




Research Article

Antifibrotic Therapy in the Treatment of Patients with Pulmonary Manifestations in Complicated COVID-19

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Abstract

The study assessed the efficacy and safety of Longidaza® (bovhyaluronidase azoximer, 3000 IU) in patients with lung damage after complicated COVID-19. Two groups of 30 patients each were compared: the first received Longidaza® via intramuscular injections (3000 IU every five days, 15 injections total); the second was under dynamic observation without active therapy. The trial ran from August to December 2023. Participants were over 18 years old, had lung manifestations after severe COVID-19, started outpatient treatment within two months after hospital discharge, and provided informed consent. Exclusion criteria included pregnancy, lactation, severe comorbidities, etc. Key parameters after 10 weeks (day 71) were changes in: resting capillary blood oxygen saturation (SpO₂,%); laboratory markers (lymphocytes, C-reactive protein [CRP], D-dimer, fibrinogen). Statistical analysis used Stata 14.0 (significance level: $p < 0,05$; Mann-Whitney test). Mean age was 59.8 ± 15.2 years (Longidaza group) and 56.06 ± 13.7 years (observation group). Common comorbidities: hypertension and coronary heart disease. Results: CRP levels decreased more than twofold in both groups (to 3.66 ± 3.84 mg/L and 1.24 ± 0.7 mg/L, respectively). Blood oxygen saturation stayed $\geq 96\%$ in most patients. In the Longidaza group, some parameters were statistically significantly lower — possibly indicating antifibrotic activity. No adverse effects were reported. Conclusion: Longidaza® is safe and potentially effective for preventing and treating early pneumofibrosis and managing established lung fibrosis.

Keywords

Complicated COVID-19, Pneumofibrosis, B Bovhyaluronidase Azoximer

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1. Introduction

Idiopathic interstitial pneumonias (IIPs) are a group of lung diseases of unknown etiology, distinguished from each other by the pathomorphological type of non-infectious inflammation and fibrosis, predominantly in the lung interstitium. The development of connective tissue hyperplasia in the lung is characteristic of interstitial lung diseases, in particular, pneumofibrosis (syn. pneumosclerosis) and idiopathic fibrosing alveolitis (syn. idiopathic pulmonary fibrosis) [1, 3, 12]. Analysis of patients with COVID-19 upon hospital discharge indicates a high frequency of lung function impairment due to fibrosis [4]. In 47% of patients, gas transfer disorders are observed, and in 25%, a decrease in total lung capacity is determined [2].

Only two drugs have proven efficacy in the treatment of IPF: pirfenidone and nintedanib [3]. These drugs have a primary indication of idiopathic pulmonary fibrosis; they are known to have a number of gastrointestinal side effects and adverse effects on the liver, and furthermore, the long-term results of this treatment have been insufficiently studied.

However, both drugs belong to the group of expensive orphan drugs, which makes them largely inaccessible for widespread use among the population.

The drug Longidaza® (international nonproprietary name [INN]: bovine hyaluronidase azoximer), lyophilisate for the preparation of solution for injection, 3000 IU, manufactured by NPO Petrovax Pharm LLC, due to its hyaluronidase activity [8], acts at various stages of the pathological process (both in the acute inflammation phase and against the background of pronounced fibrosis). This explains its antifibrotic property, which is manifested not only in the attenuation of fibrosis progression with early treatment initiation, but also in the regression of formed granulomatous nodules [10, 11]. Biochemical, histological, and electron microscopy studies have proven that Longidaza at doses up to 500 IU/kg administered once weekly does not damage normal connective tissue, but rather causes destruction of connective tissue altered in composition and structure in the area of fibrosis; it is characterized by safety and sufficient clinical experience in use for fibrosis of other localizations and etiologies [5, 6]. Thus, the drug is effective both at the stage of prevention and treatment of early development of the pneumofibrotic process, and at the stage of formed fibrosis in lung tissue [7, 9].

