CLINICAL EFFECTIVENESS OF BRONCHO-VAXOM (BV) IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Summary: *Sixty-two adult patients of both sexes with chronic obstructive pulmonary disease (COPD) participated in a double-blind, placebo-controlled trial to determine the effects of treatment with Broncho-Vaxom (BV), an immunomodulating agent, administered orally in capsule form. Clinical manifestations, frequency, duration and severity of acute exacerbations, consumption of conventional medications and serum immunoglobulin levels were observed over a period of 6 months during the autumn/winter of 1990–1991. Treatment with BV produced a statistically significant decrease, especially after the third month, in the mean score of the clinical signs, as well as in the cumulative index and in the number, severity and duration of acute exacerbations. In addition, a significant reduction in the use of conventional therapy was noticed.*

Introduction

Chronic obstructive pulmonary disease (COPD) describes a condition of persistent, largely irreversible, airway obstruction, in which the underlying pathophysiology is not precisely known. The term excludes conditions characterized by persistent obstruction, in which the mechanism of obstruction is known, such as asthma, bronchiectasis, cystic fibrosis and alpha 1-protease inhibitor deficiency (1, 2). It is a worldwide health problem exhibiting an increase in death and disability rates with an important economic impact (2). Acute exacerbations, which probably accelerate deterioration of the lung function (3), caused by viral and bacterial infections, are precipitated by impaired immunological responses at the bronchial level (4).

Knowledge of the properties of mucosal-associated lymphoid tissue (MALT) has led to the concept of strengthening the natural immune defence mechanisms, particularly against infections, as an essential measure in the prevention of the acute exacerbations of COPD and better control of the disease (5). Purified bacterial extracts have been found to possess immunomodulating activity capable of enhancing both the specific and non-specific immune responses (6).

Broncho-Vaxom (OM Laboratories, Geneva, Switzerland) is a bacterial extract drawn from eight strains that are commonly responsible for respiratory tract infections. Its therapeutic efficacy has been demonstrated in double-blind trials in adults and children with recurrent respiratory tract infections (7–17). The aim of this double-blind, placebo-controlled trial was to evaluate the effect of Broncho-Vaxom (BV) on the clinical manifes-

tations, frequency, duration and severity of acute exacerbations, use of conventional therapy and on serum levels of certain immunoglobulins.

Patients and methods

The trial took place over a period of 6 consecutive months during the autumn/winter of 1990–1991. Out of 104 patients who were initially chosen for the trial, only 62 completed the 6-month period of follow-up. The rest interrupted the observations for reasons unrelated to treatment (20 in the BV and 22 in the placebo group). The two groups were comparable regarding pretreatment characteristics. Table I summarizes the general characteristics of the 62 patients. Patients eligible to participate in the trial were those with COPD and who were susceptible to recurrent exacerbations (at least three during the corresponding period of the previous year). Patients who had been treated with corticosteroids, immuno-suppressive or immuno-stimulant agents were excluded.

The patients were randomly allocated to either the Boncho-Vaxom (BV) or the placebo group. They received 1 capsule daily of either BV or placebo during the first month and then 1 capsule on each of the first 10 days of the third, fourth and fifth month. No therapy was given during the second and the sixth month. The taste, size and colour of the BV capsules and placebo were identical.

Only three patients in the BV and five patients in the placebo group were on medication with $\beta2$-adrenergics, while the rest in both groups were receiving no medication prior to the trial. During the trial, conventional therapy (antibiotics, bronchodilators and antitussives) was given as needed.

Clinical examination was performed at the beginning and then monthly up to the end of the 6-month period. Symptoms and signs (dyspnoea, cough, expectoration, signs on auscultation) were recorded on a five-point scale ranging from 0 (not present) to 4 (very severe), while a cumulative index defined the sum of the graded symptoms or signs.

The quantity and quality of the morning expectoration were also evaluated. The morning expectoration was collected in dosimetric cups and the quantity was grade as nil, small (<5 ml), medium (5–15 ml) and large (>15 ml). The quality was defined as purulent (yellowish colour without distinction between neutrophils or eosinophils) or non-purulent. The number, the severity and the duration of the acute exacerbations were recorded as well as the concomitant treatment of the exacerbations. The exacerbations were characterized by the appearance of fever or the increase in one of the following symptoms: dyspnoea, cough and sputum production.

