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Justification of treatment and possible outcomes of severe COVID-19

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Abstract

The role of hyaluronic acid in the pathogenesis of acute respiratory distress syndrome, including those associated with severe COVID-19, is known. Pro-inflammatory cytokines (interleukin-1, tumor necrosis factor) are strong inducers of hyaluronic acid synthase (HAS2) in $CD31^+$ endothelial cells, $EpCAM^+$ cells of the alveolar epithelium of the lungs and fibroblasts. Hyaluronic acid can absorb water in quantities significantly exceeding its own molecular weight. Reducing the presence or inhibiting of hyaluronic acid synthesis is of great importance for facilitating the breathing of COVID-19 patients. Hyaluronidase-based preparations can reduce the accumulation of hyaluronic acid and promote pulmonary alveoli cleansing. Respiratory viral infections, including pandemic strains of coronaviruses, especially in severe cases with acute respiratory distress syndrome, can be complicated by the development of pulmonary fibrosis. It has been shown that changes in X-ray Computed Tomography findings characteristic of fibrosis in the first year after COVID-19 can significantly regress. A clinical case from the practice of treating a patient with a severe course of COVID-19, significant cardiovascular comorbidity, grade 2 obesity, which was regarded as significant risk factors for an unfavorable outcome, is presented. The patient with signs of progressive respiratory failure was admitted to the intensive care unit. Pulse therapy with glucocorticosteroids and anticoagulants was started. Deterioration of the condition is regarded as the beginning of acute respiratory distress syndrome, which complicated the cytokine storm induced by the coronavirus. The patient was taken for high-flow oxygenation. An anti-cytokine therapy was prescribed. Reduction of inflammatory markers was obtained, but severe respiratory failure persisted. The bovgialuronidase azoximer was included in the treatment. The patient's condition began to stabilize then she was discharged in stable condition without oxygen support. The available data on the negative role of hyaluronic acid in the pathogenesis of acute respiratory distress syndrome in patients with COVID-19, as well as the need to reduce the likelihood of developing residual fibrous changes in the lungs in patients who have undergone acute respiratory distress syndrome, suggest the need for further studies of domestic azoximer bovgialuronidase properties in the treatment of severe forms of COVID-19.

Keywords: COVID-19, pulmonary outcomes, treatment.

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Since the onset of the global pandemic of the coronavirus disease 2019 (COVID-19) in mid-August 2021, over 205 million COVID-19 cases have been officially registered worldwide, including more than 4.3 million lethal outcomes. For Russia, these figures amounted to 6.5 million morbidities (44.7 per 1000 population) and 170 thousand mortalities. In the Republic of Tatarstan, 24.5 thousand people were infected (6.3 per 1000 population) and >600 patients died [1].

Autopsy findings from patients who died from acute respiratory distress syndrome (ARDS) complicating the course of severe COVID-19 demonstrated filling of the lungs with a gel-like substance. It was somewhat reminiscent of the lungs of drowning patients. The nature of this phenomenon has yet to be clarified; however, the role of hyaluronic acid in the pathogenesis of ARDS, including that associated with severe COVID-19 in which the metabolism of hyaluronic acid is impaired, is known [2, 3]. The lungs of patients with COVID-19 have elevated levels of inflammatory cytokines (interleukin-1 and tumor necrosis factor). These cytokines are strong inducers of hyaluronic acid synthetase (HAS2) in $CD31^+$ endothelial cells and $EpCAM^+$ cells of the alveolar epithelium of the lungs and fibroblasts.

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Hyaluronic acid can absorb water in quantities 1000 times its molecular weight. Thus, reducing the presence or inhibiting hyaluronic acid synthesis is important in facilitating breathing in patients with COVID-19. Hyaluronidase preparations can reduce the accumulation of hyaluronic acid and thus cleanse the alveoli [3]. In experimental animal models, oxygenation disorders induced by the influenza virus were reduced by intranasal administration of hyaluronidase [4].

