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Efficacy and Safety of Bovhyaluronidase Azoximer (Longidaza) in Patients with Post-COVID-19 Syndrome: Results of the Open-label Prospective Controlled Comparative Multicenter Clinical Trial Dissolve

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1. Abstract

1.1. Introduction: Post-COVID-19 syndrome is a condition that develops in the patients recovered from COVID-19 resulting into the cumulative effects of dyspnoea and impaired lung function. Notably, higher concentrations of HA have been found in patients with respiratory inflammation and COVID-19. As, bovhyaluronidase azoximer (Longidaza®) catalyses the hydrolysis of HA, the treatment has the potential to lower HA concentrations and improve lung function in patients with post-COVID-19 syndrome.

1.2. Aims and Objectives: The DISSOLVE trial was undertaken at initial phase of the pandemic and aimed to study the efficacy and safety of bovhyaluronidase azoximer in patients with post-COVID symptoms.

1.3. Methodology: The study was an open-label, prospective, controlled, comparative, multicenter clinical trial (NCT04645368) conducted in 160 adult patients with post-COVID-19 syndrome. The Treatment group (n = 81) received bovhyaluronidase azoximer and the Control group (n = 79) was used as a dynamic observation group. Study parameters included physical examination, forced vital capacity (FVC), dyspnoea modified Medical Research Committee (mMRC) scale, 6-minute walking test (6MWT) and pulse oximetry that were collected on three visits: Day 1 (Baseline), Day 75, and Day 180.The number of patients with adverse events (AEs) and serious adverse events (SAEs) were recorded.

1.4. Results: Baseline characteristics were similar for the Treatment group and the Control group. In the Treatment group, residual pulmonary abnormalities decreased significantly after Visit 2 (Day 75) and Visit 3 (Day 180), additionally, forced vital capacity (FVC), pulse oximetry, functional exercise capacity of the Treatment group increased significantly from baseline to Day 75 and Day 180. mMRC dyspnoea score of the Treatment group significantly decreased over a 75-day period. Patients reported a favourable safety profile throughout the trial.

1.5. Conclusion: Patients with post-COVID syndrome may benefit from treatment with bovhyaluronidase azoximer, as indicated by patients displaying an improvement in their FVC, pulse oximetry (SpO(2)), functional exercise capacity and dyspnoea mMRC score.

2. Introduction

By February 2022, over 420 million people had been infected with coronavirus disease 2019 (COVID-19) and there had been over 5.87 million fatalities [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes pulmonary inflammation and progressive respiratory impairment. Though the majority of individuals fully recover from SARS-CoV-2 infection, symptoms persist in 10–20% of individuals. Mid- and long-term symptoms, i.e., symptoms that persist for more than 12 weeks, are collectively known as post-COVID-19 condition or 'long COVID' [2,3]. Persistent dyspnoea is a common symptom of long COVID [4,5]. A recent study reported severe dyspnoea occurring in patients for 2 months after the initial COVID-19 infection [6]. Long COVID can cause significant impairment in lung function [7,8].

Hyaluronic acid (HA: also known as hyaluronan) is a key constituent of the pulmonary extracellular matrix (ECM). Degradation products of HA may play a role in the physiopathology of the respiratory system, and they have been detected at high levels in the respiratory secretions of patients with various forms of respiratory inflammation [9-13]. Importantly, the accumulation of HA in alveolar spaces has been linked to hypoxemia, respiratory failure in cases of severe COVID-19 [14]. and on the CT scan it look as "ground glass" pattern due to HA hygroscopic properties [15,16]. Human Identical Sequences (HIS) of SARS-CoV-2 can upregulate HA, which may contribute to the progression of COVID-19 [17] by enhancing of the cytokine storm and such event is known as "HA storm"[15].