2. Study Objective

To compare outcomes in patients with pulmonary manifestations following complicated COVID-19 between two groups: a group of patients who, in routine clinical practice and in accordance with the prescribing information, received the drug Longidaza® (bovine hyaluronidase azoximer), lyophilisate for solution for injection, 3000 IU, for the treatment or prevention of post-inflammatory pulmonary fibrosis and intersti-

tial lung diseases; and a group of patients who underwent follow-up observation without receiving Longidaza®.

3. Materials and Methods

A single-center, open-label, prospective cohort study of the efficacy and safety of the drug Longidaza®, lyophilisate for the preparation of solution for injection, 3000 IU, for the treatment of patients with pulmonary manifestations following complicated COVID-19.

Population: Patients over 18 years of age with pulmonary manifestations following complicated COVID-19 who, in routine clinical practice, were either prescribed the drug Longidaza®, lyophilisate for the preparation of solution for injection, 3000 IU (hereinafter referred to as Longidaza®), or underwent follow-up observation without receiving active therapy.

Group 1 (Longidaza®): patients receiving the drug Longidaza®

Group 2 (follow-up observation): patients not receiving active therapy

Study Period: August 2023 – December 2023

Total Number of Patients Enrolled in the Study: 60 (30 patients in each group)

Inclusion Criteria:

- 1) Patients with pulmonary manifestations following complicated COVID-19 who initiated outpatient treatment/follow-up no later than two months after hospital discharge
- 2) Patient age over 18 years
- 3) Patients who, in routine clinical practice in accordance with the Summary of Product Characteristics (SmPC), prior to enrollment in the study, were prescribed intramuscular treatment with Longidaza® at a dose of 3000 IU as one injection every 5 days for a total course of 15 injections, or follow-up observation without active therapy
- 4) Patient has not participated in other drug clinical trials within 1 month prior to Visit 1
- 5) Patient or the patient's guardian agrees to participate in the trial and signs the informed consent form
- 6) Understands and agrees to comply with the scheduled procedures
- 7) Women of childbearing potential must agree to use at least one method of contraception until completion of study participation

Non-inclusion Criteria:

Patients cannot be included in the study if they meet any of the following non-inclusion criteria:

- 1) Women during pregnancy and lactation, and women planning to become pregnant during the study period.
- 2) Severe underlying diseases such as severe heart failure

(NYHA class IV), severe liver and kidney diseases, severe bronchial asthma, severe COPD, bronchiectasis, bullous pulmonary emphysema, and previously diagnosed interstitial lung diseases, neurological diseases, tumors, etc.

- 3) A history of chronic respiratory diseases (interstitial lung diseases, chronic obstructive pulmonary disease, bronchial asthma, bronchiectasis, disseminated tuberculosis, lung cancer).
- 4) Clinical signs or medical history data indicating the presence of diseases which, in the opinion of the investigator, could lead to restrictive changes in respiratory function (severe kyphoscoliosis, pleural effusion, neuromuscular diseases), morbid obesity, etc.
- 5) Dyspnea of any other etiology: thyrotoxicosis, anemia (hemoglobin less than 100 g/L), morbid obesity (BMI \geq 40 kg/m²), metabolic acidosis, neuromuscular diseases according to medical history or screening examination.
- 6) Presence of an acute infectious process of any etiology and localization.
- 7) Long-term bed rest, regardless of its cause.
- 8) Increased individual sensitivity to the components of the study drug.
- 9) Pathological conditions that make the patient's participation in the study impossible (as determined by the investigator).
- 10) Medication history which, in the investigator's opinion, precludes the patient's inclusion in the study.
- 11) Complicated allergy history which, in the investigator's opinion, precludes the patient's inclusion in the study.
- 12) Use of other enzyme drugs and drugs that suppress pulmonary fibrosis (nintedanib, pirfenidone, azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, rituximab, cyclophosphamide, or oral glucocorticoids (at a dose of more than 20 mg per day)) less than 4 weeks prior to Visit 1.
- 13) Use of furosemide, benzodiazepines, phenytoin, as well as maximum permissible daily doses of: salicylates, cortisone, ACTH, estrogens, and antihistamines.

