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Effects of Pleuran (β-glucan from *Pleurotus ostreatus*) Supplementation on Incidence and Duration of Bronchiectasis Exacerbations

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Abstract

BACKGROUND: Patients with non-cystic fibrosis bronchiectasis (BE) have frequent exacerbations that are causes of significant morbidity and sometimes mortality, and which it is desirable to prevent.

AIM: We aimed to assess the effects of pleuran on the incidence and duration of exacerbations in patients with BE.

METHODS: A prospective, observational, open-label, and active-controlled study was realized as a comparison of the frequency and duration of exacerbations between a group of patients with BE (30 patients, 14 males and 16 females, aged 44–72 years) who received a combination supplement containing pleuran 100 mg, Vitamin C 60 mg and zinc 5 mg over a 3-month period and a group of patients with BE (31 patients, 15 males and 16 females, aged 45–74 years) treated over a 3-month period with a combination supplement containing Vitamin C 60 mg and zinc 5 mg.

RESULTS: Over the study period, altogether 46 exacerbations were documented (19 in the patients receiving pleuran and 27 in the patients who did not receive pleuran), nine of which required hospital treatment (four in the patients receiving pleuran [21.5%] and five in the patients who did not receive pleuran [18.6%]). The mean number of exacerbations over the study period was significantly lower in the patients receiving pleuran (0.6 ± 0.4) as compared to the mean number in the patients who did not receive pleuran (0.8 ± 0.3) (p = 0.0297). The mean duration of exacerbations, expressed in days, needed for cure or clinical improvement in the patients receiving pleuran (11.2 ± 1.7 days) was significantly shorter than that of exacerbations in the patients who did not receive pleuran (12.4 ± 1.3 days) (p = 0.0029). We found significantly lower incidence and significantly shorter duration of exacerbations in the patients with BE who received pleuran as compared to their incidence and duration in the patients with BE who did not receive pleuran.

CONCLUSION: Our findings indicated a need for further investigations in this domain to define the possible role of pleuran in the prevention of BE exacerbations.

Introduction

Non-cystic fibrosis bronchiectasis (BE) is a chronic disorder of the major airways characterized by permanent dilatation and destruction [1]. The origin of BE varies, but the presence of microbial infection and a persistent inflammatory response are typical characteristics of the disease [2], [3]. There is evidence for increased incidence as well as increased mortality of BE in recent decades in developed countries [4], [5]. The reasons for this are not clear, but may be due to improved diagnostics of BE; i.e., to increased use of computed tomography (CT) in diagnosis of the disease [6].

Patients with BE have frequent exacerbations that are a cause of significant morbidity and sometimes mortality, which it is desirable to prevent [7]. BE exacerbation is defined as a deterioration of three or more of the following key symptoms for at least 48 h: cough; sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise tolerance; fatigue and/or malaise; and hemoptysis; or a clinician determines that a change in BE treatment is required [8]. The diagnosis of a bacterial infection should be established when a combination of symptoms exists. A positive sputum culture, by itself, does not indicate an exacerbation, as it is usually positive in patients with stable disease, but it can be helpful in guiding future antibiotic use [9]. An exacerbation is classified as severe in the presence of tachypnea, acute respiratory failure, exacerbated chronic respiratory failure, a significant decline in oxygen saturation of arterial blood or respiratory function or hypercapnia, fever of more than 38°C, and hemoptysis. In addition, an exacerbation is classified as very severe in the presence of hemodynamic instability, altered mental status, or a need for intensive or intermediate care admission [10].

During an exacerbation, there is often a proliferation of bacterial pathogens and increased airway and systemic inflammation. Treatment with antibiotics has been shown to reduce bacterial burden, as well

as inflammation. More than 80% of BE exacerbations can be treated in an outpatient setting. In the cases of positive sputum culture, the antibiotic therapy should follow its findings. The empirical choice of antibiotic should be based on previous sputum isolates where possible, as well as on any local pattern of resistance, availability of medication, and patient response. The appropriate duration of antibiotic therapy is 14 days. Indications for hospital treatment of BE exacerbations include respiratory failure with respiratory rate higher than 25/min, hypoxic respiratory failure with oxygen saturation of arterial blood lower than 92%, hypotension, fever of more than 38 °C, patients with *Pseudomonas aeruginosa* resistant to ciprofloxacin, or failure to improve after a course of oral antibiotics [8], [9], [11].

