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# MECHANISMS OF CYTOKINE STORM DEVELOPMENT IN COVID-19 AND NEW POTENTIAL TARGETS OF PHARMACOTHERAPY

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The development of a "cytokine storm", characteristic of severe COVID-19 forms, can be defined as a state of uncontrolled release of a large number of inflammatory mediators.

The attachment of SARS-CoV-2 S-glycoprotein to angiotensin-converting enzyme 2 is considered a process that triggers complex molecular interactions that lead to hyperinflammation. In its turn, it is realized through several systems: renin-angiotensin-aldosterone, kallikrein-kinin and a complement system. Knowledge of these mechanisms suggests potential therapeutic interventions that can be targeted by existing therapeutic agents to counter the cytokine storm and treat the acute respiratory distress syndrome associated with COVID-19.

**The aim** of the review article is to summarize the currently known data on the molecular processes underlying the uncontrolled "cytokine storm" in the patients with severe COVID-19, and possible options for their pharmacological correction.

**Materials and methods.** The data base was represented by such systems as Medline, Cochrane Central Register of Controlled Trials, Scopus, Web of Science Core Collection, Cochrane Library, ClinicalTrials.gov, Elibrary, Google-Academy. A search was carried out for the following keywords and combinations: COVID-19, renin-angiotensin-aldosterone system, bradykinin, complement system, hyaluronic acid, pharmacotherapy.

**Results.** The development of a "cytokine storm" in COVID-19 is mediated by pathogenetic changes in the body in response to the penetration of SARS-CoV-2 into the cell. In the RAAS, suppression of ACE2 leads to a decrease in its ability to degrade ATII, which, on the one hand, leads to a decrease in the amount of AT1-7, and, on the other hand, to the effect of ATII on AT1R with the subsequent development of vasoconstriction and lung damage. The disturbances in the kallikrein-kinin system are associated, on the one hand, with the increased expression of kallikrein and an increase in the formation of bradykinin and its metabolite des-Arg 9-bradykinin. On the other hand, the disturbances are associated with the suppression of the expression of the C1-esterase inhibitor which prevents the formation of kallikrein, and impaired inactivation of des-Arg 9-bradykinin under the action of ACE 2. The nucleocapsid protein SARS-CoV-2 triggers the activation of the complement system through the lectin pathway. It leads to the production of anaphylatoxins C3a and C5a, which stimulate the synthesis of pro-inflammatory cytokines. Proinflammatory cytokines are potent inducers of the HAS 2 gene in the endothelium, which encodes the membrane enzymes of hyaluronate synthase. The sweating of the fluid into the alveoli caused by the "bradykinin storm" in combination with the overproduction of hyaluronic acid, which accumulates water 1000 times its own mass, can lead to the formation of a dense jelly-like substance that prevents gas exchange.

**Conclusion.** Promising areas of pharmacotherapy for "cytokine storm" are associated with its impact on the dysfunction of the listed above systems. However, the efficacy and safety of most drugs for the treatment of COVID-19, is to be studied through carefully designed clinical trials.

**Keywords:** SARS-CoV-2; "cytokine storm"; pharmacotherapy for COVID-19

**Abbreviations:** ACE – angiotensin converting enzyme; AT – angiotensin; GCS – glucocorticosteroids; CI – confidence interval; IL – interleukine; ARDS – acute respiratory distress syndrome; RAAS – renin-angiotensin-aldosterone system; RCS – randomised controlled study; TNF – tumour necrosis factor; AT1R – angiotensin receptor; BK – bradykinin; BKB 1R – type 1 Bradykinin Receptor; BKB 2R – type 2 Bradykinin Receptor 2; MASP-2 – Mannan-binding lectin-associated serine protease-2; MCP-1 – Monocyte chemotactic protein-1; MAPK – mitogen-activated protein kinase

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# МЕХАНИЗМЫ РАЗВИТИЯ ЦИТОКИНОВОГО ШТОРМА ПРИ COVID-19 И НОВЫЕ ПОТЕНЦИАЛЬНЫЕ МИШЕНИ ФАРМАКОТЕРАПИИ

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Для тяжёлых форм COVID-19 характерно развитие «цитокинового шторма» – состояния неконтролируемого высвобождения большого количества медиаторов воспаления. Присоединение S-гликопротеина SARS-CoV-2 к ангиотензин-превращающему ферменту 2 рассматривается как процесс, запускающий сложные молекулярные взаимодействия, которые приводят к гипервоспалению, которое в свою очередь реализуется через несколько систем: ренин-ангиотензин-альдостероновую, калликреин-кининовую и систему комплемента. Знание данных механизмов позволяет предположить потенциальные точки терапевтического вмешательства, на которые можно воздействовать существующими терапевтическими средствами для противостояния «цитокиновому шторму» и лечения острого респираторного дистресс-синдрома, связанного с COVID-19.

**Цель.** В обзоре обобщаются известные на сегодняшний день данные по молекулярным процессам, лежащим в основе неконтролируемого «цитокинового шторма» у пациентов с тяжёлой формой COVID-19 и возможные варианты их фармакологической коррекции.

