths per minute,  $SpO_2 \geq 93\%$  on room air, all maintained for at least 48 h.

The statistical analysis was performed using SPSS Statistics v 24.0 (IBM, USA). Continuous variables were reported as median value [interquartile range (IQR)]. The differences between groups were analyzed by two-sided Student's *t*-test or two-sided Mann–Whitney *U* test. Wilcoxon signed-rank test was used to assess change from baseline to day 3 in netakimab group. Categorical variables were reported as number and percentage. Primary efficacy outcomes (WHO Scale on Day 3) were analyzed utilizing a proportional odds model with adjustment for baseline values of age, CRP level,  $SpO_2/FiO_2$  and a baseline Scale score. Adjusted Odds Ratios and corresponding 95% confidence intervals were calculated from final proportional odds models. Groups were compared by other categorical variables using the two-sided Fisher's exact test. A *p*-value  $< 0.05$  was considered significant for all tests.

## 3. Results

One hundred seventy-one hospitalized patients with severe COVID-19 were enrolled in the study. The baseline demographic, clinical and laboratory characteristics at baseline did not differ significantly between the groups (Table 1).

Analysis of WHO Scale score at day 3 demonstrated better efficacy in netakimab group in comparison with control group (adjusted odds ratio is equal to 2.20 [0.89–5.42]), however lower limit of the 95% confidence interval is below 1 (Table 2). On day 3 after the administration of netakimab, significant improvements were observed in respiratory rate, in body temperature, in  $SpO_2/FiO_2$ , in the NEWS2 score, in the number

**Table 1**

Main characteristics of patients at baseline and at day 3 of the treatment, and clinical outcomes.

Parameters	Control group (n = 88)	Netakimab group (n = 83)	P value
Age, years	60 [49–68]	61 [51–69]	0.51
Male, n (%)	42 (47.7%)	50 (60.2%)	0.13
Smokers and ex-smokers, n (%)	13 (14.8%)	17 (20.5%)	0.41
BMI, kg/m <sup>2</sup>	29.1 [25.4–32.7]	29.5 [26.6–33.7]	0.23
Time from symptoms onset, days	9 [7–10]	9 [7–12]	0.29
<b>Comorbidities</b>			
Cardiovascular diseases, n (%)	45 (51.1%)	47 (56.6%)	0.52
Chronic lung disease, n (%)	3 (3.1%)	5 (6.0%)	0.32
Diabetes mellitus, n (%)	20 (22.7%)	25 (30.1%)	0.39
Chronic kidney disease, n (%)	2 (2.3%)	4 (4.8%)	0.37
Active malignant neoplasm, n (%)	4 (4.5%)	6 (7.2%)	0.41
<b>At baseline</b>			
Body temperature, °C*	37.7 [37.2–38.5]	37.5 [37.1–38.0]	0.18
Respiratory rate, breaths per min	22 [20–24]	22 [20–23]	0.99
$SpO_2/FiO_2$	253 [250–321]	267 [238–342]	0.32
NEWS2 scale, points	7 [5–7]	7 [2–7]	0.29
WBC, 10 <sup>9</sup> /L	5.9 [4.6–6.9]	5.7 [4.6–7.7]	0.79
Neutrophil count, G/L	4.1 [3.3–5.2]	3.7 [3.1–5.3]	0.74
Lymphocyte count, G/L	0.9 [0.7–1.2]	0.9 [0.7–1.3]	0.56
C-reactive protein, mg/L	102 [79–132]	113 [83–164]	0.1
Lactate dehydrogenase, IU/L	604 [520–774]	616 [507–758]	0.49
Ferritin, mg/L	394 [202–529]	494 [191–519]	0.95
D-dimer, µg/mL	0.7 [0.4–1.6]	0.7 [0.4–1.4]	0.84
<b>Day 3</b>			
Body temperature, °C*	36.9 [36.6–37.4]	36.7 [36.5–37.0]	0.01
Respiratory rate, breaths per min	20 [18–22]	18 [17–22]	0.11
$SpO_2/FiO_2$	266 [238–323]	272 [240–452]	0.03
NEWS2 scale, points	5 [2–5]	3 [2–5]	0.05
WBC, 10 <sup>9</sup> /L	6.1 [5.3–7.6]	7.4 [5.4–8.7]	0.16
Neutrophil count, G/L	3.9 [3.1–5.4]	4.4 [3.0–6.9]	0.29
Lymphocyte count, G/L	1.3 [0.9–1.7]	1.2 [0.9–1.7]	0.94
C-reactive protein, mg/L	57 [46–79]	29 [12–46]	0.0001
Lactate dehydrogenase, IU/L	531 [473–710]	533 [441–879]	0.79
Ferritin, mg/L	508 [318–528]	513 [291–533]	0.90
D-dimer, µg/mL	0.9 [0.5–1.7]	0.8 [0.4–1.2]	0.97
<b>Outcomes</b>			
Length of hospitalization, days	16 [14–20]	15 [11–19]	0.02
Transfer to ICU, n (%)	10 (11.4%)	8 (9.6%)	0.81
Intubation and IMV, n (%)	9 (10.2%)	8 (9.6%)	0.89
Non-invasive ventilation, n (%)	8 (9.1%)	6 (7.2%)	0.78
28-day mortality, n (%)	9 (10.2%)	7 (8.4%)	0.79