However, the role of HA in the pathogenesis of COVID-19 has yet to be fully elucidated. Bovhyaluronidase azoximer (Longidaza®, NPO Petrovax Pharma LLC, Moscow, Russia) is a bovine hyaluronidase that is conjugated to azoximer bromide (Polyoxidonium®, NPO Petrovax Pharma LLC, Moscow, Russia), which increases enzymatic resistance in the presence of inhibitors and increased temperatures [18]. Bovhyaluronidase azoximer regulates the concentration of HA and retains the pharmacological properties of the azoximer bromide with chelating, antioxidant, anti-inflammatory and immunomodulating activity. Figure 1 illustrates the proposed mechanism of action of bovhyaluronidase azoximer. We postulated that bovhyaluronidase azoximer may improve respiratory symptoms in patients suffering the effects of long COVID by reducing the elevated levels of HA.

Herein, we present data from a comparative trial to study the efficacy and safety of bovhyaluronidase azoximer in patients with post-recovery respiratory impairment after COVID-19. Following bovhyaluronidase azoximer treatment, this study assessed objective indicators of pulmonary rehabilitation (e.g., FVC, pulse oximetry and exercise tolerance) and mMRC dyspnoea scale at 2.5 months and 6 months in patients with long-COVID. We determined if marked improvement in lung function corresponded with marked changes in residual pulmonary abnormalities using high-resolution computed tomography.