Pleuran is an insoluble 1,3/1,6-β-glucan from the mushroom *Pleurotus ostreatus*. A number of experimental studies on animal models, as well as a number of experimental and clinical studies in humans, indicated immunomodulatory properties of pleuran based on its effects on immune cells of Peyer's patches in the gut. After oral administration, pleuran comes into contact with immune cells of Peyer's patches that express several receptors (e.g., Dectin-1, complement receptor-3, and scavenger receptors) capable of recognizing β-glucans. On the binding of pleuran to these receptors, a cascade of intracellular signaling is initiated, which stimulates innate and subsequently adaptive immune responses, mainly through the modulation of pro-inflammatory and immunoregulatory cytokine production (complement components, interleukin-1α/β, interleukin-6, interleukin-8, interleukin-12, tumor necrosis factor-α, and eicosanoids), which improve the resistance to invading pathogens. Moreover, pleuran possesses many other beneficial biological activities useful in the management of inflammatory diseases, for example, anti-inflammatory, anti-oxidant, regenerative, and anti-infectious activities [12], [13], [14].

The aim of the present study was to assess the effects of pleuran on the incidence and duration of exacerbations in patients with BE. This study is a continuation of our investigation into the effects of pleuran on the incidence and severity of bacterial exacerbations in chronic obstructive airway diseases, following on from a previous study in which the incidence and severity of exacerbations were investigated in patients with stable chronic obstructive pulmonary disease (COPD) treated with pleuran (COPD patients with accompanying BE were not included in the study) [15].

Methods

Study design and setting

A prospective, observational, open-label, and active-controlled study (a real-life study) was realized as a comparison of the frequency and duration of exacerbations between a group of patients with BE who received a combination supplement containing pleuran 100 mg, Vitamin C 60 mg, and zinc 5 mg over a 3-month period with a group of patients with BE treated over a 3-month period with a combination supplement containing Vitamin C 60 mg and zinc 5 mg. It was performed over the period November 2017–April 2018 at the Institute for Occupational Health of R. Macedonia, Skopje.

Study subjects

The study population included 61 BE patients divided into two groups. The first group (Group 1) included 30 patients (14 males and 16 females, aged 44–72 years) who took the combination supplement containing pleuran 100 mg, Vitamin C 60 mg, and zinc 5 mg once daily over the period of 3 months. The second group (Group 2) included 31 BE patients (15 males and 16 females, aged 45–74 years) who received the combination supplement containing Vitamin C 60 mg and zinc 5 mg once daily, matched to the first group by sex, age, and smoking status. Patients with accompanying COPD from both groups took their maintenance treatment for stable disease as recommended.

Patients with a history of asthma, lung cancer or other significant respiratory disease, as well as those unable to complete diary cards, were excluded from the study. All study subjects were recruited in the stable phase of the disease, i.e., without any evidence of exacerbation for at least 3 weeks.

All study subjects were informed about the study and their written consent was obtained.

Daily stable respiratory symptoms (baseline symptoms), medication use and history of exacerbations were noted for all subjects before entering the study. All study subjects underwent baseline and post-bronchodilator spirometry according to the recommendations of European Respiratory Society and American Thoracic Society [16]. In addition, in all study subjects, a microbiological evaluation of sputum was performed in the stable phase of the disease, as well as when the exacerbation was diagnosed, according to the recommendations [17].

The body mass index (BMI), as a measure of body fat based on height and weight as applied to the adult population, was determined in all study subjects by computer calculation using a BMI calculator [18].