The morphological foundation of ARDS, the most common cause of lethal outcomes in patients in the acute COVID-19, is severe diffuse damage to the alveoli, verified in 93.3% of cases, which was manifested mainly by acute alveolar damage (32%), with organizing (25%) and/or fibrosing (43%) patterns [5].

Mechanical ventilation of the lungs in ARDS complicating the course of COVID-19 severe, recognized as a contributing factor to the development of a fibroproliferative response, not only induces the secretion of transforming growth factor β_1, but also activates collagen synthesis and inhibits collagenase synthesis [6].

Some patients with ARDS who survived the acute phase of the disease may subsequently die (>3 weeks) because of progressive pulmonary fibrosis. Although a direct link between respiratory viral infections and development of progressive fibrosis has not been established, data from previous global outbreaks of atypical pneumonia with severe acute respiratory syndrome and the Middle East respiratory syndrome demonstrate a clear relationship between coronavirus infection, persistent impairment of lung function, and abnormal radiological findings consistent with pulmonary fibrosis [7].

In a long-term study with a dynamic assessment of X-ray computed tomography (XCT) data in patients infected with the pandemic strains of coronaviruses from 2003 to 2018, changes in the pulmonary parenchyma were detected, including ground-glass opacity and linear induration in 38% of the patients. Evaluation of these changes in these patients for >15 years revealed a noticeable regression during the first 12 months after infection. However, fibrotic changes persisted and remained stable for years; thus, in 2018, they were detected in 4.6% of the cases [7]. Other respiratory viruses, including influenza (strains H1N1 and H5N1), can also contribute to the development of pulmonary fibrosis. Moreover, the hepatitis C virus, human cytomegalovirus, and Epstein–Barr virus can act as viral cofactors in the development of idiopathic pulmonary fibrosis [8].

Fibrosis can be the final result of many chronic inflammatory diseases (heart, liver, lungs, and kidneys). In response to tissue damage, myofibroblasts from multiple sources (including resident fibroblasts, mesenchymal cells, circulating fibroblasts, and other cell types) can initiate wound healing by altering the extracellular environment to restore tissue integrity and contributing to parenchymal cell replacement. This process usually ends after tissue healing [9].

However, repeated injury and recovery (severe COVID-19) can disrupt the balance of this process, which leads to excessive abnormal deposition of extracellular matrix protein, accompanied by an increase in myofibroblast activity. This can promote a chronic inflammatory environment of macrophages and immune cell infiltration. In such a cellular environment, various pro-inflammatory and pro-fibrotic cytokines are released, activating fibrosis-associated pathways [9].

Many studies have presented the therapeutic potential of low or medium doses of glucocorticoids in cases with nonspecific interstitial pneumonia or organizing pneumonia in the recovery phase of patients with signs of progressive fibrosis [10]. A high prevalence of residual radiological changes after acute COVID-19 (30%–60%) was noted; moreover, in contrast to bacterial pneumonia, several patients showed the possibility of a good regression of these changes within 6–12 months after the coronavirus infection [10].

Searching for new methods of treating severe COVID-19 is important to prevent complications of acute infection, primarily ARDS, which determines largely the probability of immediate and long-term adverse complications and outcomes in the post-COVID period.

A promising Russian innovation that could help patients in the Russian Federation in reducing the probability of developing residual fibrotic changes in the lung tissue after severe COVID-19 is the drug bovhyaluronidaze azoximer. Its official indications include the treatment of pneumosclerosis, fibrosing alveolitis, and tuberculosis (cavernous-fibrous, infiltrative, and tuberculoma) [11]. The antifibrotic effect of bovhyaluronidaze azoximer is attributed to the enzymatic activity of hyaluronidase, which cleaves glycosaminoglycans and represents the basis of the extracellular matrix of connective tissues. A recent publication demonstrated the therapeutic and prophylactic effects of bovhyaluronidaze azoximer on pulmonary fibrosis in patients with a history of COVID-19, regardless of severity. The authors recommended at least three treatment courses with an interval of 6 months for a greater pathogenetic effect [12].