Patients are discontinued from the study in the following cases:

- 1) The investigator decides that the patient must be withdrawn in the patient's best interests.
- 2) Withdrawal of informed consent (patient's unwillingness to continue participation in the study).
- 3) Major deviation from the study protocol.
- 4) Individual intolerance to the study drugs that developed during the period of drug administration.
- 5) Development of an AE/SAE which, in the investigator's opinion, could have a detrimental effect on the patient's health or a significant impact on the procedures of this study.
- 6) Patient fails to comply with the rules of participation in the study.
- 7) Erroneous enrollment.

- 8) Patient receives/requires additional treatment that could affect the study outcome or patient safety.
- 9) Other conditions or events which, in the investigator's opinion, necessitate the patient's exclusion from the study.

Informed consent for examination and treatment was obtained from all patients enrolled in the study.

Two groups of patients were formed: the main group (n=30), whose treatment included bovine hyaluronidase azoximer, and the follow-up observation group (n=30). Patients in the main group received Longidaza 3000 IU intramuscularly once every 5 days for a course of 15 injections.

VISIT 1 (DAY 1)

- 1) Collection of demographic data;
- 2) Anthropometric data (height, weight);
- 3) Collection of medical history;
- 4) Collection of complaints (weakness, fatigue, dry cough, productive cough, dyspnea on exertion, dyspnea at rest, feeling of chest congestion, dizziness, myalgia, headaches, anxiety, palpitations, other);
- 5) Assessment of prior and concomitant therapy;
- 6) Assessment of vital signs (body temperature, blood pressure [BP], heart rate [HR], respiratory rate [RR]);
- 7) Physical examination according to routine clinical practice;
- 8) Pulse oximetry (SpO₂);
- 9) Spirometry (FVC, FEV₁, FEV₁/FVC assessment);
- 10) Assessment of dyspnea severity using the mMRC scale;
- 11) Determination of HABP level;
- 12) Determination of KL-6 marker level;
- 13) Blood test parameters (lymphocytes, C-reactive protein, D-dimer, fibrinogen).

VISIT 2 (DAY 71 \pm 2, WEEK 10)

- 1) Collection of complaints (weakness, fatigue, dry cough, productive cough, dyspnea on exertion, dyspnea at rest, feeling of chest congestion, dizziness, myalgia, headaches, anxiety, palpitations, other);
- 2) Assessment of concomitant therapy;
- 3) Assessment of vital signs (body temperature, blood pressure [BP], heart rate [HR], respiratory rate [RR]);
- 4) Physical examination according to routine clinical practice;
- 5) Spirometry (FVC, FEV₁, FEV₁/FVC assessment);
- 6) Pulse oximetry (SpO₂);
- 7) Assessment of dyspnea severity using the mMRC scale;
- 8) Determination of HABP level;
- 9) Determination of KL-6 level;
- 10) Blood test parameters (lymphocytes, C-reactive protein, D-dimer).

PRIMARY EFFICACY PARAMETER

1. Change in FVC (% predicted) in the Longidaza group compared to the follow-up observation group after 10 weeks (day 71) relative to baseline values.

SECONDARY EFFICACY PARAMETERS

2. Change in FEV₁ (mL) in the Longidaza group compared

to the follow-up observation group after 10 weeks (day 71) relative to baseline values.

3. Change in FEV₁/FVC (Tiffeneau index,%) in the Longidaza group compared to the follow-up observation group after 10 weeks (day 71) relative to baseline values.

4. Change in dyspnea severity according to the mMRC scale (score) in the Longidaza group compared to the follow-up observation group after 10 weeks (day 71) relative to baseline values.

5. Change in HABP level (ng/mL) relative to baseline after 10 weeks in the Longidaza group compared to the follow-up observation group.