\*The highest temperature during the day was recorded.

Continuous variables are presented as median value [interquartile range (IQR)]. Categorical variables are presented as number and percentage (%).

Abbreviations. BMI, body mass index; WBC, white blood count; CRP, C-reactive protein; ICU, intensive care unit; IMV, invasive mechanical ventilation.

of leukocytes, lymphocytes, and in the levels of CRP (all *p*  $< 0.0001$ ) (Table 1).

When compared with the control group, patients who received netakimab showed on day 3 significant differences in body temperature (36.7 [36.5–37.0] vs 36.9 [36.6–37.4], *p* = 0.01),  $SpO_2/FiO_2$  (272 [240–452] vs 266 [238–323], *p* = 0.03), NEWS2 score (3 [2–5] vs 5 [2–5], *p* = 0.05) and CRP (29 [12–46] vs 57 [46–79], *p* = 0.0001). There were no significant differences in the clinical outcomes of the disease

**Table 2**  
Assessment by WHO 7-point ordinal scale at Day 1 and Day 3.

	Control group (N = 88)	Netakimab group (N = 83)
WHO scale, Day 1		
n/nmiss	88/0	83/0
4	27 (30.7%)	31 (37.3%)
5	58 (65.9%)	51 (61.4%)
6	3 (3.4%)	1 (1.2%)
WHO scale, Day 3		
n/nmiss	77/11	83/0
4	22 (25.0%)	39 (47.0%)
5	55 (62.5%)	44 (53.0%)
Odds Ratio, Netakimab vs Control group (95% CI)		2.20 (0.89–5.42)

Variables are presented as number and percentage (%).

Odds Ratio was estimated by proportional odds model with adjustment for age, CRP level, SpO<sub>2</sub>/FiO<sub>2</sub> and WHO Scale value at baseline.

(need for NIV and IMV, transfer to ICU, and mortality), although a decrease in the duration of hospitalization in the netakimab group was observed (15 (11–19) vs 16 (14–20) days,  $p = 0.02$ ) (Table 1).

At least one adverse event was reported for 57 patients in the netakimab group and for 55 patients in the control group (Table 3). All adverse events were mild, there were no other moderate and severe adverse events. Overall (related and not related to study drug) adverse event analysis demonstrated a very similar safety profile in both groups.

#### 4. Discussion

In this trial, administration of anti-IL-17 therapy in patients with severe COVID-19 was associated with improvement of clinical and laboratory parameters, although there was no significant effect on clinical outcomes, including mortality. To the best of our knowledge, this is the first study to evaluate the efficacy of anti-IL-17 therapy for COVID-19.

