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Nebulized myo-inositol increases mucus clearance in patients with Bronchiectasis: a retrospective study

R. VERNA[1], S. PROIETTI[2], A. SPIGA[3], V. UNFER[4,5], M. BIZZARRI[1,5,6]

[1]Systems Biology Group Lab, Sapienza University, Rome, Italy
[2]R&D Dept. of Lo.Li Pharma srl, Rome, Italy
[3]Azienda per la Tutela della Salute (ATS), Cagliari, Italy
[4]UniCamillus - Saint Camillus International University of Health and Medical Sciences, Rome, Italy
[5]The Experts Group on Inositol in Basic and Clinical Research (EGOI), Rome, Italy
[6]Department of Experimental Medicine, Sapienza University, Rome, Italy

Abstract. – OBJECTIVE: This retrospective study aimed at ascertaining the clinical usefulness of nebulized myo-inositol in the management of patients affected by bronchiectasis.

PATIENTS AND METHODS: 19 patients, aged between 63 and 73 years old, with bronchiectasis, were treated for 15 days with nebulized myo-inositol or placebo. Lung functionality [forced expiratory volume in the 1st second (FEV1)], solid content of expectorate, and surfactant tension were analyzed.

RESULTS: All patients treated with nebulized myo-inositol had a significant decrease in the percentage of solid content in the expectorate (T0 7.9±2.8% *vs*. T1 5.2±2.7%; $p<0.001$) and surfactant tension (T0 81.5±6.9 mN/m *vs*. T1 77.4±7.2 mN/m; $p<0.001$). Among treated patients, these variations correlated with FEV1 (rs=- 0.79; $p<0.01$) and forced expiratory flow at 25-75% of FVC (FEF25-75%) (rs=-0.81; $p<0.01$) scores. Also, variation of surfactant tension correlated with FEV1 (rs= -0.74; $p<0.05$) score.

CONCLUSIONS: Nebulized myo-inositol increases lung functionality and mucus clearance in patients affected by bronchiectasis.

Key Words:
Nebulized myo-inositol, Bronchiectasis, Mucus clearance, Lung function, FEV1.

Introduction

Bronchiectasis is an abnormal, permanent, dilation of the bronchi, recognized as a major clinical problem since its first description by the French physician René Laennec in 1819[1]. Before the discovery of antibiotics, bronchiectasis was considered only a severe consequence of pneumonia and tuberculosis. Therefore, physicians estimated that after the broad diffusion of antibiotics, bronchiectasis would have disappeared. However, the number of patients has risen inexorably in the past decades and today, bronchiectasis represents an increasing burden on healthcare systems worldwide[2,3]. The estimates of the bronchiectasis economic burden are like the actual expenses caused by chronic obstructive pulmonary disease (COPD), the latter representing one of the three most common causes of death worldwide[4]. The economic impact of bronchiectasis depends on the severity of the disease, the hospitalizations, the need for intensive care, and the use of inhaled antibiotics[5]. Its prevalence increases with age, and ranges from 53 to 566 cases per 100,000 inhabitants depending on different estimates[6,7]. The main symptom of bronchiectasis is excess mucus production, which can make the lungs more vulnerable to infection, and increase the possibility of developing other symptoms such as cough, chest discomfort, and weight loss[8]. The literature indicates the involvement in the complex pathogenesis of bronchiectasis of an impaired mucociliary clearance (MCC), the process in which airway mucus and substances trapped within move out of the lungs[8].

The progression of the disease is linked to failed mucus clearance, airway bacterial colonization, airway inflammation, and airway structural damage. Therefore, the goals of therapy should be to stop or reverse these processes and thereby "break the cycle", thus reducing exacerbations. In this regard, despite current approaches, European registry data[6] showed that approximately 50% of European bronchiectasis patients have two or

Corresponding Author: Mariano Bizzarri, MD; e-mail: mariano.bizzarri@uniroma1.it

more exacerbations per year, and one-third require at least one hospitalization per year. Among the treatments used to counteract this disease, inhaled antibiotics are among the most diffused. They are used to reduce a bacterial load, which increases the local and systemic inflammatory response, thus worsening symptoms of the disease and increasing the rate of exacerbations. Therefore, inhaled antibiotics are only used in patients with confirmed bacterial airway infection[9]. Also, inhaled corticosteroids and bronchodilators, which have an established role in managing asthma and COPD[10,11] have a controversial role in bronchiectasis. An updated Cochrane review[11] of seven randomized controlled trials in adults with bronchiectasis found that inhaled corticosteroids did not improve lung function or exacerbation frequency. Inhaled mucolytics and hyperosmolar agents are adjuvant therapies for airway clearance[12]. Although mucolytics, such as N-acetylcysteine and carbocisteine, are used widely in clinical practice, there is no published evidence of benefit from these agents for the management of bronchiectasis[13].