**Материалы и методы.** В системах Medline, Cochrane Central Register of Controlled Trials, Scopus, Web of Science Core Collection, Cochrane Library, ClinicalTrials.gov, Elibrary, Google-академия был проведен поиск по ключевым словам и комбинации этих слов: COVID-19, ренин-ангиотензин-альдостероновая система, брадикинин, система комплемента, гиалуроновая кислота, фармакотерапия.

**Результаты.** Развитие «цитокинового шторма» при COVID-19 опосредованно патогенетическими изменениями, происходящими в организме в ответ на проникновения SARS-CoV-2 в клетку. В РААС подавление АПФ2 приводит к снижению его способности расщеплять АТII, что, с одной стороны, ведет к уменьшению количества АТ1-7, а с другой – к воздействию АТII на АТ1R с последующим развитием вазоконстрикции и повреждения лёгких. Нарушения в калликреин-кининовой системе связаны, с одной стороны, с повышенной экспрессией калликреина и усилением образования брадикинина и его метаболита des-Arg 9-брадикинина, с другой стороны, с подавлением экспрессии ингибитора С1-эстеразы, который препятствует образованию калликреина, и нарушением инактивации des-Arg 9-брадикинин под действием АПФ 2. Нуклеокапсидный белок SARS-CoV-2 запускает активацию системы комплемента по лектиновому пути, что приводит к продукции анафилатоксинов С3а и С5а, которые стимулируют синтез провоспалительных цитокинов. Провоспалительные цитокины являются сильными индукторами гена HAS 2 в эндотелии, который кодирует мембранные ферменты гиалуронатсинтазы. Вызванное «брадикининовым штормом» пропотевание жидкости в альвеолы в сочетании с гиперпродукцией гиалуроновой кислоты, которая накапливает воду в 1000 раз больше собственной массы, может приводить к образованию плотного желеобразного вещества, препятствующего газообмену.

**Заключение.** Перспективные направления фармакотерапии «цитокинового шторма» связаны с влиянием на дисфункцию перечисленных систем. Однако эффективность и безопасность применения большинства препаратов для лечения COVID-19 еще предстоит изучить с помощью тщательно спланированных клинических исследованиях.

**Ключевые слова:** SARS-CoV-2; «цитокиновый шторм»; фармакотерапия COVID-19

**Список сокращений:** АПФ – ангиотензин-превращающий фермент; АТ – ангиотензин; ГКС – глюкокортикостероиды; ДИ – доверительный интервал; Ил – интерлейкин; ОРДС – острый респираторный дистресс-синдром; РААС – ренин-ангиотензин-альдостероновая система; РКИ – рандомизированное контролируемое исследование; ФНО α – фактора некроза опухоли α; АТ1R – ангиотензиновый рецептор первого типа; БК – брадикинин; BKB 1R – рецептор брадикинина 1 типа; BKB 2R – рецептор брадикинина 2 типа; MASP-2 – маннан-связывающая лектин-ассоциированная сериновая протеаза 2

## INTRODUCTION

The novel coronavirus infection (COVID-19), which has spread on a pandemic scale in 2020, was caused by SARS-CoV-2, the enveloped RNA virus, which belongs to the Coronaviridae family, a beta coronavirus genus. Structural and auxiliary proteins of the virus are involved in the penetration into the cell and affect the immune response of the infected [1].

The scientific evidence suggests that the immune response to viral infection contributes to the development of severe infections such as MERS-CoV, SARS-CoV and SARS-CoV-2 [2]. The immune responses in severe COVID-19 are known as cytokine storms. “Cytokine storm” is a massive and uncontrolled release of cytokines. This phenomenon is observed in some infectious and non-infectious diseases, leading to a hyperinflam-

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matory response of the body associated with a poor clinical prognosis [3]. This hyperimmune response correlates with a high rate of admissions to intensive care units and a high rate of deaths from COVID-19.

The initial phase of penetration by SARS-CoV-2 into the cell is mediated by the binding of the S-glycoprotein of the viral envelope to the membrane-bound form of the angiotensin converting enzyme (ACE2) on the target cell [1]. The attachment of the virus to ACE2 as its cellular receptor provides penetration into the target cell by viropexis, which leads to the penetration (internalization) of the enzyme into the cell and suppression of its function [4]. The internalization of ACE2 can potentially lead to an increase in the concentration of angiotensin II (AT II) and a decrease in the level of AT1-7, which subsequently leads to the triggering of inflammatory reactions associated with an imbalance in the functioning of the renin-angiotensin-aldosterone system (RAAS) [4].

There are other key mechanisms for the onset of the cytokine storm. Thus, the analysis of bronchoalveolar lavage showed that SARS-CoV-2 causes an increase in the level of bradykinin in the cells (the so-called "bradykinin storm"). It is known that bradykinin is involved in the formation of pain and dilates blood vessels, increasing their permeability, which leads to edema and inflammation. Besides, it was found out that in the patients with COVID-19, the production of hyaluronic acid increases, and the synthesis of hyaluronidase enzymes that could destroy it, decreases [5]. The sweating of fluid into the alveoli, caused by the "bradykinin storm," in combination with the overproduction of hyaluronic acid, leads to the formation of a dense jelly-like substance, preventing gas exchange. Thus, not only an imbalance in the RAAS system, directly leading to a "cytokine storm", but also a "bradykinin storm" with an overproduction of hyaluronic acid, can cause a severe course of COVID-19. However, the potential cellular and molecular mechanisms for the development of severe forms in COVID-19, have not been well studied yet.