The serum immunoglobulin (IgG, IgA and IgM) levels were measured before treatment and after the third and sixth month.

Table I *Patients' characteristics at the outset of the study.*

Characteristics	BV (n = 33)	Placebo (n = 29)	p value
Age (years)	56.03 ± 12.67	59.75 ± 12.89	n.s.
Sex (male/female)	23/10	20/9	n.s.
FVC (litres)	3.9 ± 0.85	4.14 ± 0.94	n.s.
FEV1 (litres)	2.8 ± 0.74	2.95 ± 0.65	n.s.
Medication ($\beta2$-adrenergics)	3	5	n.s.
Smokers	20	16	n.s.
Non-smokers	13	13	n.s.

The results were analysed using the Mann-Whitney test for evaluation of group differences, the Wilcoxon test for comparison of values before and after every month of Broncho-Vaxom administration, and the non-parametric Z-test for the difference between the two groups with respect to quantity and quality of the morning expectoration.

Results

At the beginning of the trial, the two groups were well-matched considering age, sex, duration of the disease, smoking habits and clinical characteristics (Table I).

Clinical manifestations

The severity of the clinical features (dyspnoea, cough, expectoration and auscultatory signs) showed a statistically significant improvement in the BV group compared to the placebo group,

especially after the 3rd month. However, the mean cumulative index of severity was statistically significantly lower in the BV group (p < 0.001), compared to the placebo group starting from the 3rd month onwards. In the 4th month, it had decreased in the BV group by 3.22%, while in the placebo group it had increased by 50.13%. At the end of the six-month period, it had decreased in the BV group by 43.97% (p < 0.001) compared to the period before treatment, whereas in the placebo group it had increased by 9.67% (Table II and Fig. 1).

Morning expectoration

The patients in the BV group showed a marked tendency towards a lower amount of retention of morning expectoration in comparison to those of the placebo group. Thus, in the 4th month, 39% of the BV group patients showed a small amount of morning expectoration compared with only 7% in the placebo group. In contrast, only 18% of the BV group had a large amount of morning expectoration

Table II *Changes in the mean severity indices of the clinical features at different stages of the 6-month period.*

Clinical features	Group	Before treatment	After 3 months	After 4 months	After 5 months	After 6 months
Dyspnoea	BV	0.24 ± 0.49	0.21 ± 0.48	0.24 ± 0.57	0.06 ± 0.31	0.03 ± 0.18
	Placebo	0.31 ± 0.47	0.48 ± 0.51	0.48 ± 0.48	0.38 ± 0.52	0.28 ± 0.28
			n.s*	n.s*	p < 0.005*	p < 0.001*
Cough	BV	1.36 ± 0.77	1.39 ± 0.94	1.27 ± 0.87	1.06 ± 0.78	0.94 ± 0.91
	Placebo	1.31 ± 0.83	1.76 ± 0.91	1.83 ± 0.91	1.69 ± 0.76	1.48 ± 0.82
			p < 0.001*	p < 0.001*	p < 0.001*	p < 0.001*
Expectoration	BV	1.24 ± 0.57	1.48 ± 0.76	1.27 ± 0.70	1.06 ± 0.81	0.73 ± 0.48
	Placebo	1.31 ± 0.64	1.90 ± 0.92	2.00 ± 1.02	1.83 ± 0.79	1.62 ± 0.79
			n.s*	p < 0.001*	p < 0.001*	p < 0.001*
Auscultatory signs	BV	0.82 ± 0.64	0.76 ± 0.79	0.79 ± 0.92	0.67 ± 0.69	0.42 ± 0.47
	Placebo	0.90 ± 0.78	1.21 ± 0.90	1.45 ± 0.89	1.28 ± 0.86	0.93 ± 0.67
			p < 0.02*	p < 0.001*	p < 0.001*	p < 0.002*
Cumulative index	BV	3.73 ± 1.87	3.79 ± 2.12	3.61 ± 1.95	2.85 ± 2.08	2.09 ± 1.72
	Placebo	3.93 ± 2.03	5.45 ± 2.75	5.90 ± 2.12	5.17 ± 2.48	4.31 ± 2.46
			p < 0.001*	p < 0.001*	p < 0.001*	p < 0.001*