In this scenario, myo-inositol (myo-Ins) has been studied[14] as a possible "non-pharmacological" adjuvant therapy to counteract airway diseases, due to its efficacy in relieving symptoms and respiratory disease complications. Moreover, thanks to its osmolar property, myo-Ins can recruit water, thus increasing mucus hydration and clearance. Myo-Ins also promotes the maturation of pulmonary surfactant phospholipids, phosphatidylcholine, and phosphatidylinositol (PI)[15,16]. Namely, the synthesis of PI in type II pneumocytes appears to depend on extracellular myo-Ins concentrations. In turn, surfactant enriched in myo-Ins content significantly improves the mechanical properties of alveoli. Myo-Ins and its phosphate derivatives recruit organic osmolytes and water within the alveolar space and foster the reconstitution of a biofilm layer (featured by a hydrophobic tail and a hydrophilic head) at the interface, thereby decreasing surface tension and antagonizing collapsing forces[17].

Finally, myo-Ins supplementation significantly reduces short-term adverse neonatal outcomes and the incidence of bronchi-pulmonary dysplasia[18].

Therefore, the aim of this retrospective study was to highlight the efficacy of nebulized myo-Ins in counteracting mucus-impaired clearance in patients with bronchiectasis, thus improving their lung function.

Patients and Methods

Patients

This is a retrospective, observational study of spirometry in which we collected data from 19 patients aged between 63 and 73 years old (16 men and 3 women), under treatment at AGUNCO. Informed consent was obtained from all individual participants. All retrospective data collected were de-identified prior to access by the authors. All patients were affected by bronchiectasis, they were not smokers, and they were not taking antibiotics. We compared retrospective data from (n=10) patients treated with nebulized myo-Ins (400 mg in 3 ml 0.9% saline) (Broncositol®, Farmares, Rome, Italy and distributed in Italy by Exipharma, Padova, Italy; Class IIb Medical Device) or (n=9) patients treated placebo (saline solution). Patients in both groups underwent a first 5-minute lasting treatment, after which we recorded FEV1 scores. Following the first 5-minute intervention, patients continued it twice a day for 15 days.

Lung Function

Briefly, we measured surface tension and performed spirometry at baseline and after two weeks of treatment. We also evaluated forced expiratory volume in the 1st second (FEV1), forced vital capacity (FVC), and the forced expiratory flow at 25-75% of FVC ($FEF_{25-75\%}$) The sputum analysis consisted of an analysis of the percentage of the solid content expelled from the patient's upper respiratory tract.

Statistical Analysis

Statistical analysis was performed using GraphPad Software 2018 (La Jolla, CA, USA). Paired *t*-test was performed to compare changes before and after treatments (T0 *vs.* T1). Unpaired *t*-test was performed to compare changes between placebo and myo-Ins. The level of statistical significance was set below p=0.05.

Correlation

To evaluate the relationship between parameters (solid content of expectorate and FEV1; solid content of expectorate and $FEF_{25-75\%}$; variation of surfactant tension and FEV1) the Spearman's rank correlation coefficient (rs) was assessed using GraphPad Software 2018 (La Jolla, CA, USA).

Table I. Forced expiratory volume in the 1st second (FEV1), forced vital capacity (FVC), and the forced expiratory flow at 25-75% of FVC ($FEF_{25-75\%}$).

	Mean values at baseline
FEV1%	86 ± 13
FEVI/FVC%	65 ± 6
$FEF_{25-75\%}$	63 ± 22

Results

We collected retrospective spirometry measurements of FEV1%, FEV1/FVC% and $FEF_{25-75\%}$ at the baseline for all patients. There were no differences between the two groups. Mean values are reported in Table I.

Initially, after receiving a placebo or nebulized myo-Ins for 5 minutes, patients performed spirometry. Although patients in both groups had a significant decrease in FEV1 values, nebulized myo-Ins stabilized FEV1 values compared with placebo (p<0.001) (Figure 1).

Patients also performed spirometry after 15 days. In patients treated with placebo, expectorate properties and surfactant tension did not change compared to baseline (data not shown), while in patients treated with nebulized myo-Ins, percentage of the solid content (T0 7.9±2.8 *vs*. T1 5.2±2.8; p<0.001) (Figure 2A), and surfactant tension (T0 81.5±6.9 mN/m *vs*. T1 77.4±7.2 mN/m; p<0.001) (Figure 2B) significantly decrease. Variation in the percentage of the solid content of expectorate correlated with FEV1 (rs=-0.79; p<0.01) and $FEF_{25-75\%}$ (rs=-0,81; p<0.01) scores. Also, variation of surfactant tension correlated with FEV1 (rs= -0.74; p<0.05) score.