Classification of smoking status was by the World Health Organization (WHO) recommendations [19]. Passive smoking or exposure to environmental tobacco smoke was defined as an exposure to tobacco combustion products from smoking by others (at home, in the workplace, etc.), i.e., as the presence of at least one smoker in the household and/or the workplace [20].

Diagnosis and assessment of BE

Diagnosis of BE was based on the findings of high-resolution CT (HRCT), as it is currently considered as the best tool for its diagnosis. According to the recommendations, the main diagnostic features for BE are the internal diameter of a bronchus wider than its adjacent blood vessel, a failure of the bronchi to taper, and the visualization of bronchi in the outer 1–2 cm of the lung fields [7], [21], [22]. BE was scored in each lobe by consensus, using the grading system proposed by Smith *et al*. [23] as follows: 0 if no BE was present; 1 if less than 25% of the bronchi were bronchiectatic; 2 if 25–49% of the bronchi were bronchiectatic; 3 if 50–74% of the bronchi were bronchiectatic; and 4 if 75% or more of the bronchi were bronchiectatic. As previous studies have shown that more than 50% of healthy volunteers may have at least one dilated bronchus on HRCT, only patients with a total BE score of 2 or more were considered to have changes consistent with clinically significant disease for the study objectives.

Once the diagnosis was established by HRCT scanning, patients underwent a range of investigations to determine the underlying cause, as well as to determine the severity, of the disease [24]. Diagnosis and assessment of COPD were made following the recommendations of Global Initiative for COPD [25]. In addition, following the recommendation of the BE severity index (BSI), BE was classified as mild (low BSI score), moderate (intermediate BSI score), or severe (high BSI score) [26], [27].

Diagnosis and treatment of BE exacerbation

BE exacerbations were diagnosed according to the criteria from the guidelines mentioned above [7], [8], [9]. The antibiotic therapy lasted 14 days, being etiological or empirical depending on the results of sputum culture [9], [10], [11]. The course of exacerbation was evaluated as a function of the resolution of symptoms, and the treatment was considered successful if cure or clinical improvement (i.e., return of the symptoms to their baseline severity) was achieved.

Data collection (daily diary card)

Data collection was realized following the model used by Patel *et al*. in their study on BE and exacerbation indices [28]. All study subjects maintained daily diary cards on which they noted the appearance or increase in intensity of three or more symptoms (cough, sputum volume and/or consistency, sputum purulence, breathlessness and or exercise intolerance, fatigue and/or malaise, hemoptysis, fever, etc.). A member of the study team saw study subjects within 48 h of the detection of deterioration in symptoms and diagnosis was confirmed in each case. Exacerbation and its resolution were defined as mentioned above. Exacerbation number and their duration were calculated for each study subject based on data from diary cards for a 3-month period of follow-up.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 11.0 for Windows. Continuous variables were expressed as mean values with standard deviation (SD), and the nominal variables as numbers and percentages. Analyses of the data included testing the differences in prevalence and comparison of the means by Chi-square test (or Fisher's exact test where appropriate) and independent-samples t-test. $p < 0.05$ was considered statistically significant.

Results

Demographic and other characteristics of the study subjects are shown in Table 1.

