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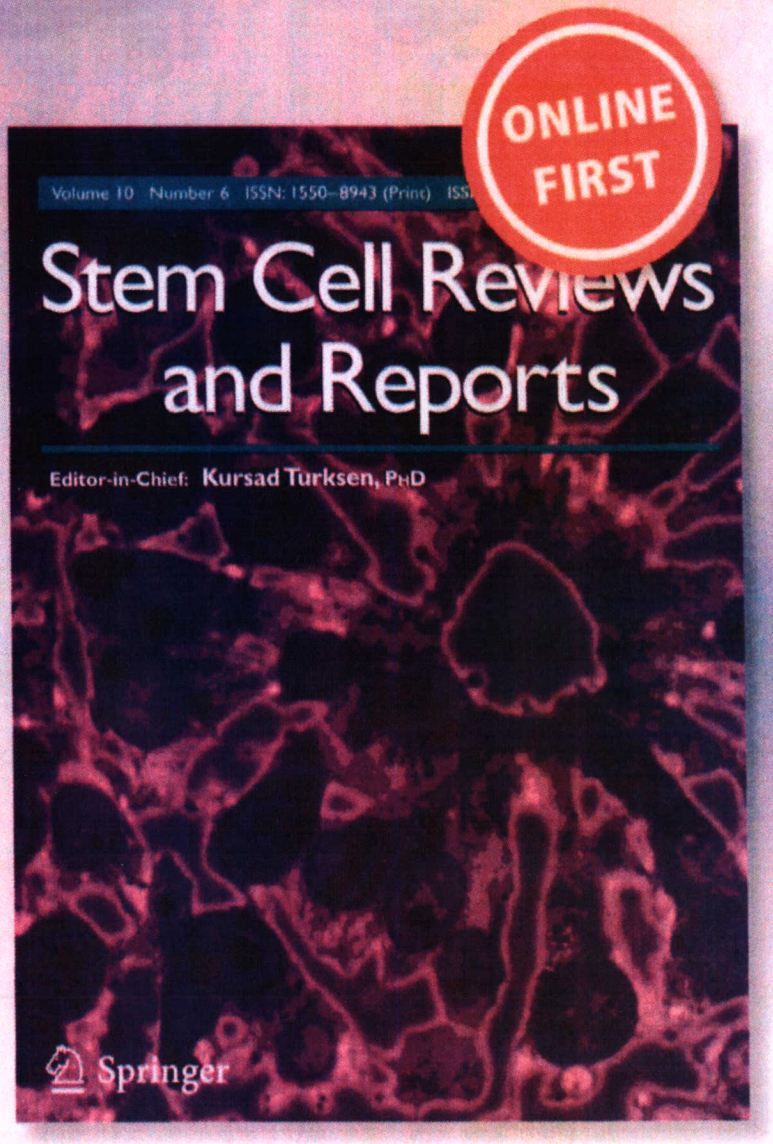


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# Results and Prospects of Using Activator of Hematopoietic Stem Cell Differentiation in Complex Therapy for Patients with COVID-19

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## Abstract

The paper presents the results of a standard and complex treatment method using the peptide drug thymus thymalin in patients with COVID-19. One of the mechanisms of the immunomodulatory effect of thymalin is considered to be the ability of this peptide drug to influence the differentiation of human hematopoietic stem cells (HSCs). It was found that, as a result of standard treatment, patients in the control group showed a decrease in the concentration of the pro-inflammatory cytokine IL-6, C-reactive protein, D-dimer. The addition of thymalin to standard therapy accelerated the decline in both these indicators and the indicators of the T cell system. This has helped reduce the risk of blood clots in COVID-19 patients. The revealed properties of the thymus peptide preparation are the rationale for its inclusion in the complex treatment of coronavirus infection.

