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Value of adding a polyvalent mechanical bacterial lysate to therapy of COPD patients under regular treatment with salmeterol/fluticasone

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***Abstract*:**
Background: This study investigated the value of adding Ismigen®, a polyvalent mechanical bacterial lysate, to therapy of COPD patients ($FEV_1 < 60\%$ predicted) under regular treatment with salmeterol/fluticasone (SFC).
Methods: 63 patients enrolled from September to December 2007 were randomly divided into two groups (A and B). All patients were treated with salmeterol/fluticasone (SFC) 50/500 μg BID. Thirty-three subjects also received Ismigen one capsule daily the first 10 days of three consecutive months (group B). This treatment was reaped three months after the end of the first course. We assessed at inclusion and at scheduled (every 2 months) or intercurrent visit: symptoms (amount and colour of sputum, severity of dyspnoea, frequency of cough, fever), diagnosis of exacerbation, concomitant medications (antibiotics and oral corticosteroids) and hospitalization.
Results: During the course of the study two patients died. At the end of the observation period (12 months), another six patients could not be visited because they had withdrawn. Compared with SFC, adding on Ismigen reduced the total number of exacerbations (23 out of 30 patients in group A and 21 out of 33 patients in group B), the number (rate) of exacerbations per patient per year (18 out of 27 patients [0.67] in group A and 15 out of 28 patients [0.54] in group B), the number of exacerbations that needed treatment with oral corticosteroids (12 out of 23 [52%] in group A and 9 out of 21 [43%] in group B) and the total number (rate) of hospitalizations (4/30 [0.13] in group A and 3/33 [0.09] in group B). There were no significant differences between treatments with respect to their effect on the symptoms of exacerbations. A decrease in the need for antibiotics was also observed in group B.
Conclusion: Our data suggest that COPD patients benefit from the addition of Ismigen on top of the routine maintenance treatment with SFC.

***Keywords*:** COPD, exacerbations, fluticasone, propionate, salmeterol polyvalent mechanical bacterial lysate

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Introduction

The Towards a Revolution in COPD Health (TORCH) trial, a double-blind, placebo-controlled, randomized, parallel-group study comparing salmeterol plus fluticasone propionate (SFC) with each of the components alone and with placebo over a 3-year period, documented that SFC caused a reduction of 25% of the annual rate of exacerbations when compared with placebo [Calverley *et al*. 2007]. This is an important outcome considering that patients prone to frequent exacerbations have impaired health status, reduced physical activity, increased lower airway bacterial colonization and a faster decline in lung function [Hirschmann, 2000].

Nonetheless, the annual rate of exacerbations still was 0.85 in the SFC group [Calverley *et al*. 2007]. Moreover, an important safety finding was the excess of patients who received a diagnosis of pneumonia among those receiving study medications containing fluticasone propionate [Calverley *et al*. 2007]. These findings document

a need for more effective therapies or, at least, an integration of existing therapies.

There is a general agreement that, given the high prevalence of COPD, the impact of exacerbations on quality of life and the costs incurred, effective ways for the prevention of exacerbations and for reductions in the severity and duration of COPD symptoms are needed [Steurer-Stey *et al.* 2004]. Although not strictly a pathogen-directed therapeutic approach, vaccination has assumed an important role in the patient with COPD [Martinez, 2007].

Bacterial immunostimulation has been advocated as a management strategy in COPD for the purposes of preventing acute exacerbations. Previous data [Centanni *et al.* 1997] showed some interesting synergic effects of bacterial extracts in extending the immunological response to influenza vaccine in COPD patients. Considering that infection is one of most important risk factors in COPD exacerbations, this could be an interesting clinical outcome. It is not surprising, therefore, that use of bacterial immunostimulants is an option included in the management recommendation of some guidelines [Jindal *et al.* 2004]. Inactivated micro-organisms offer certain advantages as a potential vaccine for mucosal immunization [Cazzola *et al.* 2008]. They are naturally occurring microparticles, which possess multiple antigens and are relatively inexpensive to produce. These immunomodulatory bacterial extracts are commonly administered by the oral route. The aim of the present pilot study was to investigate the value of adding Ismigen, a polyvalent mechanical bacterial lysate (PMBL), to therapy of COPD patients under regular treatment with SFC in preventing the onset of exacerbations.