**THE AIM** of the review article is to summarize the currently known data on the molecular processes underlying the uncontrolled "cytokine storm" in the patients with severe COVID-19. Understanding these processes will be critical to the selection of an effective therapeutic target in the pathogenesis of COVID-19. Understanding these processes will be crucial for the selection of an effective therapeutic target in the pathogenesis of COVID-19.

## MATERIALS AND METHODS

The data base was represented by such systems as Medline, Cochrane Central Register of Controlled Trials, Scopus, Web of Science Core Collection, Cochrane Library, ClinicalTrials.gov, elibrary, Google-Academy. A search was carried out for the following keywords and combinations: COVID-19, renin-angiotensin-aldosterone system, bradykinin, complement system, hyaluronic acid, pharmacotherapy – both in Russian and English equivalents. There was no limitation by date. The references were checked in manual way, and electronic archives of the clinical trials were used to search for additional studies on the topic. The date of the application was 12/14/2020. The search was carried out by two researchers, and the disagreements were solved by reaching a consensus.

## RESULTS

### Renin-angiotensin-aldosterone system

RAAS is a system of vasoactive peptides that regulates blood pressure, the volume of circulating fluid, the balance of plasma ions, and also participates in the maintenance of inflammation. One of the key enzymes of this system, ACE2, is expressed in the heart, kidneys, testes, gastrointestinal tract, and lungs [6]. It cleaves ATI to form the AT1-9 peptide, which can be converted to the AT1-7 peptide using ACE or other peptidases. ACE 2 can also directly metabolize ATII with the formation of AT1-7 [7]. AT1-7 is a vasodilator peptide that has antiproliferative, antithrombotic and anti-inflammatory kinds of activity, weakens the effects of activation of type 1 angiotensin receptors (AT1R) [8], reduces the expression of inflammatory factors such as interleukin (IL)-6, tumor necrosis factor α (TNFα) and IL-8 [9].

The positive effects of AT1-7 listed above, occur under the influence of the MasR receptor [9]. MasRs are expressed in the epithelium and smooth muscles of the bronchi; therefore, AT1-7 can modulate acute and chronic inflammatory processes in the lungs by activating MasR [10]. AT1-7 also indirectly affects the production of IL-10, which, in its turn, induces the differentiation of T-helpers into T-helpers of type 2 [11]. Type 2 T-helpers regulate immune responses by producing anti-inflammatory cytokines: IL-4, IL-5, IL-9 and IL-13 [12]. In addition, IL-10 can be involved in the prevention of tissue alteration [13].

Thus, the RAAS can be considered as a hormonal system with two axes: the ACE/ATII/AT1R axis – pathological – and, opposite to it, the protective axis – ACE2/AT1-7/MasR (Fig. 1).

The penetration of SARS-CoV-2 into the cell and its subsequent binding to ACE2 leads to a deviation of the system towards the pathological axis, since the ability of ACE2 to break down ATII decreases. On the one hand, it leads to a decrease in the amount of AT1-7; and on the other hand, to the effect of ATII on AT1R with the subsequent development of vasoconstriction and damage to the lungs [14].

The obtained clinical data confirm the influence of the RAAS imbalance in the pathogenesis of the development of acute respiratory distress syndrome (ARDS). In laboratory studies, the patients with COVID-19 showed higher concentrations of ATII, which linearly correlate with the severity of lung damage [15]. In addition, the use of ACE inhibitors and angiotensin receptor blockers for the treatment of hypertension, is associated with a

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lower severity of the disease and a trend towards low IL-6 levels in the patients with COVID-19 [16]. The beneficial effects of RAAS inhibitors are confirmed in a meta-analysis of a total of 24,676 patients with COVID-19, which showed a reduction in the risk of deaths and/or development of critical illnesses by about 23% (the odds ratio of 0.768.95% confidence interval (CI): 0.651–0.907, p = 0.0018) [16].

The accumulated clinical and epidemiological data on COVID-19 show that in the patients with an initially reduced level of ACE2, the expression or an impaired RAAS function (elderly patients, males and suffering from diabetes mellitus, hypertension, obesity), ACE2 depletion associated with the action of SARS-CoV-2, leads to a more severe clinical course [17].

### Kallikrein-kinin system

The kallikrein-kinin system includes an inactive precursor kininogen. Bradykinin is formed from it under the action of the serine protease of kallikrein, the active metabolite of which is des-Arg 9-bradykinin. These peptides can act on two types of receptors associated with the G-protein: the type 1 bradykinin receptor (BKB 1R), the main agonist of which is des-Arg 9-bradykinin, and the type 2 bradykinin receptor (BKB 2R), which is activated by bradykinin [18].

Fundamentally different effects are associated with the stimulation of these receptors, as the activation of the BKB 2R receptor induces vasodilation, increases sodium excretion and lowers blood pressure, while the exposure to BKB 1R leads to the release of pro-inflammatory chemokines and enhances the neutrophil migration to tissues (Fig. 2).