**Keywords** COVID-19 · Standard therapy · Thymalin · Peptides · Immunity · Hemostasis

The search for effective and safe antiviral agents during the global pandemic caused by the SARS-CoV-2 virus is the primary task of modern medicine [1–3]. Regenerative medicine offers a variety of cell-tissue therapies: stem cell therapy, chimeric antigen receptor (CAR) T cell therapy, natural killer (NK) cell therapy, exosomes, and tissue products. Recently, there have been publications that mesenchymal stem cells (MSCs) can reduce inflammatory symptoms and protect against the cytokine storm that contributes to the progression of COVID-19. In addition, it was revealed that NK cells are able to exert a cytotoxic effect on infected cells and induce the production of interferon in patients with COVID-19 [4, 5]. As is known, the pathogenetic factor of viral infection COVID-19 is the activation of the synthesis of proinflammatory cytokines by macrophages, leading to the development of an inflammatory response, distress syndrome and cytokine storm [6, 7]. In addition, in a severe course of the disease, patients have disorders in the T cell system: a decrease in the number of T lymphocytes, including T helpers (CD4+), cytotoxic lymphocytes (CB8+), as well as a change in the CD4+/CD8 + ratio [8]. At the same time, a significant increase in the level of C-reactive protein and ferritin is noted [9, 10]. Patients with COVID-19 have a high level of risk factors for venous thromboembolism. An increased concentration of inflammatory mediators promotes increased intravascular blood coagulation, which is accompanied by an increase in the level of D-dimer, which is an indicator of the severe condition of patients with COVID-19 [11–13]. Additional risk factors are age and chronic illnesses. The combination of all these factors can lead to thrombotic microangiopathy, deep vein thrombosis, pulmonary embolism, disseminated intravascular coagulation, stroke, and multiple organ failure, which are the main causes of death [14].

It is known that human hematopoietic stem cells (HSCs) play a significant role in maintaining antiviral immunity.

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HSCs are called pluripotent because they give rise to myeloid and lymphoid blood cells. Myeloid cells differentiating from HSCs include monocytes, macrophages, granulocytes (neutrophils, basophils, eosinophils), erythrocytes, megakaryocytes, platelets, and myeloid dendritic cells. The lymphoid cell line, which is derived from HSCs, includes T and B lymphocytes, NK cells, and lymphoid dendritic cells. Thus, HSCs are an important reserve for the differentiation and maintenance of the pool of functionally active immune competent cells. Therefore, the use of a drug in the treatment of patients with coronavirus infection, which promotes HSC differentiation at the stage of immunity suppression in an unfavorable course of a viral infection, is advisable.

One of these drugs is thymalin, which is a complex of peptides isolated from the thymus of calves with a molecular weight of up to 10 kDa [15]. Thymalin, as an immunomodulator, has been approved by the Ministry of Health of the Russian Federation for medical use since 1982, currently the drug is manufactured by Samson-Med LLC (St. Petersburg, Russia, registration certificate 82/1108/8).

Forty years of experience, in the use of thymalin in the treatment of various viral and bacterial diseases accompanied by impaired immune system function, has proven its high clinical effectiveness [16–18]. One of the mechanisms of the immunomodulatory action of thymalin is considered to be the ability of this peptide preparation to influence the differentiation of human hematopoietic stem cells (HSCs). [19]. It was found that under the action of thymalin, the expression of the stem cell marker CD44 and the molecule of the intermediate stage of differentiation of HSC CD117 decreases by 2–3 times. Thymalin also increases the expression of the mature T lymphocyte marker CD28 by more than 6 times. This property of the peptide preparation plays an important role in the activation of the differentiation of mature T lymphocytes and the stimulation of antiviral immunity.

It is known that the CD28 glycoprotein is expressed on thymocytes, CD4+, CD8 + lymphocytes and is required for the activation of mature T cells. The expression of CD28 is increased in antigen-presenting cells upon activation of cellular Toll-like receptors, which leads to the stimulation of cytokine synthesis. Thus, the CD28 molecule plays an important role in the activation of immunity in various viral diseases, including COVID-19. In patients with a mild form of coronavirus, the number of CD28+, CD4+, CD8 + lymphocytes increases, which indicates the activation of the functions of the immune system. In a severe course of coronavirus infection, the number of T helpers and cytotoxic lymphocytes decreases with a simultaneous decrease in the expression of the glycoprotein CD28 on their surface. This indicates a pronounced suppression of immunity. It should be assumed that the coronavirus leads to an impaired differentiation of hematopoietic stem cells, and this leads to a decrease in the number of differentiated immunocompetent cells. [20]. Therefore, an increase in the expression of the marker of mature T lymphocytes CD28 may indicate that, under the action of thymalin, the immune system is activated: immature CD117 + cells differentiate into mature CD28 + T lymphocytes. Thus, the antiviral effect of thymalin is expressed in the compensatory stimulation of HSC differentiation into CD28 + T lymphocytes at the stage of immunity suppression in an unfavorable course of viral infection. The results obtained are important to understand the immunoprotective activity of thymalin in patients with acute respiratory diseases of viral etiology, including coronavirus infection COVID-19.