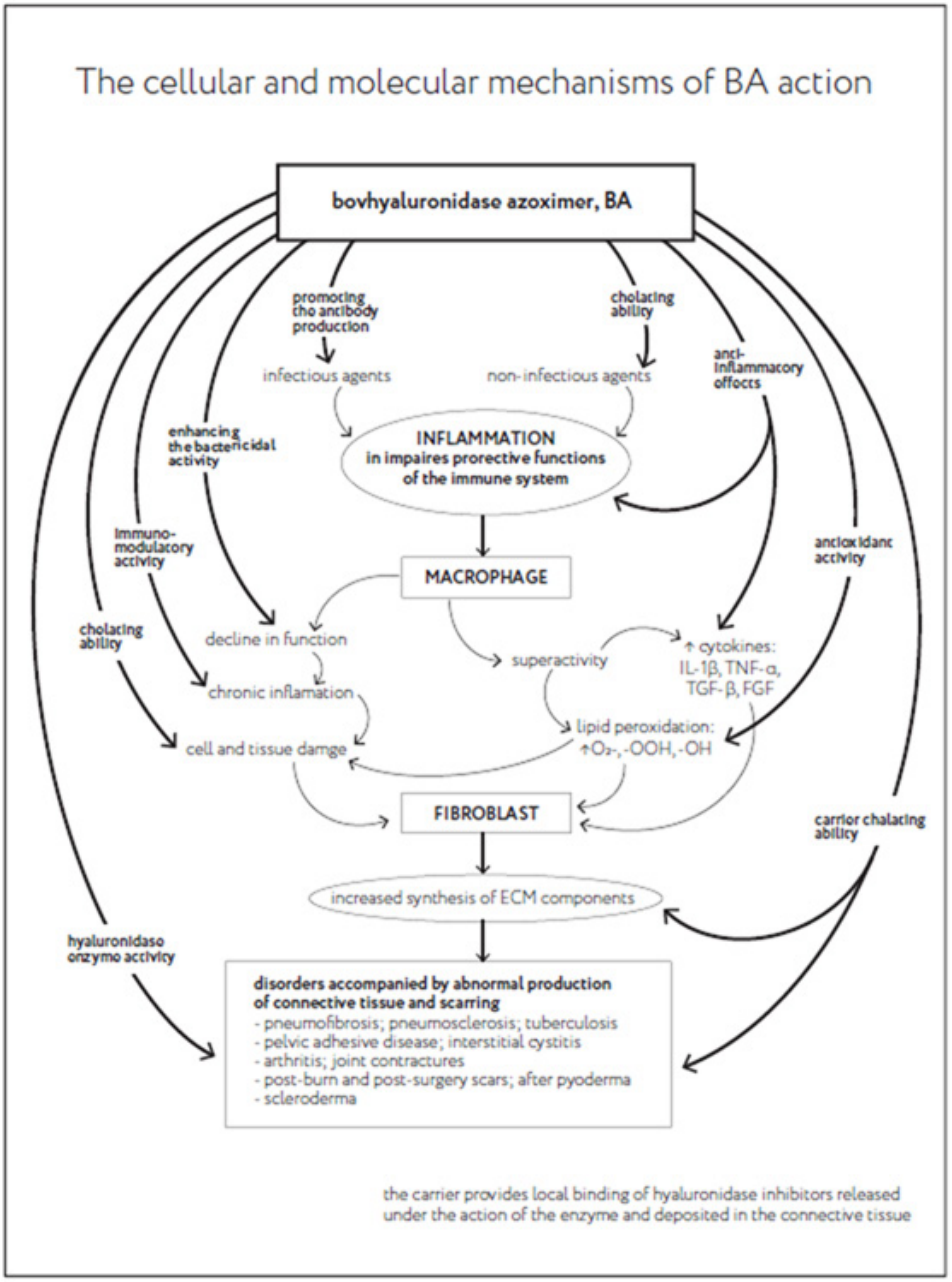

Figure 1: Proposed mechanism of action of bovhyaluronidase azoximer
(Adopted from: Nekrasov AV, Ivanova AS, Puchkova NG. Longidaza - a modern treatment approach to disorders, accompanied by abnormal production of connective tissue. Signature (1). 44-52. 2006)

3. Materials and Methods

3.1. Study Design

This was an open-label, prospective, controlled, comparative, multicenter clinical trial (NCT04645368) to evaluate the efficacy and safety of bovhyaluronidase axozimer (Longidaza®, lyophilized powder for solution for injection, 3000 IU) in patients with post-COVID-19 syndrome complicated by respiratory manifestations (Figure 2).

Patients >18 years with residual pulmonary changes, detected no later than 2 months after discharge from inpatient treatment, were eligible to participate in the study. The main non-inclusion criteria were the presence of severe underlying disease, such as severe heart failure, liver and kidney disease, severe bronchial asthma, or severe chronic obstructive pulmonary disorder.

The DISSOLVE trial evaluated the efficacy and safety of bovhyaluronidase azoximer in controlled conditions with the post-treatment follow-up period. The study was conducted during the initial phase of the COVID-19 pandemic as pulmonary fibrosis is a post-COVID condition. Antifibrotic properties of bovhyaluronidase azoximer was particularly confirmed in a clinical trial on the patients of cryptogenic fibrosing alveolitis with concurrent pneumofibrosis [19].

The objective of the study was to determine the dynamics of alleviating post-COVID pulmonary complications using chest high-res-

olution computed tomography (HRCT) scans in patients after a course of bovhyaluronidase azoximer (2.5 months) in comparison with the Control group. The secondary objective of the study was to evaluate the other parameters of the efficacy and the safety of bovhyaluronidase azoximer in post-COVID-19 syndrome. Participation duration with follow-up period was 180 ± 6 days.

A total of 160 adult patients of either sex was enrolled in the trial at 13 study sites (Table 5). The Treatment group (n=81 patients) received bovhyaluronidase azoximer (3000 IU; intramuscularly) once every 5 days with a course of 15 injections and the Control group (n=79 patients) performed a dynamic observation alone. All the parameters were measured at Day 1, Day 75 and Day 180.

The first visit was undertaken on Day 1 and baseline characteristics were recorded. The second study visit, assessed at 75 ± 2 Day, corresponded to completing the course of therapy in the first study group. The third visit took place after the follow-up period at 180 ± 6 Day Figure 4.