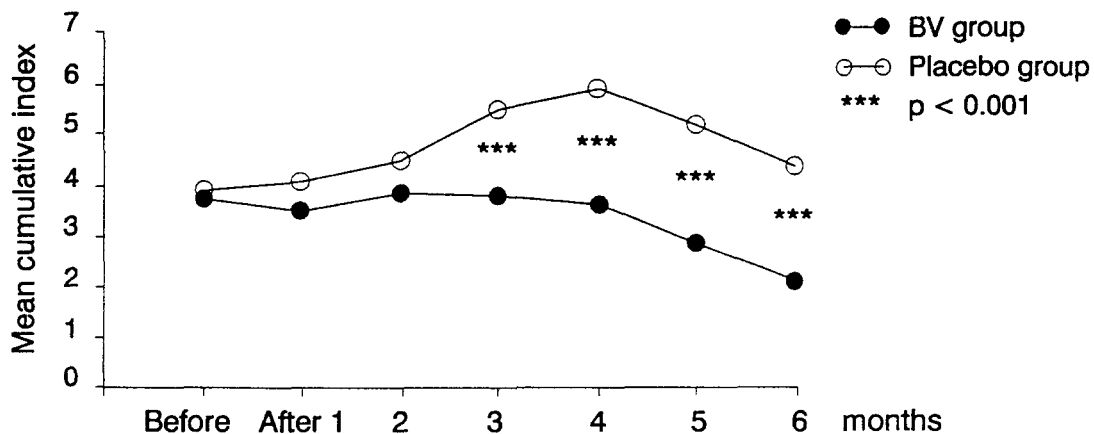* Mann-Whitney test for evaluation of the two group differences.

Fig. 1 Changes in the mean cumulative index of severity during the six-month period.

compared to 69% in the placebo group, while in the group experiencing a medium amount, the figures were 42% and 24% respectively. The same conditions were apparent after the 5th and 6th months (Table III). It is worth mentioning that after the 6th month 18% of the BV group did not have any morning expectoration at all compared to 3%

in the placebo group. As far as the purulence of the expectoration was concerned, the proportion of patients with purulent expectoration was significantly lower in the BV group than in the placebo group starting from the 3rd month and remaining so up to the end of the 6-month period (Table III, Fig. 2).
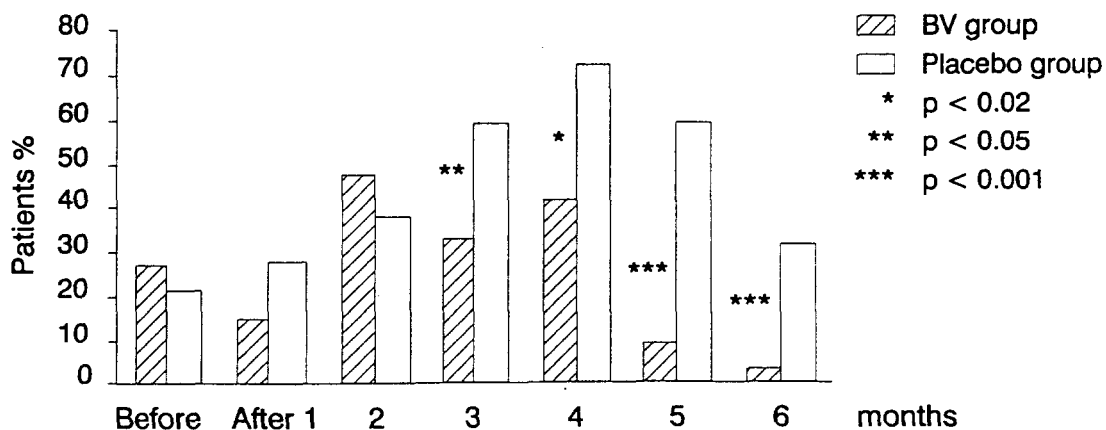

138   **Fig. 2** Changes is the percentage of patients with purulent morning expectoration during the 6-month period.