Discussion

In this retrospective observational study, we collected data about the efficacy of nebulized myo-Ins in increasing mucus clearance in patients with bronchiectasis. At first, patients performed spirometry after receiving 5 minutes of placebo or nebulized myo-Ins. Although patients in both groups had a significant decrease in FEV1 values, nebulized myo-Ins stabilized FEV1 values compared with placebo (p<0.001). This beneficial effect of nebulized myo-Ins was also evident after 15 days of treatment. In fact, in patients treated with nebulized myo-Ins, the percentage of the solid content of expectorate (p<0.001) and surfactant tension (p<0.001) significantly decreased. These modifications correlated with FEV1 (p<0.01) and $FEF_{25-75\%}$ (p<0.01) scores. These results are in accordance with other studies[19], in which myo-Ins was used as a therapeutic strategy for treating airway diseases, including COVID-19.

Myo-Ins is an important osmolyte, with the great ability to bind and retain large quantities of water, especially in the tissues of the respi-

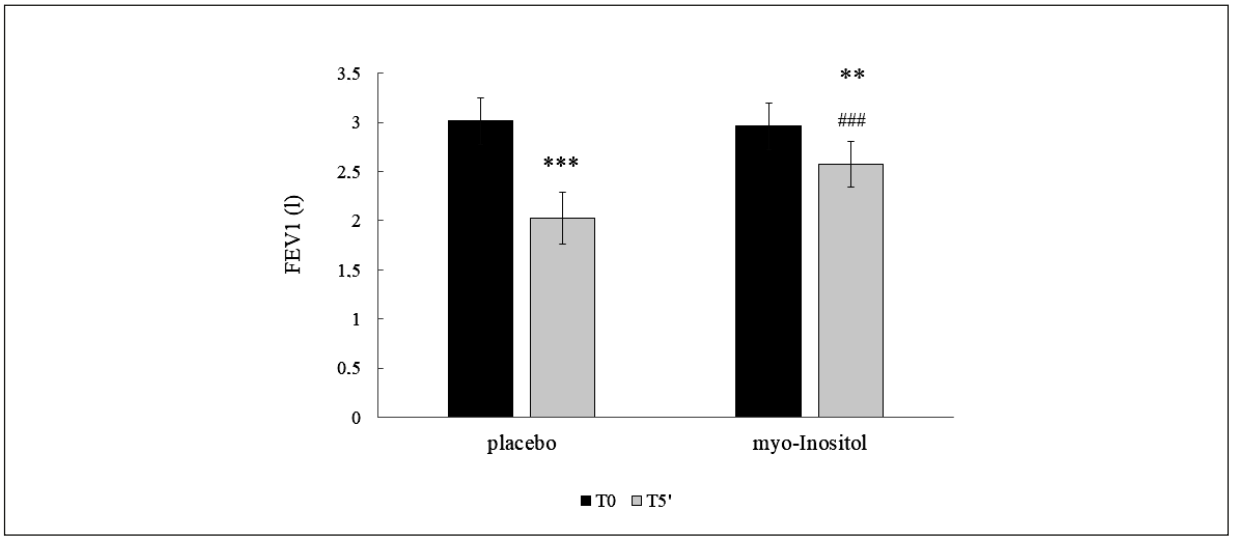

Figure 1. FEV1(l) values at T0 and T5' with placebo or nebulized myo-Ins. The level of statistical significance was set as p<0.05. Paired t-test T0 *vs.* T5' **p<0.01 and ***p<0.001. Unpaired t-test placebo *vs.* nebulized myo-Ins $^{###}p$<0.001.