The kallikrein-kinin system is closely related to the RAAS, since signaling of the bradykinin receptor is enhanced by the exposure to AT1-9, and ACE2 inactivates bradykinin [19]. Experimental studies have shown that des-Arg 9-bradykinin is a substrate of pulmonary ACE2, and weakening of its activity leads to impaired inactivation of des-Arg 9-bradykinin and, thus, to an increase in signaling through BKB 1R [18].

Studying the expression of separate genes in the samples of bronchoalveolar lavage from the patients with COVID-19 showed a pronounced expression of kininogen and kallikreins, which was not found in controls [5].

The expression of ACE, which cleaves bradykinin, is suppressed by a factor of 8, and the expression of BKB 2R is increased by a factor of 207, BKB 1R – by a factor of 2945. It should be notified that BKB 1R is usually expressed in a very low amount in almost all the tissues, but in this case, the expression of this receptor is pronounced, while in the controls it is practically not detected.

Circulating plasma kallikrein is activated by factor XIIa (Hageman factor) of the intrinsic coagulation pathway, which is suppressed by the C1 esterase inhibitor encoded by the SERPING1 gene [20]. In bronchoalveolar lavage samples from the patients with COVID-19, the expression of Hageman factor was not altered, while the SERPING 1 gene was suppressed by a factor of 33, which led to a decrease in the concentration of the C1 esterase inhibitor and, as a consequence, insufficient suppression of Hageman factor. This promoted the synthesis of bradykinin from kininogen and an even greater increase in the concentration of this neurotransmitter in the patients with COVID-19 [20]. The resulting "bradykinin storm" is potentially responsible for most of the symptoms seen in COVID-19: dry cough, fatigue, headaches, myalgia, dyspeptic disorders, cognitive decline, arrhythmias, and sudden cardiac deaths [5].

### Complement system

The complement system includes many proteins and their cleavage products that can coordinate the inflammatory response in the sites of infection. The activation of the complement system occurs through several mechanisms, which include three main pathways: classical, lectin and alternative. The lectin pathway and its effector enzyme, mannan-binding lectin-associated serine protease 2 (MASP-2), are directly related to the lung damage in the coronavirus infection. In particular, it was found out that the nucleocapsid protein SARS-CoV-2, as well as the SARS and MERS proteins activate MASP-2, and the traces of MASP-2 are observed in the vasculature of the lung tissue of the patients with COVID-19 [21]. Activated MASP-2 initiates a series of enzymatic reactions that lead to the production of anaphylatoxins C3a and C5a, and to the formation of a membrane attack complex C5b-9 [22].

Factor C5a is the strongest inflammatory peptide in the complement system, which triggers the release of a number of pro-inflammatory cytokines [22] and TNF-α [23]. The membrane attack complex C5b-9 induces the release of IL-6 by activating the nuclear transcription factor, activating protein-1 [24] and chemotactic protein-1 of monocytes [25]. The increased concentration of C3a leads to the overproduction of IL-1, IL-6 and TNF-α [26]. In addition, the lectin pathway of the complement activation is associated with endothelial damage and thrombosis [27].

The hypothesis for the role of the components of the complement system in the pathogenesis of ARDS in the coronavirus infection has been confirmed in experimental and clinical studies. In particular, in the study by Gralinski et al, the course of SARS-CoV-1 in the mice with and without C3 deficiency (the control group) was investigated. It was established that the mice with C3 deficiency showed significantly less weight loss and less respiratory dysfunction compared to the control group, despite an equivalent viral load in the lungs [28]. And in the autopsy studies of the patients who had died from COVID-19, there were deposits of complement components (C3, C3a and C5b-9) in the lungs, and increased levels of C5a in plasma [27].

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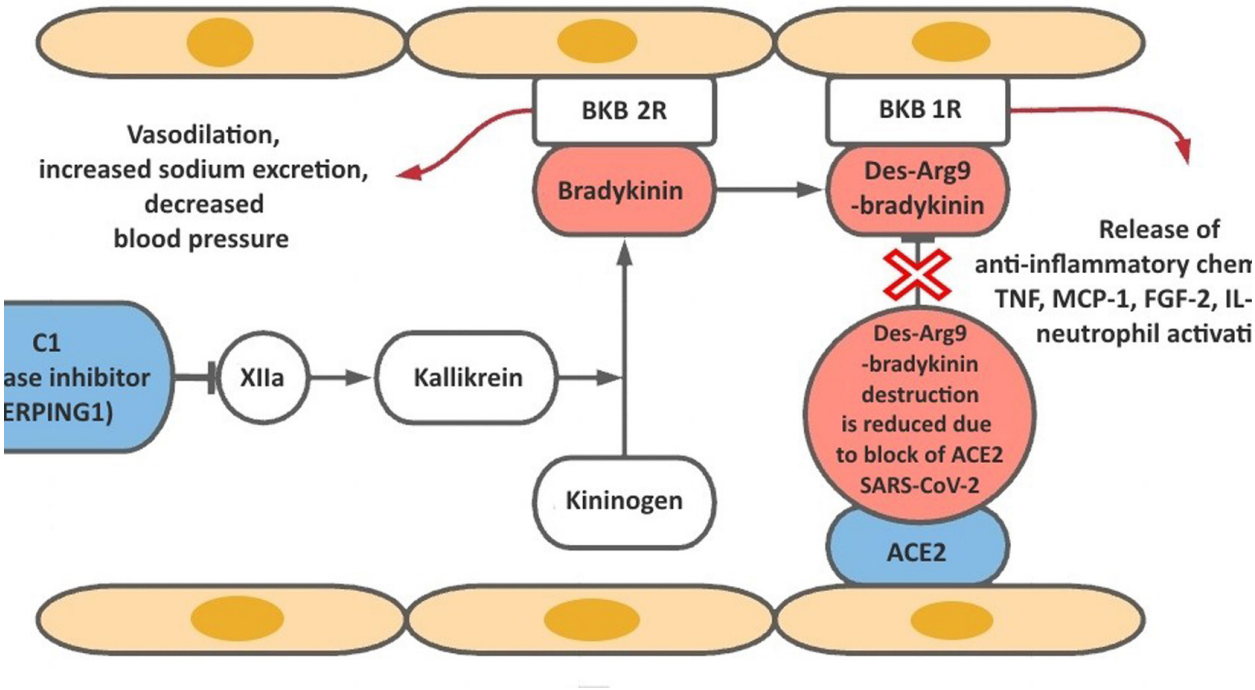