The active components of thymalin are dipeptides (Glu-Trp, Lys-Glu) and a tripeptide (Glu-Asp-Pro) that regulate gene expression, protein synthesis, differentiation, proliferation and apoptosis of immune cells, and also have induction activity on stem cells. [21–23]. It was found that short peptides accelerate the processes of differentiation of various subpopulations of lymphocytes, and modulate the number of T helpers, cytotoxic T lymphocytes, regulatory T cells (Treg), as well as the CD4+/ CD8 + ratio. It was found that the administration of these peptides to animals led to a statistically significant change in the expression of mitochondrial genes, as well as genes regulating the synthesis of proteins related to the defense systems of the cell and the body. [18, 24, 25]. Therefore, the activity of thymalin is due to the effects of its constituent peptides, which have their own specific mechanisms of action and points of application.

It should be noted that in addition to the immunomodulatory effect, thymalin stimulates the processes of regeneration and hematopoiesis, the blood coagulation system in cases of suppression, and also improves the course of the processes of cellular metabolism [16]. In addition, under hypoxic conditions, one of the active components of thymalin (Glu-Trp dipeptide) enhances tissue oxygenation by inhibiting the synthesis of HIF 1$\alpha$ [26]. These properties of thymalin were fundamental for the beginning of the study of the peptide drug in the complex treatment of patients with COVID-19. The first positive results obtained, which confirmed not only the immunomodulatory effect, but also the regulating effect on hemostasis in the conditions of a cytokine storm, allowed continuing clinical studies in this direction. [27–29].

Taking into consideration all of the above, the purpose of this work was to study the effect of thymalin as part of a complex therapy on the parameters of peripheral blood, immune system, and blood biochemistry in patients with COVID-19.

## Materials and Methods

### Patient Characteristics

The single-center, open-label, prospective, randomized, controlled trial included patients hospitalized in St. Petersburg

City General Hospital No. 2 with a clinical diagnosis of U07.1, COVID-19, virus identified, during April - July 2020. Patients were randomized using the envelope method. The inclusion criteria for the study were: moderate and severe forms of the course of the disease, the presence of absolute (< 1.2*109/L) and/or relative (< 19%) lymphopenia in the clinical blood test, the presence of bilateral polysegmental pneumonia, confirmed by spiral computed tomography with a CT1-CT3 lesion index with symptoms of respiratory failure (SpO2 ≤ 95%).

All patients were divided into 2 groups: the main group consisted of 42 patients (25 women and 17 men) who received treatment according to the standard regimen in combination with thymalin; the control group included 50 patients (27 women and 23 men) who received treatment according to the standard regimen. The average age of patients in the main group was 59.8 ± 7.8 years, and in the control group 61.7 ± 5.4 years.

## Treatment Regimen and Drugs

Treatment of patients in both groups was carried out in accordance with the "Temporary guidelines. Prevention, diagnosis and treatment of new coronavirus infection (COVID-19). Version 7 (03.06.2020), Ministry of Health of the Russian Federation". Patients of the main group were additionally prescribed thymalin (Samson-Med, Russia, drug series 70,519). The drug was used according to the following scheme: 10 mg daily intramuscularly once for 5 days.

Patients in both groups received antibacterial and, if necessary, antiviral off-label and glucocorticosteroid therapy. Low molecular weight heparin sodium enoxaparin (Clexane, Sanofi-Aventis, France) was used as a direct anticoagulant daily in a prophylactic dose of 4000 IU subcutaneously (40 mg) once a day or as an intermediate dose, 4000 IU subcutaneously (40 mg) 2 times a day, depending on the severity of the disease. Low molecular weight heparin was used throughout the hospital stay. In the main group, 8 people received levofloxacin (Levofloxacin, Dalkhimfarm, Russia), 33 patients received ceftriaxone (Ceftriaxone, Makiz-Pharma, Russia). One patient in the main group received simultaneously ceftriaxone and levofloxacin. In the control group, all patients received ceftriaxone (Ceftriaxone, Makiz-Pharma, Russia). The course of treatment in both groups varied from 10 to 14 days, averaging 12 ± 4 days.