6. Change in KL-6 level (ng/mL) relative to baseline after 10 weeks in the Longidaza group compared to the follow-up observation group.

7. Change in resting capillary blood SpO₂ (%) relative to baseline after 10 weeks (day 71) in the Longidaza® group compared to the follow-up observation group.

8. Change in blood test parameters (lymphocytes, C-reactive protein, D-dimer, fibrinogen) after 10 weeks (day 71) in the Longidaza group compared to the follow-up observation group.

4. Statistical Analysis

The Stata 14.0 software package (Stata Corp, USA) was used for statistical analysis.

A p-value < 0.05 was considered the level of statistical significance. P-values are reported to three decimal places.

Quantitative parameters are described using the number of observations (N), mean, standard deviation (SD), 95% confidence interval (CI) for the mean, median (Me), minimum (Min), and maximum (Max) values. Qualitative parameters are presented as absolute number of observations, percentages, and two-sided 95% CIs.

The choice of criteria for comparing patients based on parameter values was determined by the parameter type. The Mann-Whitney test was used for quantitative parameters.

The primary analysis population was the intention-to-treat population of all patients enrolled in the study.

The study population included all patients.

5. Clinical Characteristics of Patients and Results

The mean age of patients enrolled in the study was 59.8±15.2 years in the Longidaza group and 56.06±13.7 years in the observation group. Males accounted for 23% in the Longidaza group, females 77%. In the observation group, males accounted for 37%, females 63%.

Among the concomitant diseases in patients of both groups, hypertension and coronary heart disease were noted.

Patients reported complaints of dry cough with difficult-to-clear sputum in 100% of cases, dizziness, dyspnea on exertion

(100% of cases), weakness and headaches (100% of cases).

At the first visit, the levels of leukocytes, erythrocytes, and hematocrit were within normal limits in both groups.

At the first visit in the Longidaza group, the C-reactive protein (CRP) level was 5.85±14.2 mg/L, in the observation group - 3.67±7.3 mg/L.

At the first visit in the group receiving Longidaza, the KL-6 level was 346.85±520.11 U/mL, in the observation group - 283.48±312.87 U/mL.

The leukocyte count and ESR in both groups upon repeated examination remained within normal limits, with no significant differences.

C-reactive protein levels also decreased over time in both groups, reaching 3.66 ± 3.84 mg/L and 1.24±0.7 mg/L in the main group and observation group, respectively, which is more than two times lower than the baseline level in both groups.

Blood oxygen saturation during the follow-up period remained normal in most patients, not falling below 96%.

In the early convalescent period, parameters in both groups increased, although they remained within the reference range, but in the group receiving Longidaza they were statistically significantly lower, which may likely indicate the antifibrotic activity of the drug.

All patients tolerated therapy including Longidaza well, with no side effects noted. No negative dynamics were observed in any patient during the therapy.

6. Discussion

The inclusion of Longidaza in therapy is effective both at the stage of prevention and treatment of early development of the pneumofibrotic process, and at the stage of formed fibrosis in lung tissue.

Thus, Longidaza, which possesses a number of positive effects justifying its administration to patients with developing pneumofibrotic process, as well as at the stage of formed fibrosis in lung tissue, can be considered a safe drug for patient therapy.

Abbreviations

RR	Respiratory Rate
BP	Blood Pressure
HR	Heart Rate
CRP	C-Reactiv Protein

Author Contributions

Mukhamadiyeva Lyaysan Ramilevna: Conceptualization, Resources

Mavzyutova Guzel Anvarovna: Conceptualization, Resources

Mirsaeva Gulchagra Khanifovna: Data curation, Methodology

Aleksandrovich Natalia Victorovna: Resources

Ibragimova Anna Aleksandrovna: Data curation, Methodology

Galieva Guzel Akhmetovna: Data curation, Methodology

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Mavziutova Alsu Airatovna: Investigation

Gayanova Maya Marsovna: Software

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Conflicts of Interest

There is no conflicts of interest.

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