**Figure 1 – RAAS is a system with two axes: the ACE/ATII/AT1R axis – pathological – and, opposite to it, the anti-inflammatory axis – ACE2/AT1-7/MasR. The penetration of SARS-CoV-2 into the cell and its subsequent suppression of ACE2, shifts the balance towards the pathological axis and, as a result, an increased total ratio of ATII to AT1-7 leads to a deterioration of lung function and lung damage**

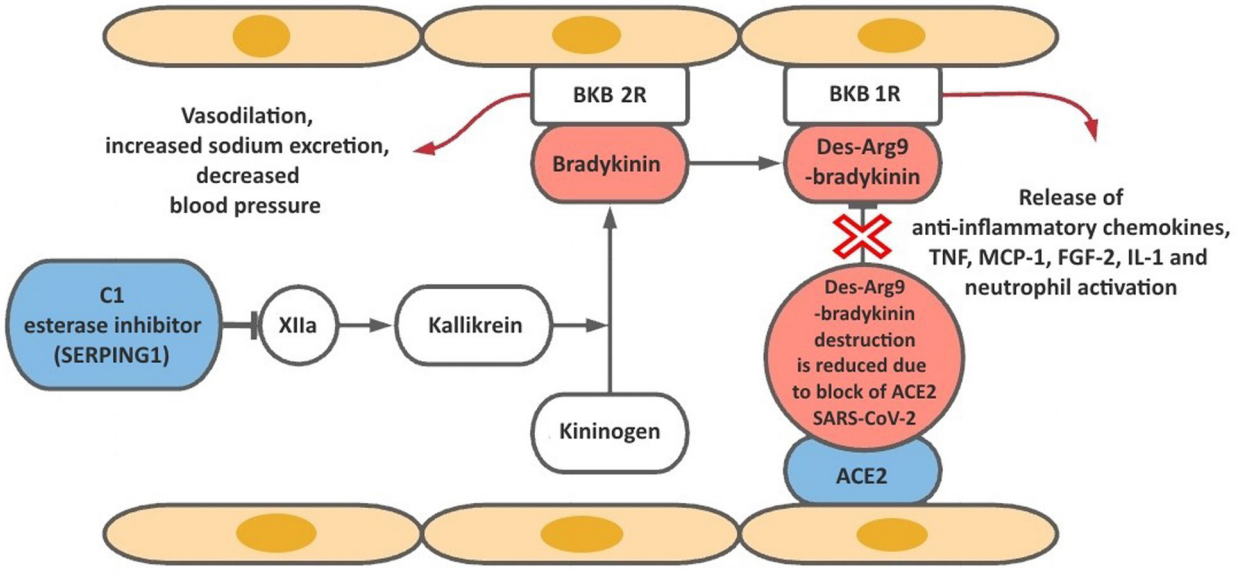


**Figure 2 – Disturbances in the kallikrein-kinin system are associated, on the one hand, with increased expression of kallikrein and an increase in the formation of bradykinin and its metabolite des-Arg 9-bradykinin; on the other hand, with the suppression of the expression of the C1-esterase inhibitor, which prevents the formation of kallikrein, and violation of des-Arg 9-bradykinin inactivation by ACE2**

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**Table 1 – Potential targets of "cytokine storm" pharmacotherapy in COVID-19**

| Impact target | Therapeutic solution |
|---|---|
| | Plasmapheresis is an elimination of the components of the complement system, immune complexes and cytokines, circulating in the plasma |
| Renin-angiotensin-aldosterone system | Human recombinant soluble ACE2 |
| | Administration of exogenous AT1-7 |
| | Administration of Vitamin D |
| Kallikrein-kinin system plasmic | Selective BKB 1R blockers |
| | Conestat alfa is a recombinant form of a C1 inhibitor |
| | Lanadelumab is a human monoclonal antibody that binds plasmic kallikrein |
| | Icatibant is a selective BKB 2R antagonist |
| Complement system | Narsoplimab is a high affinity human monoclonal IgG4 antibody that binds MASP-2 and blocks the lectin pathway |
| | Eculizumab is high affinity monoclonal antibody to C5 protein |
| | Compstatin AMY-101 inhibits the cleavage of C3 to C3a and C3b by C3 convertases |
| Hyaluronic acid | Intranasal administration of exogenous hyaluronidase |
| | Gimecromone (4-methylumbelliferone) is an inhibitor of the expression of hyaluronate synthases (HAS2 and HAS3) |
| Other components of pathogenesis | Siltuximab is a preparation of monoclonal antibodies against IL-6 and tocilizumab, sarilumab preparations against IL-6 receptor<br>Systemic glucocorticosteroids |