Off-label antiviral therapy was prescribed to 27 patients in the main group (64% of the group) and 35 patients in the control group (70% of the group). The following were used as antiviral drugs: hydroxychloroquine (Plaquenil, Sanofi-Synthelabo, Great Britain); lopinavir and ritonavir 200/50 (Kaletra, AbbVie Deutschland, Germany) and interferon alpha-2b (Grippferon, FIRN M, Russia). Hydroxychloroquine was used in 8 patients of the main group (19%) and in 5 patients of the control group (10% of the group) according to the following scheme: 800 mg (400 mg 2 times a day), then 400 mg per day (200 mg 2 times a day) for 6 days. Lopinavir and ritonavir 200/50 were received by 17 patients in the main group (40.5% of the group) and 28 patients in the control group (56% of the group) according to a 400 mg + 100 mg *per os regimen* every 12 hours for 14 days. Interferon alpha-2b was received by 2 patients of the main group (4.8% of the group) during the first 5 days, 3 instillations in each nasal passage. Dexamethasone (Dexamethasone, Shreya Life Sciences, India) at a dosage of 12 mg per day was used as glucocorticoid therapy. This drug was received by 10 patients in the main group and 12 patients in the control group, which amounted to 24% of the total in both groups. The average duration of dexamethasone use was 2.5 days in the main group and 4 days in the control group.

## Laboratory Research

Patients of both groups underwent the following laboratory studies before and after therapy: clinical blood test, a coagulogram (fibrinogen, prothrombin time, D-dimer), blood biochemical composition (C-reactive protein, glucose, ferritin), and an immunogram (CD3, CD4, CD8, interleukin-6). For the study, fasting blood test was taken by venipuncture from the cubital vein into special vacuum tubes. The collection of biological material was carried out completely in accordance with the requirements of the preanalytical stage of the hematological study. Laboratory studies were performed using reagents from the following manufacturers: hematological studies and determination of CD3, CD4, CD8 lymphocytes were done using an automatic hematological analyzer Cell-Dyn Sapphire, manufactured by Abbott Laboratories (USA); ESR measurement was done on the Test 1 analyzer manufactured by Alifax (Italy); coagulogram was analyzed on an automatic coagulometer ACL9000, manufactured by Instrumentation Laboratory (USA); the level of glucose and C-reactive protein was determined using a biochemical analyzer ARCHITECT c4000, manufactured by Abbott Laboratories (USA); ferritin concentration was measured on an ARCHITECT i2000 immunochemiluminescence analyzer, manufactured by Abbott Laboratories (USA); and the level of interleukin-6 was determined on equipment designed for ELISA, with reagents from the "Vector-Best" company.

## Statistics

The results were statistically processed using the SPSS Statistics 17.0 software. To test the hypothesis that each of the samples under study fits normal distribution, the Kolmogorov-Smirnov test was used. The hypothesis that normal distribution of data was confirmed for all samples presented in the study. In this regard, the assessment of differences

**Table 1** Laboratory indicators of the immune system in patients

| Indicators | Norm | Control group (n=50) (X̄±SE) | | Main group (n=42) (X̄±SE) | |
|---|---|---|---|---|---|
| | | Before treatment | After standard treatment | Before treatment | After standard treatment with thymalin |
| Leukocytes ($\times 10^9$/l) | 4,00–9,00 | 8,92±0,78 | 9,33±0,63 | 7,85±0,51 | 7,02±0,71 |
| Lymphocytes ($\times 10^9$/l) | 1,20–3,00 | 0,96±0,12 | 1,08±0,13 | 0,89±0,13 | **1,38±0,17*^** |
| CD3 ($\times 10^9$/l) | 0,88–2,40 | 0,44±0,04 | 0,47±0,05 | 0,47±0,04 | **0,77±0,08*#** |
| CD4 ($\times 10^9$/l) | 0,54–1,46 | 0,26±0,03 | 0,28±0,07 | 0,27±0,05 | **0,51±0,09*#** |
| CD8 ($\times 10^9$/l) | 0,21–1,20 | 0,16±0,03 | 0,17±0,02 | 0,18±0,02 | 0,20±0,01 |
| CD4/CD8 | 1,00–3,50 | 1,63 | 1,66 | 1,5 | **2,55*^** |
| IL-6 (pg/ml) | 0,00–7,00 | 23,71±2,75 | **16,80±2,22*** | 20,35±3,82 | **3,69±0,41**#** |