Patients and methods

Sixty-three patients suffering from moderate-to-very severe COPD, who were under regular treatment with SFC, were enrolled from September to December 2007 (Table 1). All of them were 50 years of age or older, and were current or former smokers with a 20 pack-year or more history. Inclusion criteria required a baseline FEV_1 of less than 60% of predicted but more than 0.50 l, and a postbronchodilator $FEV_1/FVC < 70\%$ following salbutamol, 400 µg. Exclusion criteria were as follows: current evidence of asthma as primary diagnosis; unstable respiratory disease requiring oral/parenteral corticosteroids within 4 weeks prior to beginning the study; upper or lower respiratory tract infection within 4 weeks of the screening visit; treatment with antibiotics within 1 week before the trial start, previous concomitant immunosuppressive or immunostimulant therapy during the past 3 months before study entry, unstable angina or unstable arrhythmias. All patients received influenza vaccination. They were allowed to take any other medication required for the treatment of their comorbidities and exacerbations of COPD but not concomitant treatment with systemic corticosteroids (exceeding two weeks), or concomitant treatment with an unregistered drug during the whole trial. The study was conducted in accordance with guidelines for good clinical practise issued by the European Commission, in 1990, and with the Declaration of Helsinki of 1975, as revised in 1983.

Patients were randomly divided into two groups (A and B). All patients were regularly treated with SFC 50/500 µg b.i.d. Thirty-three subjects also received Ismigen (group B) that was administered as one capsule daily the first 10 days of three consecutive months. This treatment was reaped 3 months after the end of the first course. We assessed at inclusion and at scheduled (every 2 months) or intercurrent visit: symptoms (amount and colour of sputum, severity of dyspnoea, frequency of cough, fever), diagnosis of exacerbation, concomitant medications (antibiotics and oral corticosteroids) and hospitalization. The symptoms were scored as follows.

- Cough: 0, no cough; 1, occasional cough, which does not interfere with daily activities; 2, moderate cough, with a tickling sensation in the throat, but which does not interfere with daily activities; and 3, severe persistent

Table 1. Clinical profile of the two groups

Variables	Group A ($n = 30$)	Group B ($n = 33$)
Male sex (%)	86.7	75.8
Age, years	66.2 (8.0)	66.6 (7.8)
Still smoking (%)	53.3	57.8
FEV_1 (% pred.)	46.2 (8.9)	47.7 (9.0)
FVC (% pred.)	57.2 (10.3)	58.3 (10.7)
Past hospitalization (%)	44.3	54.5
At least one use of antibiotics for a respiratory problem in last 6 months,%	30.0	36.4

cough, which interferes with daily activities and disturbs sleep at night.
- Sputum: 0, no sputum; 1, small amount (10–15 ml) expectorated per day; 2, medium amount (15–50 ml) expectorated per day; and 3, large amount (more than 50 ml) expectorated per day.
- Dyspnoea: 0, no dyspnoea; 1, dyspnoea following an amount of exercise equivalent to going up two floors at medium pace; 2, dyspnoea following an amount of exercise equivalent to walking 100 meters on a flat surface; and 3, dyspnoea after even slight physical movement.
- Pulmonary rales: 0, no rale; 1, few and occasional rales, or rales heard only after coughing and deep breathing; 2, dispersed, moderate rales; and 3, frequent, massive rales.

At each visit, patients performed a spirometry.

Results

During the course of the study two patients died (one in group A and in one group B) because of causes that were not related to COPD. At the end of the observation period (12 months) another six patients (two in group A and four in group B) could not be visited because they withdrew prematurely from the study for non-medical reasons.

Compared with SFC, added on Ismigen reduced the total number of exacerbations (23 out of 30 patients in group A and 21 out of 33 patients in group B), the number (rate) of exacerbations per patient per year (18 out of 27 patients [0.67] in group A and 15 out of 28 patients [0.54] in group B), the number of exacerbations that needed treatment with oral corticosteroids (12 out of 23 [52%] in group A and 9 out of 21 [43%] in group B) and the total number (rate) of hospitalizations (4/30 [0.13] in group A and 3/33 [0.09] in group B). A decrease in the need for antibiotics was also observed in group B (Table 2). There were no substantial differences between treatments with respect to their effect on the symptoms of exacerbations and lung function in those patients that completed the trial (Table 3).

Discussion

This pilot study suggests that COPD patients benefit from the addition of Ismigen on top of the routine maintenance treatment with SFC. Ismigen is a PMBL prepared by bacteria (*Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans*, *Klebsiella ozaenae*, *Haemophilus influenzae* serotype B, *Moraxella catarrhalis* and *Streptococcus pneumoniae*) obtained by mechanical lysis. The mechanical method is particularly efficient in that it achieves lysis of 80–100% of the bacteria. It is even more interesting that, compared with other methods of lysis (such as alkaline lysis which brings about fragmentation significant enough to cause loss of immunogenicity), mechanical lysis does not alter the structure of the antigens: this ensures a preparation having excellent antigenic properties. The lysate thus induces a specific immunostimulation against the seven bacterial strains composing it, selected among those most often responsible for respiratory infections.