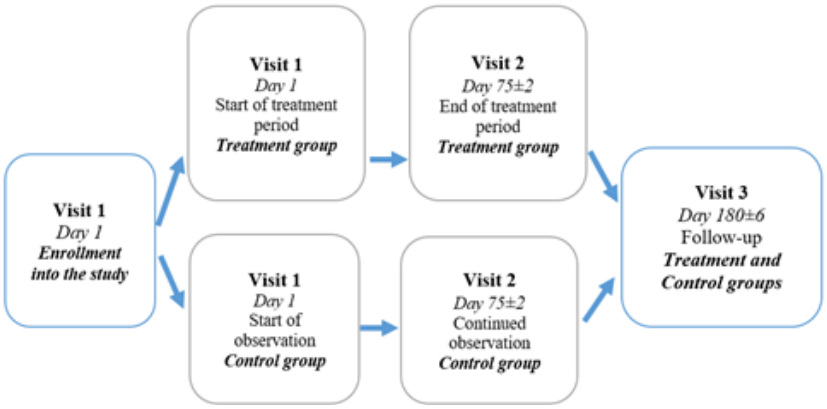

Figure 2: Study flow diagram

3.2. Patients

Patients were required to be over 18 years old with pulmonary manifestations detected no later than 2 months after hospital discharge owing to prolonged COVID-19 infection. Patients were required to provide negative polymerase chain reaction (PCR) test results for SARS-CoV-2 infection on two occasions in respiratory tract samples.

3.3. Assessments

3.3.1. Vital signs assessment and physical examination: Vital signs were recorded (heart rate, normalized pulse volume, blood pressure, body temperature) after resting, and physical examination were performed. The physical examination evaluated the mucous membranes and skin, palpation of lymph nodes, assessment of the musculoskeletal system and auscultation of the heart, lungs and other organs.

3.4. Instrumental methods

Instrumental analyses including HRCT of lungs and spirometry were performed. Residual pulmonary abnormalities were recorded as percentage of lung volume with HRCT-detected lesions. Forced vital capacity (FVC) was assessed by utilizing a spirometry measurement which was undertaken with ATS/ERS 2005 guidelines [20].

3.5. mMRC dyspnoea scale

Assessment of the dyspnoea using the mMRC dyspnoea scale [21] was applied at Days 1, 75 and 180 and scored as follows: 0, shortness of breath occurs only during heavy physical exertion; 1, shortness of breath occurs when walking briskly on level ground or when climbing a slight elevation; 2, due to shortness of breath, patients walk slower than their peers or walking at their own pace on flat terrain, must stop to catch their breath; 3, after walking approximately 100 m or after a few minutes of walking on level ground, the patient must stop to catch their breath; 4, shortness of breath does not allow the patient to leave the house and appears when dressing or undressing [22].

3.6. Six-minute walk test

The distance walked in 6 min along a long straight corridor (≥30 m) at the patient's own pace was measured to evaluate functional physical capacity.

3.7. Finger pulse oximetry

The finger pulse oximetry was carried out before performing the 6MWT to determine the peripheral capillary oxygen saturation (SpO(2)), which was then recorded as the change from the baseline.

3.8. Statistical methods

Demographic and other initial characteristics were tested using analysis of variance for quantitative indicators and using the Chi-square test ($\chi 2$) for qualitative parameters. Intergroup comparison of all endpoints, which represented changes from initial values, were performed using analysis of covariance (ANCOVA) with Treatment group as a factor and initial parameter value as a continuous covariate. Statistical tests were performed two-tailed with a 5% significance level.

3.9. Safety

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA). The number (proportion) of patients with adverse events (AEs)/serious adverse events (SAEs) and the

number of AEs/SAEs were recorded by organ system class and preferred term, and in relation to study therapy and severity, by treatment group. In this case, each patient was counted once with the aim to study therapy and the severity of the maximum expression.

4. Results

4.1. Demographic details and baseline characteristics

Total number of patients enrolled in the study was 160 (Treatment group=81 patients; Control group=79 patients; Table 1). The ratio of females to males was approximately 2:1 (female=103 patients; males=57 patients) and the mean age of the patients (Treatment group=54.60 ±10.02 years; Control group =54.70 ± 12.58 years) and body mass index (Treatment group=28.70 ± 5.33 kg/m^2; Control group= 28.90 ± 5.08 kg/m^2) were similar across the groups.