*$p \leq 0.05$ compared with the corresponding column “before treatment” in each group

** $p \leq 0.01$ compared with the corresponding column "before treatment" in each group

# $p \leq 0.01$ compared to the control group "after standard treatment"

^ $p \leq 0.05$ compared with the control group "after standard treatment"

between samples was carried out using the parametric Student’s t-test. The critical level of reliability of the null statistical hypothesis (concerning the absence of significant differences) was taken equal to 0.01 or 0.05. The arithmetic mean (X̄) and the standard error of arithmetic mean (SE) were calculated for each sample. The data in the tables are presented as X̄ ±SE.

## Results and Discussion

It should be noted that there were no deaths in any of the groups. During the observation period using spiral computed tomography in the control group, the progression of pathological changes was noted in 5 cases, and in the main group in 2 cases. The results of laboratory studies of patients in both groups are presented in Tables 1, 2 and 3.

Table 1 shows the results of treatment of patients in both groups. This shows the concentration of IL-6 in the control group decreased by 1.41 times when compared with the corresponding indicator before treatment ($p \leq 0.05$). However, this therapy did not improve the parameters of the T cell system. The inclusion of thymalin in standard therapy in patients of the main group led to a statistically significant increase in the number of lymphocytes by 55%, T lymphocytes by 63.8%, CD4 by 88.9%, and the CD4/CD8 ratio increased by a factor of 1.7 when compared with the corresponding indicators before treatment. The concentration of IL-6 after the introduction of thymalin decreased by 5.5 times. Thus, the administration of thymalin to patients with COVID-19 contributed to a statistically significant change in the number of lymphocytes, which reached normal values, and the number of T lymphocytes and T helpers approached the lower limits of the normal range. Especially noteworthy is the significant decrease in the cytokine IL-6 after the introduction of thymalin.

Table 2 presents the biochemical and hematological parameters of peripheral blood in patients with COVID-19. The table shows that in the patients of the control group, the content of C-reactive protein and D-dimer significantly decreased

**Table 2** Laboratory biochemical and hematological parameters of peripheral blood in patients

| Indicators | Norm | Control group (n=50) (X̄±SE) | | Main group (n=42) (X̄±SE) | |
|---|---|---|---|---|---|
| | | Before treatment | After standard treatment | Before treatment | After standard treatment with thymalin |
| CRP (mg/dl) | 0,00–0,50 | 14,27±2,12 | **8,62±1,32*** | 13,11±1,92 | **1,35±0,17**#** |
| D-dimer (ng/ml) | 0,00–232 | 1705,71±143,21 | **815,62±72,43*** | 1820,35±172,35 | **319,47±47,31**#** |
| Fibrinogen (g/l) | 2,38−4,98 | 6,44±0,37 | 5,43±0,66 | 6,29±0,45 | **4,11±0,29**** |
| Ferritin (ng/ml) | 21,80–274,70 | 747,78±58,25 | 725,32±83,52 | 695,25±75,35 | **425,32±44,22*^** |
| Prothrombin time (sec) | 9,4–12,5 | 14,39±0,24 | 13,43±1,12 | 14,87±0,56 | **11,2±0,49**** |

* $p \leq 0.05$ compared with the corresponding column “before treatment” in each group

** $p \leq 0.01$ compared with the corresponding column "before treatment" in each group

# $p \leq 0.01$ compared to the control group "after standard treatment"

^ $p \leq 0.05$ compared with the control group "after standard treatment"