## Hyaluronic acid

Hyaluronic acid is a polysaccharide that can hold 1000 times as much as its own weight in water, to form a dense hydrogel. The HAS1, HAS2 and HAS3 genes encode membrane enzymes of hyaluronate synthase. The destruction of hyaluronic acid occurs under the action of hyaluronidase enzymes encoded by the HYAL1 genes (lysosomal hyaluronidase) and HYAL2 genes (membrane-bound hyaluronidase) [29]. The synthesis and decomposition of hyaluronic acid is regulated according to the principle of the negative feedback: hyaluronic acid stimulates CD44 (hyaluronic acid receptor), which, in its turn, induces the synthesis of hyaluronidases [30].

The hypothesis about the role of hyaluronic acid in the pathogenesis of severe forms of COVID-19 was made after the discovery of a transparent jelly-like exudate, which filled the lung tissue, at the autopsy of the patients who had died from this infection [31]. Although the nature of the detected changes had not yet been determined at that time, the assumption about hyaluronic acid was associated, first, with the fact that its accumulation in ARDS had been notified in the earlier study [32], and second, there was a violation of the regulation of hyaluronic acid production in the SARS infection [33]. Pro-inflammatory cytokines (IL-1, TNF-α), an increase in the amount of which, is observed in the lungs with ARDS, have witnessed being strong inducers of the HAS2 enzyme in the endothelium, alveolocytes and fibroblasts. The analysis of bronchoalveolar lavage of the patients with COVID-19, revealed a significant increase in the activity of the genes involved in the synthesis of hyaluronic acid: HAS1 (9113 times as active), HAS2 (493 times as active) and HAS3 (32 times as active) [5].

The CD44 gene, encoding the CD44 receptor, which is necessary for the degradation of hyaluronic acid, and the gene encoding the extracellular hyaluronidase HYAL2, were suppressed (by a factor of 11 and 5 times, respectively). As a result of the disruption of the synthesis and decay of hyaluronic acid induced by SARS-CoV-2, its accumulation occurs in the alveoli, followed by their blockage, which was later shown in the histochemical study of the lung tissue of the patients who had died from COVID-19 [34]. It is with the accumulation of hyaluronic acid in the lungs that those changes in the form of the "ground glass" on computed tomograms are established. They are found out in the pneumonia associated with SARS-CoV-2 [34].

## New Potential Targets for COVID-19 Therapy

Reducing the negative effect of the excessive production of inflammatory mediators, can be achieved by conducting plasmapheresis. The effectiveness of plasmapheresis in the treatment for severe COVID-19 has been demonstrated [35]. Currently, the safety of this method in the patients with COVID-19 has not been completed. It is advisable to consider the possibility of a therapeutic effect on individual systems involved in the pathogenesis of the "cytokine storm" development in COVID-19 (Table 1).

**Renin-angiotensin-aldosterone system.** For over a decade, work on the first human recombinant soluble ACE2 (GSK2586881) for the treatment of ARDS has been underway. Nowadays, two phases of clinical trials have been completed. In the first phase it was demonstrated that the drug is well tolerated by healthy volunteers and does not cause cardiovascular side effects [36]. In the second phase it was proven that this drug (GSK2586881)

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does not cause hypotension, but significantly more often causes hypernatremia, dysphagia and rash [37]. At the same time, its effectiveness in reducing IL-6 levels and improving clinical and instrumental parameters in a small number of sample patients with ARDS, has not been proven [37]. The second phase re-study (ClinicalTrials.gov ID: NCT04335136), including the patients with COVID-19 and ARDS, was completed at the end of 2020. In addition, it has been recently proven that human recombinant soluble ACE2 can prevent the penetration of SARS-CoV-2 into blood vessels and kidney cells [38].

It was proposed to administer AT1-7 in COVID-19 taking into consideration the role of AT1-7 in counteracting the inflammatory effects of ATII that protected endothelial cells and prevented lung damage with the subsequent development of ARDS [39]. However, the effectiveness of the use of AT1-7 in ARDS has been demonstrated only in experimental models. No studies involving patients with COVID-19, have been carried out yet [14].

Two reviews showing the potential benefit of vitamin D in the treatment of severe forms of coronavirus infection have also been published [40]. This effect was presumably associated with its ability to reduce the level of renin and consequently reduce the production of ATII, which has been displayed in a few studies [41]. The relationship between the production of renin and the concentration of vitamin D is not clear, but some studies demonstrate the relationship of its deficiency with the development of severe forms of COVID-19 [42]. However, the positive effect of vitamin D therapy on the course of coronavirus infection was recommended only in the review studies, while in randomized controlled trials (RCTs), its effect on any pathology other than skeletal, was not notified [43]. In another meta-analysis, a regular intake of vitamin D at the doses up to 2000 IU/per day is safe and protects against acute respiratory tract infection, especially in the patients with vitamin D deficiency [44]. Thus, it seems possible that prophylactic vitamin D therapy can reduce the severity of the disease caused by SARS-CoV-2, especially in the conditions where vitamin D deficiency is common [40].