Table 1: Characteristics of the study subjects

Variable	Group1 (n=30)	Group 2 (n=31)
M/F ratio	0.9	0.9
Mean age (years)	52.4 ± 6.1	53.1 ± 7.0
Mean BMI (kg/m^2)	25.2 ± 2.6	25.5 ± 3.1
Mean duration of BE after diagnosis (years)	9.3 ± 3.1	9.5 ± 3.7
BE etiology		
Post-infective	10 (33.3%)	12 (38,7%)
COPD	6 (20.0%)	5 (19.3%)
Not determined	14 (46.6%)	14 (45.1%)
Type of BE		
Cylindrical	13 (43.3%)	14 (45.1%)
Varicose	12 (36.6%)	12 (38.7%)
Cystic	5 (16.6%)	5 (16.1%)
Classification of BE severity by the BSI score		
Mild	12 (36.6%)	13 (41.9%)
Moderate	13 (43.3%)	13 (41.9%)
Severe	5 (16.6%)	5 (16.1%)
Mean values of spirometric parameters (% pred.)		
FVC	77.3 ± 6.8	78.2 ± 8.1
FEV1	54.1 ± 5.6	55.5 ± 4.9
FEV1/FVC ratio	0.70 ± 0.06	0.71 ± 0.09
Positive sputum culture when clinically stable over the past 12 months		
Haemophilus influenzae	9 (30.0%)	10 (32.2%)
Moraxella catarrhalis	4 (13.3%)	5 (16.1%)
Streptococcus pneumoniae	3 (10.0%)	3 (9.6%)
Pseudomonas aeruginosa	3 (10.0%)	3 (9.6%)
Other	2 (6.6%)	2 (6.4%)
No bacteria isolated	9 (30.0%)	8 (25.8%)
Long-term treatment of stable BE		
Systemic antibiotics	0 (0%)	0 (0%)
Inhaled antibiotics	0 (0%)	0 (0%)
Mucoactive drugs	3 (10.0%)	4 (12.9%)
Number of exacerbations in the past 12 months	2.4 ± 0.2	2.3 ± 0.6
Smoking status		
Active smokers	12 (40.0%)	11 (35.4%)
Ex-smokers	10 (33.3%)	11 (35.4%)
Never smoked	8 (26.6%)	9 (29.0%)
Exposed to ETS	13 (43.3%)	15 (48.3%)
Accompanying COPD	6 (20.0%)	5 (19.3%)
Mild	2 (6.6%)	2 (6.4%)
Moderate	2 (6.6%)	2 (6.4%)
Severe	2 (6.6%)	1 (3.2%)
Very severe	0 (0%)	0 (0%)

Numerical data are expressed as mean value ± SD; frequencies as number and percentage of study subjects with given variable. M: Male, F: Female, BMI: Body mass index, kg: Kilogram, m: Meter, BE: Bronchiectasis, COPD: Chronic obstructive pulmonary disease, BSI: Bronchiectasis severity index, % pred.: % of the predicted value, FVC: Forced vital capacity, FEV_1: Forced expiratory volume in one second, ETS: Environmental tobacco smoke.

Over the study period, 46 exacerbations were documented (19 in Group 1 and 27 in Group 2), nine of which required hospital treatment (four in Group 1 [21.5%] and five in Group 2 [18.6%]).

Positive sputum culture was obtained in 29 exacerbations (13 in Group 1 and 19 in Group 2) (Table 2).

Table 2: Findings of sputum culture in exacerbations of the study subjects from Group 1 and Group 2

Sputum culture	Group 1 n=19 (%)	Group 2 n=27 (%)
Haemophilus influenzae	6 (31.5)	9 (33.3)
Moraxella catarrhalis	2 (10.5)	2 (7.4)
Streptococcus pneumoniae	2 (10.5)	4 (14.8)
Pseudomonas aeruginosa	3 (15.7)	3 (11.1)
Staphylococcus aureus	1 (5.2)	1 (3.7)
No bacteria isolated	5 (26.3)	8 (29.6)

Frequencies are expressed as number and percentage of study subjects with finding of sputum culture.

In addition, 34 of the 46 exacerbations (73.9%) were treated only with systemic antibiotics (14/19 [73.7%] in Group 1 and 20/27 [74.1%] in Group 2) and 12 (26.1%) were treated with systemic antibiotics and systemic glucocorticoids (5/19 [26.3%] in Group 1 and 7/27 [25.9%] in Group 2) (Figure 1):