**Table 3** Laboratory parameters of peripheral blood in patients

| Indicators | Norm | Control group (n=50) (X̄±SE) | | Main group (n=42) (X̄±SE) | |
|---|---|---|---|---|---|
| | | Before treatment | After standard treatment | Before treatment | After standard treatment with thymalin |
| Neutrophils ($\times 10^9$/l) | 2,00–5,50 | 4,28±0,35 | 3,95±0,41 | 4,72±0,37 | 3,68±0,44 |
| Eosinophils ($\times 10^9$/l) | 0,00–0,30 | 0,15±0,02 | 0,13±0,01 | 0,12±0,03 | **0,06±0,02*#** |
| Basophils ($\times 10^9$/l) | 0,00–0,10 | 0,08±0,01 | 0,06±0,01 | 0,09±0,02 | **0,03±0,01**^** |
| Monocytes ($\times 10^9$/l) | 0–0,60 | 0,53±0,04 | 0,55±0,08 | 0,50±0,07 | **0,66±0,05*^** |
| Platelets ($\times 10^9$/l) | 150–400 | 351,12±43,19 | 368,32±27,15 | 279,35±22,77 | **315,44±28,25*** |
| Plateletcrit (PCT) (% per liter) | 0,14–0,39 | 0,14±0,01 | 0,16±0,02 | 0,16±0,02 | **0,21±0,01*^** |
| Neutrophils/Lymphocytes | – | 4,46 | 3,66 | 5,30 | **2,67*** |
| Platelets/Leukocytes | – | 39,36 | 39,48 | 35,59 | **44,93*** |
| Eosinophils/Basophils | – | 1,88 | 2,17 | 1,33 | 2,00 |
| ESR (mm/h) | 2–30 | 63,84±7,25 | 58,33±3,55 | 54,42±3,82 | **44,41±3,73*^** |

* $p \leq 0.05$ compared with the corresponding column "before treatment" in each group

** $p \leq 0.01$ compared with the corresponding column "before treatment" in each group

# $p \leq 0.01$ compared to the control group "after standard treatment"

^ $p \leq 0.05$ compared with the control group "after standard treatment"

by 1.7 and 2.1 times, respectively, compared with similar indicators before treatment. This indicates a fairly effective standard therapy. The addition of thymalin to standard therapy led to a more significant decrease in C-reactive protein by 9.7 times, and the concentration of D-dimer by 5.7 times. Also, in the main group, there was a decrease in fibrinogen by 1.5 times and in ferritin by 1.6 times compared with similar indicators before treatment (from $p \leq 0.05$ to $p \leq 0.01$). The statistical differences in indicators after the use of thymalin were especially significant compared to those after standard treatment of patients in the control group (CRP, D-dimer, ferritin). These results confirm the feasibility of including thymalin in the complex therapy of patients with COVID-19.

Table 3 shows the results of the effect of thymalin on peripheral blood counts in patients with COVID-19. A decrease in the absolute number of eosinophils (by 2 times) and basophils (by 3 times) was revealed, while the absolute number of monocytes increased by 1.3 times. It should also be noted that there was a significant change in these indicators compared to those in the control group (from $p \leq 0.05$ to $p \leq 0.01$). The introduction of the drug led to a decrease in the ratio of neutrophils/lymphocytes by a factor of 2, and an increase in the platelets/leukocytes ratio by a factor of 1.3. It is necessary to point out an increase in the number of platelets (and therefore plateletcrit), as well as a decrease in ESR in patients after the use of thymalin. At the same time, the ESR indicator in the main group, after using the drug, was lower than that in the control group ($p \leq 0.05$). Especially noteworthy is the absence of changes in blood parameters after standard treatment of patients in the control group.

Analyzing the results presented in Tables 1, 2 and 3, it should be concluded that the inclusion of thymalin in the complex therapy of patients with COVID-19 contributed to the improvement of the T cell system and, most importantly, the normalization of the level of the cytokine IL-6. This fact gives reason to believe that thymalin in complex therapy prevents the development of a cytokine storm. It also seems important in significantly reducing the level of D-dimer, fibrinogen, CRP and ferritin in patients in the study group, which indicates a decrease in the risk of clotting when using the thymus preparation. These results confirm the role of the thymus in the central regulation of not only the immune system, but also the hemostasis system, which was revealed earlier [30, 31]. Thus, the inclusion of thymalin in complex therapy, taking into account the mandatory use of anticoagulants, in order to correct the function of the immune system and hemostasis in patients with COVID-19 is physiologically and pathogenetically justified.

## Compliance with Ethical Standards

**Conflict of Interest** There is no conflict of interest.

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