ORIGINAL ARTICLE

Prophylaxis for acute exacerbations of chronic bronchitis using an antibacterial sublingual vaccine obtained through mechanical lysis: a clinical and pharmacoeconomic study

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Abstract. Chronic obstructive bronchitis (COB) complicated by acute exacerbations, or exacerbations, triggered by episodes of infection is the most demanding respiratory disease in our country today, to the extent that the implementation of every possible prevention strategy, in terms of both behaviour and prophylactic vaccination, is fully justified. From this point of view, in addition to the classic anti-viral vaccines, increasing importance is also being placed on antibacterial vaccines obtained by mechanically crushing pathogen bacteria (without the use of chemicals to denature the antigenic structures), which can be sublingually administered. In this study, conducted on 57 patients aged over 75 suffering from COB and affected by at least one exacerbation over the past 12 months, we evaluated the incidence of these exacerbations during a follow-up period, subsequent to prophylaxis with polyvalent bacterial mechanical lysate. As well as the absolute number of episodes, we also evaluated the seriousness of the episodes, the length of any antibiotic therapy and the overall cost of this therapy and of the prophylactic treatment. We then compared this data with that of the same period for the previous year, during which time no antibacterial prophylaxis had been administered. Both the absolute number of exacerbations, their length and seriousness were shown to be significantly reduced during the period of treatment compared to the control period. Similarly, the need to use antibiotic treatments, as well as the overall cost of the treatment of these patients, were shown to be reduced during the period of treatment compared to the control period.

Key words: Chronic obstructive bronchitis (COB), COB exacerbations, prophylactic vaccine, polyvalent mechanical bacterial lysate (PMBL)

Introduction

Chronic obstructive bronchitis (COB) complicated by acute exacerbations triggered by episodes of infection is the most demanding respiratory disease in Italy today. More than 7 million visits/year, 130,000 hospitalizations, 1,330,000 days in hospital and an absolute mortality rate of approximately 18,000 deaths/year (ISTAT data 1993-1996): these are the dramatic figures that describe this disease (1).

When faced with this data and its clear clinical and socio-economical importance, there can be no doubt over the need to implement every possible useful health strategy that can exert a positive influence on such an important phenomenon, above all in terms of prevention.

The first level of prevention is, of course, based on improving hygienic conditions in the lives of these patients: the recommendations are well-known and range from tobacco smoke avoidance to limiting as far as possible the amount of time spent in areas with high levels of pollution, and so on.

All such actions are undoubtedly useful. But a second level of prevention should also follow and has, in fact, actually been recommended, among other things, by the Council of the European Union (2) and involves vaccination programmes, which are also seen as a way to reduce the incidence of episodes of infection and thus the need of antibiotic therapy.

Among the vaccination programmes available today, particular attention is being paid, in addition to the anti-influenza vaccines, to antibacterial or anti-catarrh vaccines, which in the form of the most recently conceived bacterial lysates achieved by mechanical lysis and sublingual administration (Polyvalent Mechanical Bacterial Lysate – PMBL), have proved to be able to guarantee a specific effective prophylactic vaccination both in experimental and clinical contexts.

Among the most recent available literature we would like to mention two interesting articles published by Prof Melioli's group at the IRCCS Gaslini (Paediatric Hospital), Genoa: the first (3) presented in April 2001, on the occasion of the Congress "From chronica bronchitis to asthma: diagnostic approaches and specialist integration" promoted in Rome by the Italian COPD Association, and the second discussed in its Abstract form at the European Respiratory Society 2002 Congress in Stockholm (Abstract, ERS 2002, Stockholm). In actual fact, the works describe the endpoints of the same study programme carried out on 41 patients suffering from recurrent respiratory tract infections, with the aim to determine the effective rise in saliva antibody titre following the administration of a new polyvalent mechanical bacterial lysate (PMBL). The results well demonstrated an increase in the mean saliva antibody titre of around 100% in terms of IgA, IgG and IgM, in approximately 70% of the patients treated.

The second publication, on the other hand, discussed the results in terms of the power of PMBL treatment to bring about an increase in the capacities of direct opsonization of pathogen bacteria (*S. aureus*) in patients affected by recurrent respiratory tract infections.

The protocol in this part of the study involved the collection of saliva samples from the patients before and after the treatment with PMBL. The saliva samples were then tested on a laboratory sample of *S. aureus*: at the end of the incubation period, granulocytes obtained from a healthy donor were added to the samples. After further 24 hours, the bacterial colonies still present on the plates were counted: in the patients treated with PMBL and in which a rise in antibody titre was noted, the number of live bacteria at the end of the study was considerably lower than that found in the pre-treatment control sample.

These laboratory results confirm that treatment with PMBL increases the specific antibody titre against the wall structures of important pathogen bacteria with increased opsonization of live microbes and, in conclusion, more effective phagocytosis and killing by the granulocytes.