Baseline characteristics of patients in both groups were also similar (Table 1). Forced vital capacity measurements were 88.8 ± 20.50 % prediction in the Treatment group, and 92.1 ± 17.55 % prediction in the Control group. The baseline dyspnoea score, according to mMRC dyspnoea scale, was 1.3 ± 0.97 in the Treatment group and 1.1 ± 0.78 in the Control group. The baseline 6MWT result was 388.9 ± 117.53 m in Treatment group and 430.16 ± 99.42 m in the Control group. The pulse oximetry (Sp(O)2) was 96.7 ± 1.45% in the Treatment group and 97.0 ± 1.10% in the Control group.

Table 1: Demographic details and baseline characteristics

Characteristics	Treatment group	Control group
Age, years	54.6 ± 10.02	54.7 ± 12.58
Female	66.70%	62.00%
Male	33.30%	38.00%
Body mass index, kg/m^2	28.7 ± 5.33	28.9 ± 5.08
FVC, % pred.	87.9 ± 21.03	92.1 ± 17.55
Dyspnoea (according to mMRC scale), score	1.3 ± 0.97	1.1 ± 0.78
6-minutes walking test result, m	388.9 ± 117.53	430.16 ± 99.42
Pulse oximetry SpO_2, %	96.7 ± 1.45	97.0 ± 1.10
Time from COVID-19 onset to Visit 1, months	1.5 ± 0.77	1.5 ± 0.89

Data are presented as mean ± SE, 95CI

4.2. Lung Function

We determined the FVC changes from the baseline within each group. Most patients in the Treatment group showed an improvement > 5% in FVC at Day 75 compared with baseline (58.4% of patients), which was greater than in the Control group (39.1%; Table 3). The percentage of patients experienced 5–10% improvement of their FVC was 13.8% in the Treatment group compared to 20.3% of the Control group, but the percentage of patients that showed over 10% improvement of their FVC was greater in the Treatment group (44.6%) compared to the Control group (18.8%). Approximately half of the patients in the Control group experienced no improvement (46.4%) compared with approximately 30% in the Treatment group (29.2%). The number of patients experienced >5% worsening of their FVC appears to be similar in the Treatment group (12.3%) and the Control group (14.4%).

Next, we investigated relative changes in lung function between the groups (Table 2). At Day 75, the rate of FVC changes was significantly higher in the Treatment group (9.02 ± 1.404%) than in the Control group (5.05 ± 1.383%; p = 0.046). At Day 180, FVC continued to be significantly higher in the Treatment group (9.97 ± 1.443%) compared with the Control group (4.48 ± 1.422%; p = 0.008).

Table 2: Relative changes in FVC

Groups	Treatment (%) Mean ± SE 95% CI	Control (%) Mean ± SE 95% CI	P-value
Day 75	9.024 ± 1.404*	5.046 ± 1.383*	
	6.248, 11.800	2.310, 7.781	0.046
Day 180	9.970 ± 1.443**	4.477 ± 1.422**	
	7.124, 12.833	1.664, 7.290	0.008

Data are presented as mean ± SE

FVC: Forced vital capacity

Table 3: Categorical analysis of FVC changes at Day 75 from baseline, % patients

Change in FVC	Treatment	Control
Worsening > 10%	7.70%	7.20%
Worsening >5-10%	4.60%	7.20%
No improvement (worsening ⩽ 5% - improvement ⩽ 5%)	29.20%	46.40%
Improvement >5 – 10%	13.80%	20.30%
Improvement over 10%	44.60%	18.80%
Total	100%	100%

4.3. Pulse oximetry

As shown in Table 4, mean increases from baseline in pulse oximetry SpO_2 were greater for patients who received bovhyaluronidase azoximer than no treatment (Day 75: 1.067 ± 0.092%, 0.573 ± 0.092%, respectively; $p < 0.001$. Day 180: 0.938 ± 0.170%, 0.50 ± 0.170%, respectively; $p = 0.081$.). The difference was statistically significant compared to the Control group at Day 75.