According to extensive and well-established literature, PMBL treatment seems to yield various beneficial effects [Cazzola *et al.* 2008], including a significant increase in antibody titre even after just one treatment cycle, in terms of IgM, IgG, and IgA [Rosaschino and Cattaneo, 2004]. This has a positive therapeutic effect on the amplitude of the spectrum of immunological production and on the production of opsonizing antigens [Blasi 2002]. In particular, it has been suggested that this PMBL exerts a therapeutic and prevention effect in acute and recurrent infections because it induces the activation and enhancement of both IgM memory B lymphocytes ($CD24^+/CD27^+$ cells) and IL-2 receptor-expressing lymphocytes ($CD25^+$ cells) involved either in humoral or cellular immunity [Lanzilli *et al.* 2006]. Moreover, it is able to induce a specific immune response in the salivary fluid of healthy subjects [Rossi *et al.* 2003].

Sublingual administration guarantees effective protection of the respiratory mucosae, which represent the first barrier to infection, making it possible to bypass the gastroenteric tract. This characteristic avoids denaturing the antigens

Table 2. Exacerbations and the use of antibiotics. Group A: treated without Ismigen; group B: treated with Ismigen. All patients enrolled in the trial have been included

Outcomes	Group A ($n=30$)	Group B ($n=33$)
Total number of exacerbations	23	21
Rate of exacerbations per patient per year	0.67	0.54
Exacerbations treated with oral corticosteroids (%)	52	43
Rate of hospitalizations	0.13	0.09
Total duration of antibiotic treatments (days)	6.7 (1.9)*	6.1 (1.3)*

*Values are mean ± SD

Table 3. Lung function and symptoms scores in both groups before and after treatment. Group A: treated without Ismigen; group B: treated with Ismigen. Only those patients that completed the trial have been included.

Outcomes	Group A ($n=27$)	Group B ($n=28$)
FEV_1 (% pred.)	46.2 (8.3)	48.1 (8.0)
FVC (% pred.)	55.8 (9.2)	57.1 (9.0)
Cough score	1.0 (0.6)	1.0 (0.5)
Sputum score	1.0 (1.0)	1.0 (0.9
Dyspnoea score	1.3 (0.7)	1.2 (0.6)
Rales score	0.9 (0.8)	0.8 (0.6)

Values are mean ± SD

and puts them directly in contact with the cells that best carry out the task of antigen-presenting cells, namely the Langherans cells [Rosaschino and Cattaneo, 2004].

These interesting pharmacological properties justify the capacity that this PMBL has in preventing exacerbations of COPD. In an Italian study conducted on 57 patients aged over 75 suffering from chronic obstructive bronchitis and affected by at least one exacerbation over the past 12 months, Ismigen significantly reduced the absolute number of exacerbations, their length and seriousness, as well as the need to use antibiotic treatments, and the overall cost of the treatment of these patients during the period of treatment compared with the same period for the previous year, during which time no antibacterial prophylaxis had been administered [Cogo *et al*. 2003]. In another study, 178 patients were randomized into two different groups: one group was treated with Ismigen (first 10 days of each month for three consecutive months) and the other with placebo [Cazzola, 2006]. The trial was double blinded. At the end of treatment, patients were followed for a further 9 months. Selected clinical endpoints were seen to be significantly lower in the group treated with the lysate than in the placebo group. Ismigen treatment led to a highly significant reduction in the frequency (215 *versus* 248 cases) and duration (10.6 days *versus* 15.8 days) of exacerbations, as well as a decrease in antibiotic consumption (−270 doses) and hospitalization time (275 days *versus* 590 days).

The results of the present study suggest that Ismigen is effective in advanced COPD patients, those with severely impaired lung function and, consequently, at high risk (the usual population that is treated with a combination of long-acting $ß_2$-agonist plus an inhaled corticosteroid according to the recommendations of international guidelines [Rabe *et al*. 2007; Celli and MacNee 2004]), and its protective effect may be additive to the other treatments. This last issue seems to be important and tries to give an answer to the fundamental question risen by Solèr [2005], who correctly highlighted that, considering that the mechanism of action of bacterial immunostimulants is distinctly different from that of the inhaled 'standard treatments' for COPD, we must understand if the combined use of an effective inhaled anti-inflammatory regimen and/or bronchodilator regimen and the immunomodulating oral bacterial immunostimulants might lead to an additive or even better protection from COPD exacerbations.

Noticeably, we must emphasize that this study does not allow a solid conclusion because it is clearly underpowered. Nevertheless, its signal is strong enough to suggest a large confirmatory study. The results of the TORCH trial are certainly encouraging and show that continued treatment is critical in patients with COPD [Calverley *et al*. 2007]. However, the persistence of the risk of exacerbations clearly indicates that treatment with a combination of long-acting $ß_2$-agonist plus an inhaled corticosteroid is not enough and there is a need for therapeutic integration. Given the crucial impact of exacerbations on the progression of COPD, a large study that will confirm the signal that we have observed will be decisive, and this fits with the opinion of the Global Initiative of Chronic Obstructive Lung Disease (GOLD) that additional studies to examine the long-term effects of immunomodulators are required before their regular use can be recommended [Rabe *et al*. 2007].

Conflict of interests statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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