This data is of great importance, as "an effective and specific immune response should guarantee the rapid destruction of the infecting agent before the onset of the symptoms, forming a complete and effective prophylaxis, reducing the frequency of episodes of fever, the use of antibiotics and the selection of further strains of antibiotic-resistant bacteria" (1). This follows precisely in the tracks of the indications of the European Commission and the works such as that of Collet et al (4) in 2001, which confirm the benefits of an antibacterial, immunoprophylactic therapy in patients suffering from chronic bronchitis.

To further prove our point, we would finally like to mention the clinical work presented by Rossi and Tazza in June 2002 (5) at the "National Congress of the Italian Section of the American College of Chest Physicians", called "Evaluation of the efficacy and tolerability of a new immunostimulant vaccine obtained through mechanical lysis in the prevention of infectious diseases of the lower respiratory tract".

In this observational clinical trial, chemically obtained bacterial lysate group vs. non-treated control group, on 69 patients with a history of recurrent respiratory tract infection in the 12 months leading up to the trial, the Authors aimed to evaluate the effective capacity of antibacterial vaccines to reduce the number and the seriousness of the episodes of bacterial infection in the lower respiratory tract. The data collected show a reduction both in the effective number of episodes occurring and in their seriousness in terms of length of the episode itself, length of the an-

tibiotic therapy and symptoms of dyspnoea. This is true both with regard to the comparison between the two types of treatment vs. the non-treated group, and in particular in the direct comparison of the mechanical lysate treatment with that using the more traditional chemically obtained lysates.

The greater effectiveness of the PMBL sublingually administered is due to the reduced risk of denaturation of the antigenic structures in the bacterial cell walls, compared to the classic chemical lysis, and the fact that the antigen, not passing through the gastric tract, is not altered: in any case, besides the advantages offered by one method as opposed to the other, we found it interesting to evaluate the effective efficacy in both clinical and pharmacoeconomic terms of a prophylactic treatment using a recently created PMBL (Ismigen®) in a group of elderly patients hospitalized in a rest home who, in the 12 months prior to the investigation, had suffered at least one infection-induced exacerbation of chronic bronchitis.

An infection-induced exacerbation of chronic bronchitis is characterized by fever and productive cough with often-purulent sputum (1). Patients suffering from chronic bronchitis are more susceptible to both bacterial and viral infections due to an immune deficit caused in particular by the alteration of the CD4/CD8 ratio in favour of the latter, characterized by a Killing/suppressor action on lymphocyte B (6), leading to a decreased capacity of the monocyte to migrate in relation to chemiotactic stimuli and a loss of phagocytic capacity as well as a lower local production of IgA (7-11).

Design and aims of the study

An open observational study was conducted with a view to evaluate, both in clinical and pharmacoeconomic terms, the prophylactic effectiveness of a PMBL (Ismigen®) against acute exacerbations of chronic bronchitis, sublingually administered in elderly patients suffering from Chronic obstructive bronchitis (COB). The study design involved the administration of the drug to a group of over-75s, hospitalized in a rest home in the province of Milan. As well as being predisposed to exacerbations due to a number of factors intrinsically linked to old age and concomitant degenerative diseases (diabetes mellitus, heart disease, etc), these patients also offered the "advantage" of staying in the same place, a setting with hotel-type, uniform eco-environmental characteristics, and this fact enabled us to draw conclusions that are, in our opinion, methodologically sustainable despite the relatively small study population involved.

The trial was conducted according to a study pattern involving a cycle of administration during the period from september-november 2002, with follow up throughout the period september 2002-february 2003.

Enrolment inclusion criteria were: age over 75 years, medical history of COB, at least one exacerbation with a score greater than 8 (Fig. 1) in the 12 months leading up to the trial. Exclusion criteria were: concomitance of serious neuro- or cardiovascular diseases that could significantly limit the autonomy of the patient, kidney or liver failure or significant alteration of the immune defences or previous prophylactic therapies using bacterial lysates or other pharmaceuticals that could interfere directly with the immune system, excluding anti-influenza prophylactic vaccination administered in the 18 months prior to the trial.