This paper also presents the clinical case of successful treatment of a patient with severe

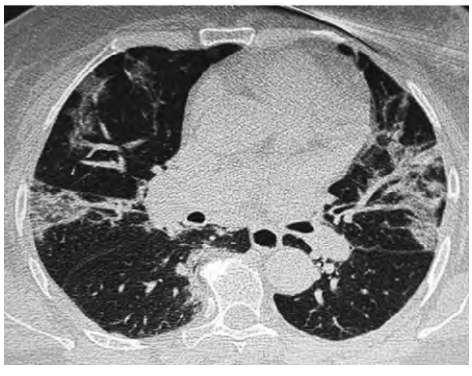

Fig. 1. X-ray computed tomogram at hospitalization (CT 2)

COVID-19. Female patient T., aged 65 years, was hospitalized with complaints of severe general weakness, fever up to 38.5°C, shortness of breath at the slightest physical exertion, and dry paroxysmal cough. Her condition started 1 week ago when her body temperature rose to 38°C, general weakness appeared, and her condition started to worsen. The patient started taking paracetamol and cough tablets independently. As there was no noticeable effect after 4 days, the treatment was supplemented with a spray of interferon alfa-2b in the nose, amoxicillin 500 mg 3 times a day, and bacterial lysate (broncho-munal) orally.

The patient visited the polyclinic on day 5 and was referred for chest X-ray imaging, which revealed bilateral pneumonia. On day 6 of illness, her general health further deteriorated, so she was taken by an ambulance team and hospitalized in a provisional infectious disease hospital. The XCT verified signs of bilateral interstitial lung changes with sites of ground-glass opacity, corresponding to viral pneumonia with CT2 lesion volume (Fig. 1).

The ribonucleic acid of the severe acute respiratory syndrome coronavirus 2 was detected in the nasopharyngeal smear material used in the polymerase chain reaction. On day 8 of illness, the patient was transferred to the temporary infectious disease hospital of the city hospital with a diagnosis of severe COVID-19 (virus identified), bilateral severe polysegmental interstitial pneumonia complicated with degree 2 respiratory failure (RF), volume of lung lesions CT2, and comorbid pathology in the form of hypertension, degree 1 chronic heart failure, diabetes mellitus type 2, and degree 2 obesity. Given the progression of RF (blood oxygen saturation of 96% with O_2 insufflation of 6 L/min), the patient was immediately hospitalized from the admission department to the intensive care unit.

Pulse therapy with prednisolone 240 mg 2 times a day was started, including anticoagulant therapy with intravenous heparin administered intravenously through a dispenser 1000 U/h under the control of activated partial thromboplastin time, and oxygen therapy through a nasal cannula.

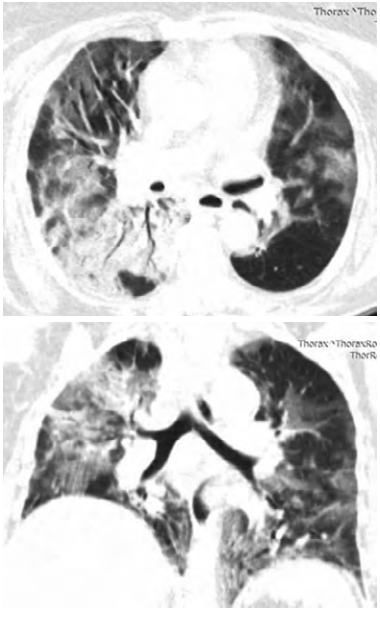

Fig. 2. X-ray computed tomography scan on the day of the telemedicine case conference (CT3)

On day 5 of hospitalization, her condition did not improve. With the aggravation of the respiratory status, the patient was switched to high-flow oxygenation; lymphopenia progressed, the level of inflammation markers increased (C-reactive protein up to 171 mg/L, ferritin up to 402 μg/L), while the body temperature was normal. Control XCT revealed a significant increase in the lesion volume registered with the expansion of the fields with ground-glass opacity and the appearance of areas of consolidation of the lung tissue (Fig. 2).