Table III *Changes in the percentage of patients according to the amount and the purulence of the morning expectoration.*

Time	Group	Morning expectoration				
		Small	Medium	Large	Nil	Purulent
Before	BV	55%	24%	12%	9%	27%
Treatment	Placebo	52%	31%	7%	10%	21%
		n.s*	n.s*	n.s*	n.s*	n.s*
After	BV	55%	33%	6%	6%	15%
1st month	Placebo	31%	41%	17%	11%	28%
		n.s*	n.s*	n.s*	n.s*	n.s*
After	BV	30%	36%	33%	1%	33%
3rd month	Placebo	24%	24%	48%	4%	59%
		n.s*	n.s*	n.s*	n.s*	$p < 0.05$*
After	BV	39%	42%	18%	1%	42%
4th month	Placebo	7%	24%	69%	0%	72%
		$p < 0.001$*	n.s*	$p < 0.001$*	n.s*	$p < 0.02$*
After	BV	36%	45%	12%	7%	9%
5th month	Placebo	14%	34%	52%	0%	59%
		$p < 0.05$*	n.s*	$p < 0.001$*	n.s*	$p < 0.001$*
After	BV	58%	18%	6%	18%	3%
6th month	Placebo	24%	52%	21%	3%	31%
		$p < 0.01$*	$p < 0.01$*	n.s*	n.s*	$p < 0.001$*

* *Z-test for evaluation of the two group differences.*

Table IV *Changes in the number, severity and duration of acute exacerbations during the 6-month period.*

Acute exacerbations	Group	1st month	2nd month	3th month	4th month	5th month	6th month
Number	BV	13	12	23	14	12	3
	Placebo	10	13	20	28	15	12
		n.s*	n.s*	n.s*	$p < 0.001$*	$p < 0.05$*	$p < 0.001$*
Mean	BV	2.08 ± 1.32	2.17 ± 1.52	2.04 ± 1.43	1.93 ± 1.39	1.50 ± 1.27	1.33 ± 1.27
severity	Placebo	2.00 ± 1.27	1.97 ± 1.34	2.00 ± 1.31	2.39 ± 1.48	1.73 ± 1.25	1.58 ± 1.26
		n.s*	n.s*	n.s*	$p < 0.001$*	$p < 0.05$*	$p < 0.01$*
Mean	BV	3.85 ± 1.72	4.17 ± 2.54	3.30 ± 1.82	3.36 ± 2.00	2.75 ± 1.80	2.67 ± 1.84
duration	Placebo	4.50 ± 1.86	3.38 ± 1.57	3.65 ± 1.74	4.50 ± 2.33	3.27 ± 1.77	2.83 ± 1.96
		n.s*	n.s*	n.s*	$p < 0.001$*	$p < 0.05$*	$p < 0.002$*

* *Mann-Whitney test for evaluation of the two group differences.*

Acute exacerbations

During the first 3 months of the trial, the differences between the two groups with respect to the mean corresponding to the number, severity and duration of acute exacerbations were not statistically significant. However, from the 4th month up to the end of the 6-month period, a statistically significant difference in favour of the

BV group was observed in the mean number, the mean score of severity and the mean duration of acute exacerbations, as shown in Table IV and Fig. 3.

Concomitant treatment

The need for concomitant medication was anal-

Table V Changes in the mean values of immunoglobulins at different stages of the 6-month period.

Immunoglobulin	Group	Before treatment	After 3 months	After 6 months
IgG	BV	1171.21 ± 187.22	1263.55 ± 211.12	1307.79 ± 208.79
(800–1800 mg %)	Placebo	1145.66 ± 174.51	1220.34 ± 194.76	1265.32 ± 197.83
		n.s*	n.s*	n.s*
IgA	BV	201.58 ± 85.64	253.79 ± 96.27	258.18 ± 97.30
(90–450 mg %)	Placebo	216.86 ± 91.28	247.14 ± 93.54	247.46 ± 94.15
		n.s*	n.s*	n.s*
IgM	BV	147.73 ± 77.42	174.55 ± 80.64	175.52 ± 79.36
(60–128 mg %)	Placebo	145.76 ± 84.17	164.72 ± 79.82	169.75 ± 81.27
		n.s*	n.s*	n.s*