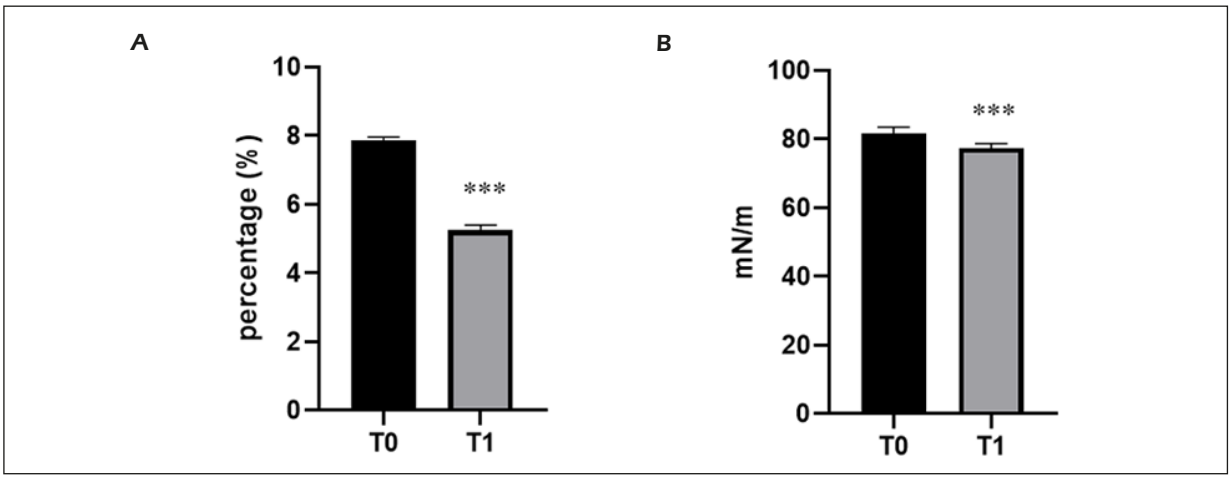

Figure 2. Percentage of the solid content (**A**) and surface tension (**B**) in patients treated with nebulized myo-Ins. Paired *t*-test ***$p<0.001$ *vs.* T0.

ratory system. These lubricating and emollient capacities are useful to relieve symptoms related to inflammation, such as difficulty in swallowing, the sensation of a foreign body in the throat, tickling and dryness. Myo-Ins, by increasing mucus hydration, may restore mucociliary clearance, which is an important defense mechanism of the human body and allows to move out of the lungs' airway mucus and substances trapped within. An alteration in mucociliary transport, a characteristic of bronchiectasis, may lead to mucus retention and predisposes to bacterial colonization. A sign of low mucus hydration is the presence of the solid content of the expectorate. In this study, patients treated with myo-Ins had a significant decrease in the percentage of the solid content of expectorate after 15 days of treatment, thus evidencing that myo-Ins increases expectorate hydration. Moreover, myo-Ins, is a component of pulmonary surfactant, the surface-active lipoprotein complex, which improves gaseous exchanges at the level of the bronchial alveoli and reduces surface tension, thereby avoiding alveolar and lung collapse[16]. Myo-Ins in the lungs promotes the maturation of the surfactant phospholipids, such as phosphatidylcholine and phosphatidylinositol (PI). Reduction in surface tension not only prevents atelectasis at the end of expiration but also increases pulmonary compliance[20]. Myo-Ins has already been used in pulmonology for the therapy of respiratory distress syndrome (RDS) in premature babies. The infants treated intravenously with inositol had a significant increase in their lung functionality due to lower mean requirements for inspiratory oxygen. They also experience a significant increase in the survival rate, showing no bronchopulmonary dysplasia or other complications compared with placebo-treated[21]. This is confirmed in our study, in which patients treated with nebulized myo-Ins had a significant decrease in surfactant tension correlated with FEV1 score. Moreover, these results are in line with a previous clinical study[14] in which patients affected by different airways diseases (BPCO, asthma, and pulmonary emphysema) experienced a significant increase in the SpO_2 levels after the treatment with nebulized myo-Ins for 15 days and had total recovery without manifesting symptoms after the end of the treatment. Although this is a retrospective study with a limited sample size, the enrolled population was widely heterogeneous. However, future clinical trials with larger cohorts of patients are necessary to confirm our findings.

Conclusions

Myo-Ins acts as pivotal molecule in several intracellular signaling pathways. In this retrospective study, we demonstrated that nebulized myo-Ins exerts benefic effects in patients affected by bronchiectasis. Although our data are in line with other studies demonstrating its beneficial activity in patients affected by different respiratory diseases, we encourage larger studies to confirm this promising therapeutic approach option.

Conflict of Interest
Proietti S. and Unfer V. are employees of Lo.Li pharma s.r.l..

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Authors' Contribution
Conceptualization, R.V. and M.B.; data curation, P.S., S.A., U.V.; formal analysis V.R.; investigation and methodology P.S., S.A., U.V project administration, V.R. and B.M.; writing-original draft, V.R.; writing and editing, V.R. and B.M. All authors have read and agreed to the published version of the manuscript.

ORCID ID
Vittorio Unfer: 0000-0002-1805-3181
Mariano Bizzarri: 0000-0003-0408-4136
Sara Proietti: 0000-0002-5716-7675
Roberto Verna: 0000-0002-1869-3912

Data Availability
The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Informed Consent
Informed consent was obtained from all individual participants.

Ethics Approval
Not applicable. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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