Theoretically, blockade of IL-17 appears to be a promising therapeutic area, since it can potentially also reduce the production of downstream pro-inflammatory molecules such as IL-1 $\beta$ , TNF, and IL-6, and neutrophil recruitment – key factors in the development of ARDS in COVID-19 [5,10]. At the same time, there are contradictions in the data on the role of IL-17 in the hyperinflammatory response in COVID-19. According to a study by Wan et al., there were no significant differences in the blood level of IL-17 in patients with mild and severe COVID-19, [11].

Indirectly, the potential role of anti-IL-17 therapy is also evidenced by the data of a retrospective observational study, which demonstrated that patients with psoriasis routinely receiving anti-IL-17 therapy did not have cases of severe COVID-19 and death [12].

The use of another IL-17 inhibitor ixekizumab is currently being investigated for the acute phase of COVID-19 [13].

The study has several limitations. It was a retrospective case-control study performed in a single medical center. Our study is also limited by its relatively small sample size which was insufficiently powered to demonstrate superiority by primary outcomes.

#### 5. Conclusions

In summary, in hospitalized adult patients with severe COVID-19, anti-IL-17 therapy was associated with clinically significant improvements of WHO Scale, a decrease of inflammatory biomarkers, and an improvement in oxygenation levels without significant adverse events. These results need to be confirmed with further randomized prospective trials in a larger cohort.

**Table 3**  
Adverse events.

	Control group (N = 88)	Netakimab group (N = 83)
Patients with at least one AE		
Weakness	15 (17.0)	19 (22.9)
Blood pressure higher than 140/90	9 (10.2)	6 (7.2)
AST > 3 * ULN	6 (6.8)	4 (4.8)
ALT > 3 * ULN	5 (5.7)	4 (4.8)
Diarrhea	4 (4.5)	6 (7.2)
Dyspepsia	3 (3.4)	3 (3.6)
Nausea	3 (3.4)	4 (4.8)
Dyspnea	5 (5.7)	5 (6.0)
Creatinine > ULN	2 (2.3)	4 (4.8)
Headache	3 (3.4)	1 (1.2)
Rashes	0 (0)	1 (1.2)

Variables are presented as number and percentage (%).

Abbreviations. AE – adverse event, ULN – upper limit of normal range.

#### Funding

No funding was received for this work.

#### CRediT authorship contribution statement

**Sergey N. Avdeev:** Conceptualization, Methodology, Validation, Resources, Data curation, Writing - original draft, Writing - review & editing, Supervision, Project administration. **Natalia V. Trushenko:** Investigation, Validation, Data curation, Writing - original draft, Writing - review & editing. **Natalia A. Tsareva:** Writing - review & editing, Formal analysis. **Andrey I. Yaroshetskiy:** Validation, Data curation, Writing - original draft, Writing - review & editing, Supervision. **Zamira M. Merzhoeva:** Writing - review & editing, Formal analysis. **Galia S. Nuralieva:** Validation, Data curation, Writing - review & editing. **Galina V. Nekludova:** Validation, Data curation, Writing - review & editing. **Svetlana Yu. Chikina:** Validation, Data curation, Writing - review & editing, Supervision. **Tatiana Yu. Gneusheva:** Validation, Data curation, Writing - review & editing. **Olga A. Suvorova:** Investigation, Validation, Data curation. **Anna E. Shmidt:** Investigation, Validation, Data curation.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Acknowledgments

The authors are grateful to physicians and nurses of University Clinical Hospital N<sup>o</sup>4 (Sechenov Moscow Medical University).