The primary endpoint of the study was to evaluate the clinical impact of the prophylactic therapy using PMBL, in terms of both number and seriousness (measured using clinical evaluation with analo-

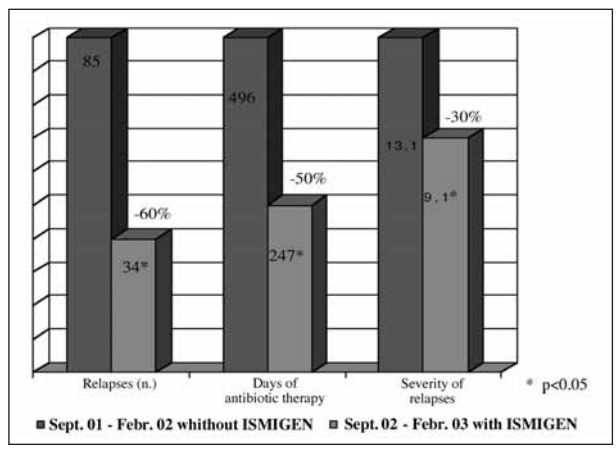

Figure 1. Comparison between treatment and control period in 57 patients

gue scale and length of any required antibiotic therapy) of the acute exacerbations that took place between september 2002 and february 2003, compared to the control period, i.e. the same period of the previous year during which no antibacterial prophylaxis had been carried out.

A secondary endpoint was the evaluation of the economic impact of the prophylactic therapy + any antibiotic therapy administered during the study vs. any antibiotic therapy administered during the same period of the previous year.

All patients enrolled declared their willingness to participate in the study by completing the informed consent form specifically drawn up for this purpose.

They all had been vaccinated against influenza both during the season covering the study and the previous season.

Materials and methods

At the beginning (T0) and end (TF) of the study, the patients underwent a full medical examination, during which the following data were recorded: personal details (main demographic information), main details of medical history with specific reference to episodes of infection over the previous year, as documented in the internal clinical records for the long-term hospitalization patients, or in suitable medical certificates for those only recently hospitalized. An objective chest and general examination was then carried out on the patient, recording any other concomitant therapies. A series of blood tests were also carried out, including haemochrome, renal and liver function parameters, glycaemia, IgA, IgM, IgG serum. The clinical evaluation of any exacerbations occurring during the study was made by the GIS (Gravity Illness Score) visual-analogue scale (Tab. 1), which we have been using for some time and which was also applied to the episodes occurred in the same patients during the control period of the previous year.

The length of any antibiotic therapies was measured in terms of days/therapy on the basis of the patients' clinical records and the cost of the various therapies was taken from the prices marked on the commercial packaging of the different administered products.

Table 1. GIS visual-analogue scale

Fever	Absent	0
	37-37.5°C	1
	37.5-38°C	2
	>38°C	3
Cough	Absent	0
	Light	1
	Medium	2
	Heavy	3
Dyspnoea	Absent	0
	Light	1
	Medium	2
	Heavy	3
Expectoration (quality)	Absent	0
	Mucous	1
	Mucous-purulent	2
	Purulent	3
Expectoration (quantity)	Absent	0
	2-5 cc	1
	5-10 cc	2
	> 10 cc	3
Cyanosis	Absent	0
	Present	1
Thoracic objectivity	Normal	0
	Whistle	1
	Wheeze	2
	Wheeze + whistle	3

The prophylactic therapy was administered using Ismigen® (Zambon), an antibacterial vaccine obtained by mechanical lysis, without the use of any chemical products to denature the antigenic structure of 8 different species of bacteria (Tab. 2). The protocol involved the sublingual administration of Ismigen® at

Table 2. Qualitative composition of Ismigen®

Streptococcus pneumoniae
Haemophilus influenzae
Moraxella catarrhalis
Staphylococcus aureus
Streptococcus pyogenes
Streptococcus viridans
Klebsiella pneumoniae
Klebsiella ozaenae

a dosage of one tablet per day for ten days for three consecutive months.

The demographic and medical history details were evaluated through descriptive statistics, expressed in terms of mean ± standard deviation. The data were compared using Student-Newman-Keuls tests with $p<0.05$ as the limit for statistical significance.

Results

Fifty-seven patients were enrolled in the study (25 males, 32 females, mean age 85.9±5.67); this number represented the total number of patients hospitalized in the rest home, during the period of the study, able to meet the inclusion criteria.

During this study period (treatment plus follow-up), from september 2002 to february 2003, the total number of exacerbations recorded in the treated patients dropped to 34 (with a maximum of two episodes and a minimum of zero episodes per patient), against the 85 episodes recorded during the control period of the previous year (with a maximum of three episodes and a minimum of two episodes for patient) with a significative statistical difference ($p<0,05$) (Tab. 3). As far as the gravity of the exacerbations is concerned, clinical evaluation (GIS scale) showed a drop in the GIS index from 13.1±3.4 during the control period from september 2001 to february 2002 ($p<0.05$) to 9.1±2.1 ($p<0.05$), during the treatment period from september 2002 to february 2003.

At the same time, the absolute number of days of antibiotic therapy dropped from 496 during the control period of the previous year to 247 following treatment with PMBL (Ismigen®) (Tab. 3, Fig. 1) with a maximum of 32 vs. 20 ($p<0.05$) days of therapy.

As far as the laboratory data is concerned, in particular an increase in serum immunoglobulin levels should be noted, maintaining the statistical significance from the beginning to the end of the study only for IgG (Tab. 4).