**Kallikrein-kinin system.** Since many studies have shown a significant role for the "bradykinin storm" in the pathogenesis of COVID-19, the exposure by inhibiting the BKB 1R could potentially have positive therapeutic effects. In the period from 2004 to 2012, several large pharmaceutical companies simultaneously filed patent applications for the registration of chemical compounds with BKB 1R selective blockade properties and showed promising results in preclinical trials [45]. Sanofi, Merck and Boehringer-Ingelheim drugs even reached Phases I and II in the clinical trials, but further studies were abruptly stopped without any explanation [45]. Such factors as limited predictability of animal models, toxicological problems, and a non-optimal pharmacokinetic profile were probably the reasons for the termination of further development of this drugs group. Anyway, there is currently no registered blocker BKB 1R drug.

A decrease in the production of bradykinin (BK) in the body can be considered another potentially promising therapeutic area.One of the ways to achieve this is influencing the activity of a C1-esterase inhibitor, which suppresses the production of Hageman factor and, as a result, reduces the amount of bradykinin. The drugs with a similar mechanism of action are used to treat hereditary angioedema, a rare genetic disease associated with a decrease in the amount or activity of a C1 esterase inhibitor. Since a number of studies have demonstrated the suppression of the SERPING1 gene and a decrease in the concentration or the activity of the C1 esterase inhibitor in the patients with COVID-19, recombinant forms of the inhibitor (Berinert – registered in the Russian Federation, Cinryze, Haegarda, Ruconest) can be used to reduce the activity of bradykinin [46]. Currently, there are no randomised controlled studies that have studied the use of this group of drugs in the patients with COVID-19. In a small uncontrolled trial five patients with the signs of hyperactivation of the kallikrein-kinin system, were prescribed conestat alfa (Ruconest), and all the patients showed positive clinical and laboratory dynamics [47].

Another drug for the treatment of hereditary angioedema is lanadelumab. Lanadelumab is a human monoclonal antibody that binds plasmic kallikrein and prevents the *cleavage* of circulating high molecular weight kininogen to bradykinin. Lanadelumab has no effect on either the C1 inhibitor or the SERPING1 gene encoding the activity of the C1 inhibitor. Icatibant blocking the binding of bradykinin to BKB 2R prevents the development of vasodilation, increases vascular permeability, the contraction of smooth muscles of visceral organs and the development of edema. The efficacy of the drug in the treatment for COVID-19 was demonstrated in a case-control study of 27 patients with less than 90% saturation. They had been prescribed icatibant or standard therapy [48].

The patients taking icatibant, showed a decrease in the need for the oxygen therapy and the improvement in oxygen saturation values within 24 hours of starting the treatment. However, there have been no full-scale randomised controlled studies to research the effectiveness of this drug in COVID-19.

**Complement system.** The main therapeutic ways of influencing the complement system, are to block the lectin pathway of its activation and suppress the proteins that provoke the development of inflammatory reactions – C5a and C3.

Narsoplimab is a high-affinity, fully human anti-immunoglobulin G4 monoclonal antibody that binds MASP-2 and blocks the lectin pathway of the complement activation. This drug has shown efficacy in the treatment of patients with thrombotic microangiopathy associated with hematopoietic stem cell transplantation

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and also undergoing the third phase of clinical trials in the treatment for immunoglobulin A nephropathy and atypical hemolytic uremic syndrome [27]. In August 2020, the results of this drug study in the treatment of the patients with severe COVID-19 infection and ARDS were published [27]. The study involved 6 patients who had received narsoplimab at the dose of 4 mg/kg intravenously twice a week for 2–4 weeks, they had also received standard therapy as recommended, and a respiratory support. All participants in the trial showed clinical and laboratory improvement, the development of adverse reactions associated with taking the drug, was not notified. Narsoplimab does not interfere with the activation of the complement system through the classical pathway and does not interfere with the adaptive immune response, and these are the positive aspects of its use.

Eculizumab is a high affinity monoclonal C5 protein antibody. The drug has demonstrated encouraging results in the treatment for severe COVID-19 complicated by ARDS. In several small studies, an improvement was reported in all of them [49].

Nowadays, the drugs for the treatment of various diseases associated with pathology of the complement system, which are protein C3 inhibitors, are under clinical research. One of the representatives of a new generation of highly selective and potent C3 inhibitors called compstatins, AMY-101 is undergoing phase II clinical trials, demonstrating good safety and tolerability in volunteers during phase I study [50]. This drug has been proposed to be used in the treatment of critically ill patients with a novel coronavirus infection and ARDS. The results of several studies indicating its effectiveness have already been published [51]. In one of the studies, eculizumab was compared with AMY-101. The advantage of the latter in the rate of the onset of the effect and evidence of clinical and laboratory improvement in ARDS associated with COVID-19, has been demonstrated [51]. The authors associate the obtained results with the fact that the activation of C3 is the convergence point of all complement pathways, and inhibition at the C3 level ensures the simultaneous blocking of the formation of all downstream pro-inflammatory mediators involved in SARS-CoV-2-induced ARDS.