#### References

- [1] L.A. Henderson, S.W. Canna, G.S. Schulert, S. Volpi, P.Y. Lee, et al., On the alert for cytokine storm: immunopathology in COVID-19, *Arthritis Rheumatol.* 72 (7) (2020) 1059–1063, <https://doi.org/10.1002/art.41285>.
- [2] D.C. Fajgenbaum, C.H. June, Cytokine Storm, *N. Engl. J. Med.* 383 (23) (2020) 2255–2273, <https://doi.org/10.1056/NEJMr2026131>.
- [3] Z. Parackova, M. Bloomfield, A. Klocperk, A. Sediva, Neutrophils mediate Th17 promotion in COVID-19 patients, *J. Leukoc. Biol.* (2020), <https://doi.org/10.1002/JLB.4COVCRA0820-481RRR>.
- [4] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, et al., Pathological findings of COVID-19 associated with acute respiratory distress syndrome, *Lancet Respir. Med.* 8 (4) (2020) 420–422, [https://doi.org/10.1016/S2213-2600\(20\)30076-X](https://doi.org/10.1016/S2213-2600(20)30076-X).
- [5] O. Pacha, M.A. Sallman, S.E. Evans, COVID-19: a case for inhibiting IL-17? *Nat. Rev. Immunol.* 20 (6) (2020) 345–346, <https://doi.org/10.1038/s41577-020-0328-z>.
- [6] R. Muir, M. Osbourn, A.V. Dubois, E. Doran, D.M. Small, et al., Innate lymphoid cells are the predominant source of IL-17A during the early pathogenesis of acute

- respiratory distress syndrome, *Am. J. Respir. Crit. Care Med.* 193 (4) (2016) 407–416, <https://doi.org/10.1164/rccm.201410-1782OC>. PMID: 26488187.
- [7] F. Raucci, A.A. Mansour, G.M. Casillo, A. Saviano, F. Caso, et al., Interleukin-17A (IL-17A), a key molecule of innate and adaptive immunity, and its potential involvement in COVID-19-related thrombotic and vascular mechanisms, *Autoimmun. Rev.* 19 (7) (2020), 102572, <https://doi.org/10.1016/j.autrev.2020.102572>.
- [8] G.M. Casillo, A.A. Mansour, F. Raucci, A. Saviano, N. Mascolo, et al., Could IL-17 represent a new therapeutic target for the treatment and/or management of COVID-19-related respiratory syndrome? *Pharmacol. Res.* 156 (2020), 104791 <https://doi.org/10.1016/j.phrs.2020.104791>.
- [9] M. Megna, M. Napolitano, G. Fabbrocini, May IL-17 have a role in COVID-19 infection? *Med. Hypotheses* 140 (2020), 109749 <https://doi.org/10.1016/j.mehy.2020.109749>.
- [10] T. Shibabaw, Inflammatory cytokine: IL-17A signaling pathway in patients present with COVID-19 and current treatment strategy, *J. Inflamm. Res.* 13 (2020) 673–680, <https://doi.org/10.2147/JIR.S278335>.
- [11] S. Wan, Q. Yi, S. Fan, J. Lv, X. Zhang, et al., Relationships among lymphocyte subsets, cytokines, and the pulmonary inflammation index in coronavirus (COVID-19) infected patients, *Br. J. Haematol.* 189 (3) (2020) 428–437, <https://doi.org/10.1111/bjh.16659>.
- [12] P. Gisondi, P. Facheris, P. Dapavo, S. Piaserico, A. Conti, et al., The impact of the COVID-19 pandemic on patients with chronic plaque psoriasis being treated with biological therapy: the Northern Italy experience, *Br. J. Dermatol.* 183 (2) (2020) 373–374, <https://doi.org/10.1111/bjd.19158>.
- [13] P. Liu, Z. Huang, M. Yin, C. Liu, X. Chen, et al., Safety and efficacy of ixekizumab and antiviral treatment for patients with COVID-19: A structured summary of a study protocol for a pilot randomized controlled trial, *Trials.* 21 (1) (2020) 999, <https://doi.org/10.1186/s13063-020-04925-8>.