In conclusion, as far as the secondary pharmacoeconomic endpoint is concerned, it should be noted that the mean cost of the antibiotic therapy during the period from September 2001- February 2002 was 3,459.60 Euro, while during the period from september 2002 – february 2003 it was only 1,499.40 Euro (-57%). This result is more important in the daily management of patients suffering from recurrent respiratory tract infections, according to the recommendations of the European Union Council to avoid improper use of antibiotics and the consequent increase of the bacterial resistances. Adding the latter amount to the cost of the prophylactic therapy with Ismigen®, according to the previously described protocol, equal to 1,295.04 Euro, the total cost of 2,794.44 Euro, obtained for the pharmaceuticals considered during the period 2002-2003, is in any case significantly lower (-20%) than the cost for the same period of the previous year (an extremely important saving for the health structure management) (Tab. 5, Fig. 2).

Table 3. Incidence and gravity of exacerbations episodes: comparison between treatment and control period

	September 2001-February 2002 without PMBL control period	September 2002- February 2003 with PMBL treatment period
No. of patients	57	57
No. of episodes of bronchial infection	85	34 ($p<0.05$)
Range per patient	(0-3)	(0-2)
Mean per patient	1.49	0.59
No. of days of antibiotic treatment	496	247 ($p<0.05$)
Range per patient	(0-32)	(0-20)
Mean per patient	8.7	4.3
Gravity of exacerbations (GIS mean: control period vs treatment period)	13.1±3.4	9.2±2.1 ($p<0.05$)

Discussion

The above-described data, which have been taken from a very simply designed observational study, seem, to all effects and purposes, to be in line with the evidence currently available in literature, consistent with the hypothesis that the sublingual administration of PMBL, i.e. products based on surface bacterial antigens, whose structure is not denatured by the use of chemicals, but obtained by simple mechanical crushing of the pathogens, can lead to a specific antibody response to the surface structure of pathogen bacteria. This can bring about unquestionable advantages, both clinical – at least in terms of the lower incidence and seriousness of acute exacerbations in elderly patients such as those examined, - and socio-economic, in view of the heavy costs incurred in connection with these diseases over the last few years in industrialized countries (12, 13). From this standpoint, we also need to consider that our evaluation is limited to what we can only define as the economics of the pharmaceutical, without entering into a more detailed evaluation in terms of general pharmacoeconomics, which also has to consider the additional expenses linked to the overall support of such "difficult" patients, if only for their age. We can, however, presume that such evaluation, when faced with lower incidence, shorter duration and reduced seriousness of the acute exacerbations themselves, is only able to confirm what has already been observed in simple pharmaceutical economics terms.

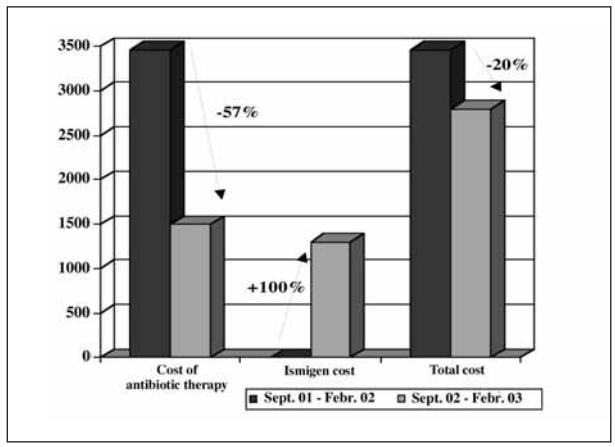

Figure 2. Graphic rappresentation of pharmaceutical costs

We can therefore conclude that a specific antibacterial prophylactic vaccination obtained by PMBL sublingually administered may represent a useful prophylactic aid in COB (6), to be used in tandem with the other consolidated prevention strategies, that range from behavioural strategies to anti-influenza vaccination (14), helping to improve the capacities to face bacterial suprainfections able to cause serious and highly dangerous episodes of infection, above all in already debilitated patients such as those included in our study.

Table 4. Variation in serum immunoglobulin

Serum immunoglobulin	T0	TF
IgA	335.9	367.1
IgG	1255.6	1435.4 ($p<0.05$)
IgM	128.7	142.5

T0 = beginning of study; TF = 3 months + follow-up period

Table 5. Cost of pharmaceuticals

September 2001- february 2002	Cost of antibiotic treatment	Cost of the Ismigen® treatment	Total
	3459,60 euro	0	3459,60 euro
September 2002- february 2003	Cost of antibiotic treatment	Cost of the Ismigen® treatment	Total
	1499,40 euro	1295,04 euro	2794,44 euro
	Saving on antibiotic treatment during the period of the study -57%	Overall saving following treatment with Ismigen® -20%	

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