The condition was regarded as a cytokine storm with clinical manifestations in the form of ARDS. By the decision of the telemedicine case conference, a single infusion of the anticytokine drug (interleukin-6 inhibitor) olokizumab was additionally prescribed. The response was observed as a significant decrease in the activity of inflammatory markers. Moreover, despite the intensification of anticoagulant therapy regimens (heparin 1800 U/h), the phenomena of severe RF persisted.

The history of ARDS, desaturation, increase in the volume of lung damage according to the XCT dynamics, high activity of markers of viral inflammation, and an aggravating comorbid background were regarded as risk factors of poor outcomes. In this regard, therapy with glucocorticoids and anticoagulants was continued, and on day 3 after the administration of olokizumab, intramuscular injections of bovhyaluronidaze azoximer (longidase) once in 5 days (3 million units) were added to the treatment.

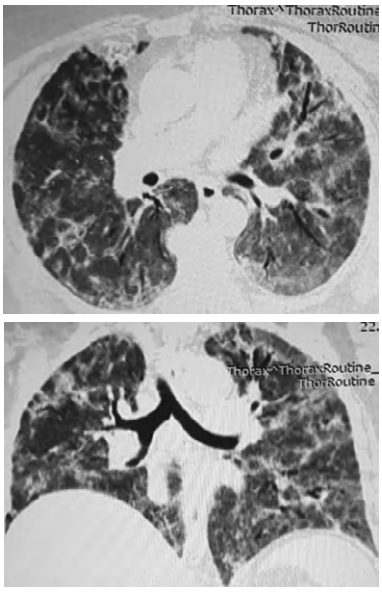

Fig. 3. X-ray computed tomography scan by the end of the inpatient stage of treatment

The patient's condition started to stabilize gradually, and it was possible to mitigate the high-flow oxygenation. After 2 weeks, the patient was switched to oxygen support through nasal cannulas (with an oxygen flow of 7 L/min; the 95% saturation was retained). There were clear trends toward a decrease in the level of inflammatory markers and regression of lymphopenia.

In subsequent week, the patient could refuse oxygen support and could move freely within the ward. The XCT data showed favorable changes observed as an increase in the lung tissue transparency (Fig. 3).

The patient was discharged in satisfactory condition. Recommendations for the outpatient stage included the continuation of anticoagulant therapy with rivaroxaban 10 mg once a day, prednisolone tablets in a reducing regimen until complete cancellation, and intramuscular injections of bovhyaluronidaze azoximer 3 million units once every 5 days (with a total duration of up to 15 injections). A control XCT of the chest 3 months after the discharge was prescribed.

This clinical example demonstrates the possibility of achieving a favorable outcome of inpatient treatment of severe COVID-19 complicated by ARDS, despite the presence of aggravating comorbid pathology, following the addition of bovhyaluronidaze azoximer to anticoagulant, glucocorticoid, and anticytokine therapy.

Although 1.5 years have passed since the onset of the COVID-19 pandemic, the issues of treating the acute phase of the disease and post-COVID complications cannot be considered completely resolved. The recognition of residual fibrotic changes in the lungs after severe respiratory viral infections is important, as it can negatively affect the quality of life of patients in the long-term, hindering the full recovery of the respiratory status of convalescents.

Existing data on the negative role of hyaluronic acid in the alveoli of the lungs of patients with COVID-19 at risk of ARDS, the need to reduce the probability of residual fibrotic changes in the lungs in patients with ARDS who have large volumes of viral lung damage, and an unfavorable somatic background, primarily in the form of obesity, diabetes mellitus, and cardiovascular pathology, suggest the need for further studies of the properties of the Russian bovhyaluronidaze azoximer in the treatment complex for severe COVID-19.

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