4.4. Functional exercise capacity

At Day 75, the percentage of relative changes in functional capacity as measured by 6MWT increased significantly in the Treatment group (27.76 ± 3.753 %) compared with the Control group (17.14 ± 3.723 %; $p = 0.049$; Table 4). A statistically significant increase occurred also at Day 180 in the Treatment group (30.58 ± 4.104 %) compared with the Control group (17.93 ± 4.070 %; $p = 0.032$).

4.5. mMRC dyspnoea score

Significant difference in mMRC dyspnoea score were observed between the Treatment group (-0.84 ± 0.058) and the Control group (-0.58 ± 0.058; $p = 0.002$) at Day 75. At Day 180, improvements in mMRC dyspnoea score appear to be similar in both groups (-1.13 ± 0.123 and -0.87 ± 0.123, $p = 0.142$ for Treatment and Control group respectively).

Differences between the groups achieved statistical significance at Day 75. Decreases in mMRC dyspnoea score were seen in more patients who received bovhyaluronidase azoximer (Figure 3). Most notably, the proportion of patients who showed no change in the Control group was approximately double of those in the Treatment group (52.2% versus 25.0%).

Table 4: Results of study parameters assessment

Groups	Treatment Mean ± SE 95% CI	Control Mean ± SE 95% CI	p-value
(a) Relative changes in pulse oximetry (%)			
Day 75	1.067 ± 0.092*** 0.884, 1.249	0.573 ± 0.092*** 0.392, 0.754	<0.001
Day 180	0.938 ± 0.170 0.594, 1.282	0.505 ± 0.170 0.161, 0.849	0.081
(b) Relative changes in functional exercise (%)			
Day 75	27.757 ± 3.753* 20.325, 35.188	17.143 ± 3.723* 9.773, 24.514	0.049
Day 180	30.576 ± 4.104 22.450, 38.702*	17.928 ± 4.070 9.869, 25.987*	0.032
(c) Changes in mMRC dyspnoea score			
Day 75	-0.836 ± 0.058** -0.951, -0.722	-0.582 ± 0.058** -0.695, -0.468	0.002
Day 180	-1.131 ± 0.123 -1.379, -0.883	-0.869 ± 0.123 -1.117, -0.621	0.142
(e) Relative changes in total lung volume with HRCT lesions (%)			
Day 75	-8.389 ± 1.024* -10.427, -6.352	-11.912 ± 1.086* -14.073, -9.751	0.021
Day 180	-13.466 ± 0.186 -13.843, -13.089	-13.754 ± 0.221 -14.202, -13.305	0.327

CI = confidence interval, mMRC: Modified Medical Research Council, SE = standard error

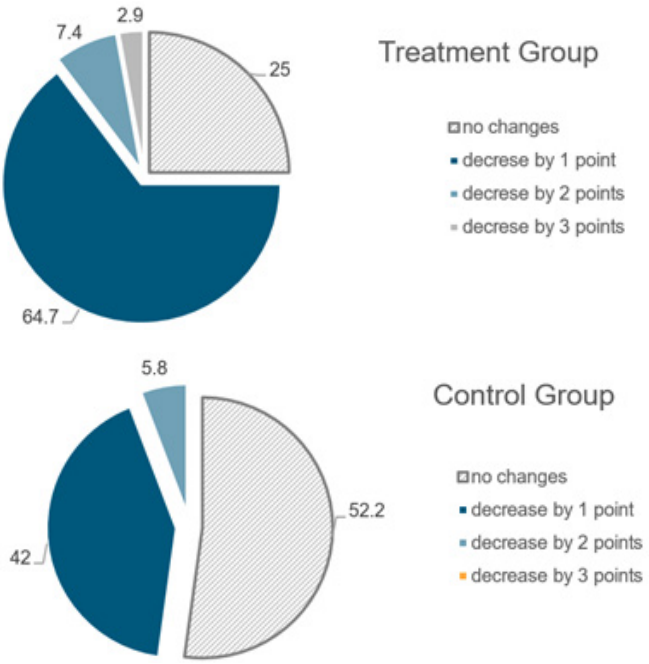

Figure 3: Categorical analysis of mMRC score changes at Day 75 from baseline, % patients