The limitations of these studies are a small population of patients, lack of control groups, and a concomitant use of other anti-COVID-19 drugs. SOLID-C19 (ClinicalTrials.gov identifier: NCT04288713), CORIMUNO19-ECU (ClinicalTrials.gov identifier: NCT04346797) and SAVE (ClinicalTrials.gov identifier: NCT04395456) are among the few ongoing studies investigating the therapeutic effect and tolerance of complement inhibitors in the patients with COVID-19 [52].

**Hyaluronic acid.** Scientists from China suggested that inhalation of hyaluronidase would degrade and decrease the amount of hyaluronic acid in the respiratory tract [53]. It has been shown experimentally that intranasal administration of exogenous hyaluronidase can reduce the quantity of hyaluronic acid in the lungs and restore the lung function after the influenza infection [33]. However, most likely, this method can be effective only in the early stages of the disease [34]. Another method of therapeutic influence on the synthesis of hyaluronic acid is the use of the drug 4-methylumbelliferone (gimecromone) which can inhibit the production of hyaluronic acid by inhibiting the expression of genes of two hyaluronate synthases (HAS2 and HAS3) and blocking the last stage of hyaluronic acid formation from glucose metabolites [54]. This drug has been approved for biliary spasm treatment, but it can cause diarrhea, followed by hypokalemia. There are currently no studies on the effectiveness of 4-methylumbelliferone in the patients with COVID-19.

**Other drugs for pathogenetic therapy.** Among the most accessible and frequently used agents in the therapy of "cytokine storm", preparations of monoclonal antibodies against IL-6 (siltuximab) or its receptors (tocilizumab, sarilumab), as well as glucocorticosteroids (GCSs), should be singled out. IL-6 inhibitors have not been approved for the treatment of COVID-19 yet, but a number of non-placebo-controlled and observational trials in the patients with severe COVID-19 and ARDS indicate the significant potential of these drugs (primarily tocilizumab) [55]. Several metaanalyses of the tocilizumab efficacy for COVID-19 have been published. One of the recently published metaanalyses evaluated the results of controlled and uncontrolled trials separately [56]. It included 16 controlled studies with a total amount of 2,545 patients and showed a 55% reduction in mortality with tocilizumab therapy, compared to controls (the odds ratio of 0.453, 95% CI 0.376–0.547, p<0.001). In 18 uncontrolled trials involving 886 people, the death rate from severe COVID-19 ranged from 0% to 42.4%.

However, this meta-analysis did not include the unpublished results of the COVACTA randomised controlled study that showed no reduction in mortality from COVID-19 with tocilizumab compared with standard therapy. This fact questioned the potential efficacy of the drug and the ethical basis for continuing other studies [56]. However, several RCSs are still ongoing to evaluate the efficacy of tocilizumab in the patients with the novel coronavirus infection (ClinicalTrials.gov identifiers: NCT04409262, NCT04372186, NCT04356937, NCT04412772).

There remains a controversial issue regarding the use of glucocorticosteroids in COVID-19. There is evidence of both improved symptoms and a reduced mortality with the administration of this group of drugs, and the studies showing that treatment with corticosteroids for COVID-19 is either not beneficial or harmful [57]. The results of the RECOVERY randomised controlled study have now been published [58]. The study included 2,104 patients who had been prescribed dexamethasone at the dose of 6 mg/per day for 10 days, and 4,321

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patients – standard therapy. Within 28 days, the percentage of deaths in the first group was 21.6%, in the second – 24.6%. Among the patients receiving invasive mechanical ventilation, the death rate was lower than in the standard therapy group (29.3% versus 41.4%; the frequency ratio of 0.64; 95% CI, 0.51-0, 81) in the dexamethasone group. Among the patients receiving oxygen without invasive mechanical ventilation (23.3% versus 26.2%; the frequency ratio of 0.82; 95% CI 0.72 to 0.94), but not among those who did not receive any respiratory support (17.8% versus 14.0%; the frequency ratio of 1.19; 95% CI 0.91 to 1.55). Based on the available data, it can be concluded that the administration of dexamethasone is recommended in small doses only for patients in a severe condition and requiring respiratory support. A randomised controlled study is currently underway to investigate the efficacy of a high-dose of dexamethasone (16 mg / per day) in the treatment of ARDS in COVID-19 [59].

## CONCLUSION

Thus, understanding the pathogenetic mechanisms of the development of a "cytokine storm" in COVID-19 opens the way for the study of new pharmacological targets and a further development of drugs that can prevent complications and reduce mortality. The efficacy and safety of most drugs for the treatment of COVID-19 remains to be studied in well-designed clinical trials.

However, already at this stage, the instruments for the treatment of pathological processes induced by a viral infection, seem to be a more reliable solution in the long term, due to the fact that viral target proteins have variability and species specificity.

This significantly limits the use of etiotropic therapy, while the typical pathological processes of the immune system's response to an infectious agent are stable, which makes it possible to use drugs without fear of therapeutic resistance.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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