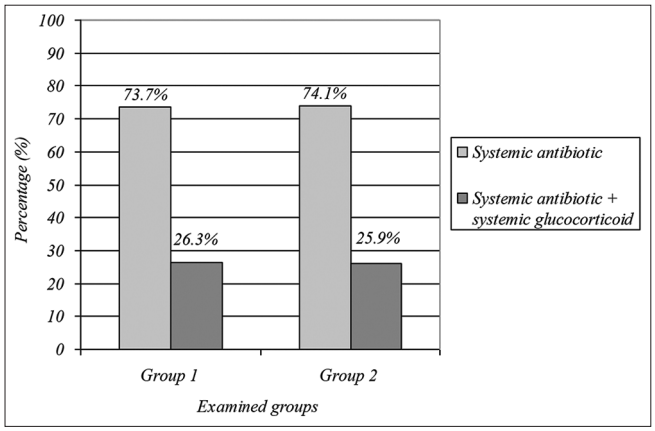

Figure 1: Treatment of exacerbation in study subjects from Group 1 and Group 2

The mean number of exacerbations over the study period was significantly lower in Group1 (0.6 ± 0.4) as compared to their mean number in Group 2 (0.8 ± 0.3) (p = 0.0297) (Figure 2):

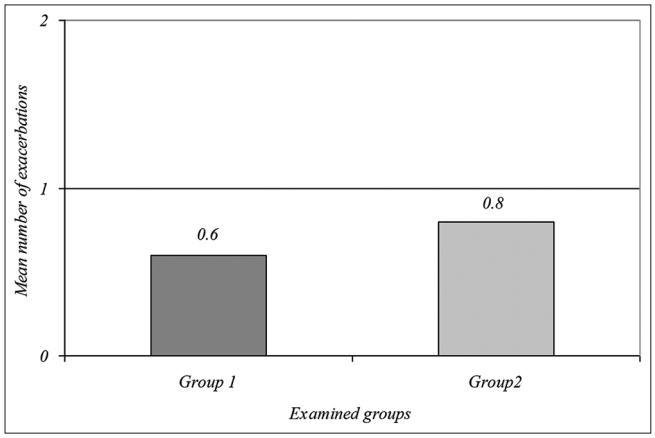

Figure 2: Mean number of exacerbations in the examined groups (p = 0.0297)

The mean duration of exacerbations, expressed in days, needed for cure or clinical improvement (i.e., complete resolution of symptoms or return of symptoms to their baseline severity) in Group 1 (11.2 ± 1.7 days) was significantly shorter than the mean duration of exacerbations in Group 2 (12.4 ± 1.3 days) (p = 0.0029) (Figure 3):

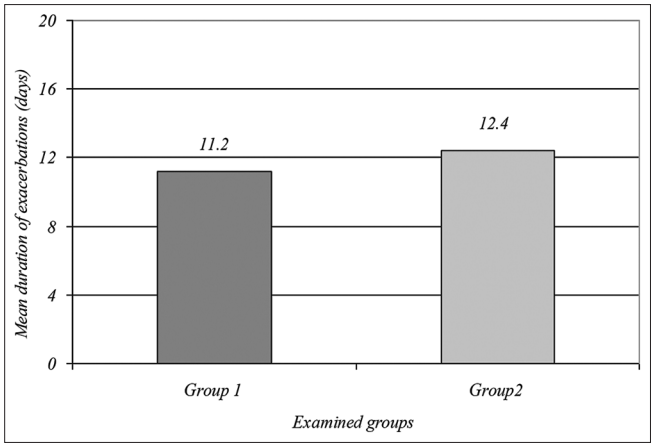

Figure 3: Mean duration of the exacerbations in the examined groups (p = 0.0029)

Adverse effects of the medicaments used over the study period were not reported by any study subject from either examined group, and the treatment was well tolerated.

Discussion

BE is a chronic progressive condition resulting from infection and inflammation of the airway, leading to destruction, and remodeling of the bronchial wall. The clinical manifestations of the disease include chronic and commonly purulent expectoration, multiple exacerbations, and progressive dyspnea. All these events cause progressive decline in the lung function and impairment of the quality of life of the patients [29], [30], [31].