Table 5: Study sites and Principal investigators

	City	Trial site	Principal investigator
1	Saint Petersburg	"Saint-Petersburg Research Institute of Phthisiopulmonology",	**Petr K. Yablonsky,** Doctor of Medical Sciences, Professor, Saint-Petersburg Research Institute of Phthisiopulmonology,
		Ministry of Health of Russian Federation	Ministry of Health of Russian Federation
2	Saint Petersburg	"City Consultative and Diagnostic Center No.1"	**Tamara V. Rubanik,** PhD, MD
3	Volgograd	"Volgograd State Medical University", Ministry of Health of Russian Federation	**Olga A. Chernyavskaya,** PhD, MD, Department for Infectious Diseases with Epidemiology, Tropical Medicine, Volgograd State Medical University, Ministry of Health of Russian Federation
4	Volgograd	"City Clinical Hospital No. 4"	**Vladimir V. Naumov,** PhD, MD
5	Moscow	"City Polyclinic No. 180", Moscow Healthcare Department	**Ludmila I. Korneva**, MD
6	Novosibirsk	"State Novosibirsk Regional Clinical Hospital"	**Lyubov' M. Kudelya,** Doctor of Medical Sciences, Professor, Department of Internal Diseases named after academician L.D. Sidorova, Novosibirsk State Medical University, Ministry of Health of Russian Federation
7	Yekaterinburg	"Central City Clinical Hospital No. 6"	**Anna Y. Petukhova,** PhD, MD
8	Perm	Medical Center "Philosophy of Beauty and Health", Ltd.	**Olga V. Masalkina,** PhD, MD
9	Chelyabinsk	"City Clinical Hospital No. 8"	**Yulia V. Argamakova,** MD
10	Chelyabinsk	"Regional Clinical Hospital No. 3"	**Galina L. Ignatova,** Doctor of Medical Sciences, Professor, Department of Therapy, Institute of Postgraduate Physician Training, South Ural State Medical University, Ministry of Health of Russian Federation
11	Krasnoyarsk	"Research Institute for Medical Problems in the North ", Siberian Branch of the Russian Academy of Sciences	**Alexander G. Borisov,** PhD, MD, Department of Infectious Diseases and Epidemiology, Krasnoyarsk State Medical University named after V. F. Voino-Yasenetsky
12	Astrakhan	"Astrakhan State Medical University", Ministry of Health of Russian Federation	**Tatyana R. Kasyanova,** Doctor of Medical Sciences, Department of Faculty Therapy and occupational diseases with a course of post-graduate education, Astrakhan State Medical University, Ministry of Health of Russian Federation
13	Moscow	"City Clinical Hospital D.D Pletneva", Moscow Healthcare Department	**Angelina K. Suleymanova,** MD, PhD, Department of Hospital Internal Medicine, Pediatric Faculty, Federal Russian State National Research Medical University named after N.I. Pirogov, Ministry of Health of Russian Federation

4.6. Residual pulmonary abnormalities

High resolution computed tomography revealed typical patterns of ground glass opacity and consolidation in patients in both groups. We use the term 'pulmonary abnormalities' to describe the total volume of these HRCT lesions. At Day 180, mean decreases in the total volume of pulmonary abnormalities appear to be similar up to almost full-volume resolution for the two groups (Treatment: -13.47 ± 0.186%, Control: -13.75 ± 0.221%, respectively; p = 0.327), although a significantly greater decrease was observed at Day 75 for the Control group (-11.91 ± 1.086%) compared with the Treatment group (-8.39 ± 1.024%; p = 0.021).

4.7. Safety and tolerability

There were no patients that discontinued treatment and no serious adverse events were reported. Early-onset local injection reactions were the most common adverse events experienced by patients in the trial. In the Treatment group, one patient experienced pruritus with local reaction at the injection site, and one patient developed local reaction. Another patient developed pruritus after the first injection, and the patient was treated with antihistamines with completely recovered. Therefore, therapy was not suspended. One patient from each group developed bronchitis. There was one case of rhinitis in the Treatment group, one case of enteric fever and one case of chest injury in the Control group.

5. Discussion

Complications of post-COVID-19 syndrome include dyspnoea and impairment of lung function, both of which can be vastly affect an individual's quality of life [23]. Here we investigated the effect of the treatment with bovhyaluronidase azoximer, which breakdowns HA, had on lung function in patients suffering long-COVID. We found that lung function was markedly improved in these patients over time.

Hyaluronic acid is a glycosaminoglycan that is a key component of the pulmonary ECM and has been shown contribute towards tissue viscoelasticity [24-28]. Degradation products of HA have been shown to be higher in the respiratory secretions of patients with various forms of respiratory inflammation [9-13]. A number of studies suggest that HA and its degradation products may underlie the physiopathology of the respiratory system. Accumulation of HA in alveolar spaces has been linked to hypoxemia and respiratory failure in severe COVID-19 [14]. Another study found higher levels of HA compared to normal lungs in the alveolar spaces and thickened perialveolar interstitium in lungs of deceased COVID-19 patients, compared with normal lungs [29]. Abnormal metabolism of HA along with other inflammatory factors may lead to complications such as acute respiratory distress syndrome (ARDS) and pulmonary edema in COVID-19 patients [30]. Furthermore, excessive HA deposits stimulate fibroblasts proliferation, thereby prompting the synthesis of new mucopolysaccharides and the conversion of fibroblasts to myofibroblasts, indicators of a reactive proinflammatory stroma [31].

Post-COVID infection can reduce gas exchange efficiency and decrease FVC values [32,33]. We found that targeting HA with a hyaluronidase conjugated to azoximer bromide improved pulmonary function in patients with post-COVID infection, as observed by marked improvements in their FVC, pulse oximetry, and mMRC dysponea scale. We investigated if the improvements in lung function could be observed by computed tomography. However, we found no significant differences in the improvement of pulmonary abnormalities between the Treatment and Control groups. Although bovhyaluronidase azoximer alleviated dyspnoea in patients with post-COVID-19 syndrome, it was not driving drastic changes of the HRCT patterns observed in DISSOLVE trial sample. While the activity of hyaluronidase may reduce the levels of HA, it is also possible that azoximer bromide, to which the hyaluronidase is conjugated, may also be active in modulating the immune system and further alleviating respiratory symptoms. Overall, data indicates that bovhyaluronidase azoximer plays an anti-inflammatory role (Grivtsova et al., 2021).

In our study, bovhyaluronidase azoximer administration benefited patients with post-COVID-19 syndrome. However, HA levels were not determined in respiratory samples of patients, a limitation of this study. The molecular mechanism by which bovhyaluronidase azoximer alleviates the respiratory symptoms of post-COVID-19 syndrome therefore has yet to be elucidated. Further work is needed to determine the effect of bovhyaluronidase azoximer on levels of HA and other molecular markers.

In conclusion, this study has demonstrated a role for bovhyaluronidase azoximer in improving lung function in patients with post-COVID syndrome. These data suggest that bovhyaluronidase azoximer is a viable treatment option to help manage post-COVID-19 syndrome.

6. Conclusion

The DISSOLVE trial aimed to evaluate the efficacy and safety of bovhyaluronidase azoximer in post-COVID-19 syndrome. Bovhyaluronidase azoximer demonstrated significant increase in lung function measured by FVC as well as significant improvements in mMRC dyspnoea scale, pulse oximetry and functional exercise capacity at Day 75 and over the study period of 180 days. Only a minimal number of subjects reported mild to moderate adverse events, indicating a favourable safety profile for bovhyaluronidase azoximer.

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