In the present study, we assessed the effects of pleuran (1,3/1,6-β–glucan from *P. ostreatus*) on the incidence and duration of exacerbations in patients with BE. To the best of our knowledge, the present study is the first to investigate the effects of pleuran on the prevention of exacerbations in adult patients with BE. Examined groups included BE patients diagnosed and classified by severity according to the recommendations. Study subjects from the examined groups had similar demographic characteristics, as well as characteristics related to their disease (mean duration of the disease after diagnosis, severity, etiology, lung function, microbiological findings in the stable phase of the disease, accompanying COPD, etc.). We found a high prevalence of active and passive smokers in both examined groups, which was similar to their prevalence registered in our previous studies [15], [32], [33].

The immunomodulatory properties of pleuran and other fungal β-glucans were studied and described almost 50 years ago. As mentioned above, many studies have reported the ability of pleuran to activate innate immunity, with effects also on adaptive immunity, and in inducing humoral and cell-mediated immune responses. Pleuran was found to increase the antimicrobial activity of mononuclear cells and neutrophils and to enhance the functional activity of macrophages. There is also evidence from experimental studies of its effects against tumor. Finally, there is evidence that β-glucans may modulate other conditions (cholesterol level, glucose tolerance, etc.). [34], [35], [36]. However, the doses of pleuran for clinical use in both children and adults, as well as the duration of the treatment, are still not well defined. Pleuran is an insoluble substance, non-absorbable and non-digestible in the gastrointestinal tract, so systemic adverse effects would not be expected. In addition, according to the results from existing evidence, local (gastrointestinal) side effects occurring during the use of pleuran are rare and mild [14], [37].

In the present study, we found significantly lower incidence of exacerbations, as well as their significantly shorter duration in the study subjects receiving pleuran as compared to their incidence and duration in those who did not receive pleuran. Similar findings were obtained in our study on the effects of pleuran on the incidence and duration of exacerbations in patients with COPD who received the same doses of pleuran over the 3-month period [15]. Similar findings were reported by several studies that investigated effects of pleuran on incidence, duration, and severity of respiratory infections in children [38], [39]. In addition, there is evidence of a significant effect of pleuran in the reduction of respiratory tract infections in athletes [40]. Furthermore, there is evidence for a significant effect of pleuran on natural killer cell activity during respiratory infection or after intensive exercise in athletes [40], [41]. As in the present study, local (i.e., gastrointestinal) adverse effects were not registered in any cited studies.

The present study must be interpreted within the context of its limitations. As in the case of the study on the effects of pleuran on the incidence and duration of COPD exacerbations, the results should be viewed with caution, since the study was neither blinded nor randomized and, therefore, can be subject to possible selection bias. On the other hand, the study design may be its strength, as is documented by other real-life studies. In addition, the small number of subjects in the examined groups and the short follow-up period could both have certain implications on the data obtained and their interpretation.

Conclusion

In a prospective, observational, open-label, and active-controlled study including a group of patients with BE who received a combination supplement containing pleuran 100 mg, Vitamin C 60 mg, and zinc 5 mg over a 3-month period, we found significantly lower incidence, and significantly shorter duration, of exacerbations as compared to their incidence and duration in a group of patients with BE treated over a 3-month period with the combination supplement containing Vitamin C 60 mg and zinc 5 mg. Further investigations, as well as comparisons with other therapeutic modalities, are needed to define the position of pleuran regarding the prevention of BE exacerbations.

Ethical Approval

The Ethical Committee of the Institute of Occupational Health of R. Macedonia, Skopje – WHO Collaborating Center and GA^{2}LEN Collaborating Center gave approval for the performance of the study and the publication of the results obtained (0302–235/20.03.2018).

Author Participations

JM participated in the study design, data collection, managing the analyses of the study, and writing all versions of the manuscript. JKB and TP participated in the study design and managing the analyses of the study. KV performed the statistical analysis and participated in managing the analyses of the study. SS and DM participated in the data collection and in managing the analyses of the study. All authors have read and approved the final manuscript.

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