Figures in parenthes are normal ranges.
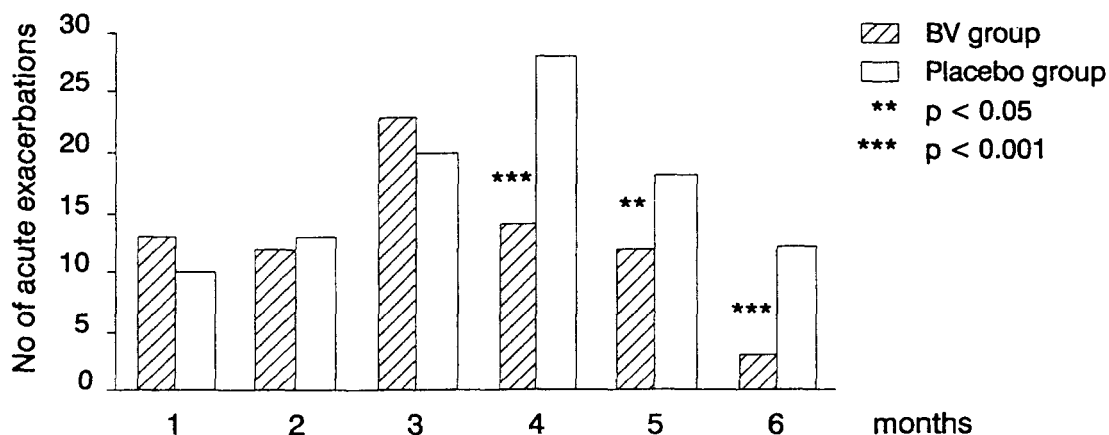* Mann-Whitney test for evaluation of the two group differences.

Fig. 3 Changes in the mean number of acute exacerbations during the 6-month period.

ogous to the evolution of the number and severity of acute exacerbations during the 6-month period. Thus, the incidence of patients who were treated with antibiotics by the attendant physicians during the first 3 months of the trial did not differ significantly between the two groups. But in the 4th month, only 30% of the BV patients received antibiotics compared to 72% of the placebo group ($p < 0.002$, Z-test). A similar difference was observed in the sixth month with rates of 3% and 34% for the BV and placebo groups respectively ($p < 0.001$).

The need for bronchodilators was high during the whole period, but the rates differed significantly in the fourth month, i.e. 30% against 59%, ($p < 0.05$) and in the sixth month 21% against 41%, ($p < 0.01$) in the BV and placebo groups respectively. The incidence of patients who received antitussive and expectorant agents reached the level of statistical significance in the fourth, fifth and sixth months, with rates of 30% against 72% (< 0.005), 27% against 45% ($p < 0.05$) and 3% against 31% ($p < 0.001$) respectively in favour of the BV group.

Immunoglobulin levels

The mean serum levels of IgG, IgA and IgM were normal before treatment in both groups and remained within normal ranges during the trial (Table V).

Discussion

The results of this double-blind placebo-controlled study in 62 adult patients with chronic obstructive pulmonary disease has demonstrated the beneficial effect of Broncho-Vaxom in the management of this disease. It should be mentioned that obvious differences between the two groups, for all parameters, were observed at least in or after the third month, a delay not reported in other studies (8, 9,

11, 14, 15). This may be due to the fact that BV has either a delayed effect, or that better weather conditions in Southern Europe mean patients suffering from COPD do not need to seek medical attention before the winter.

The symptoms and signs that are directly attributable to inflammation at the bronchial level (cough, expectoration and auscultatory signs) showed a statistically significant reduction in their mean score in the BV group, compared to the placebo group and this from the fourth month onwards. However, the cumulative index of the clinical parameters showed a statistically significant difference in favour of treatment with BV starting from the third up to the sixth month of the trial. This fact is in accordance with the improvement of bronchial mucosal lesions by BV demonstrated by other investigators (10) and its favourable influence on the evolution of the disease.

The decrease in the number, severity and duration of acute exacerbations in the BV group is in accordance with the results observed by the investigators, showing evidence that BV enhances cell-mediated immunity, increases sIgA, activates macrophages and confers active protection against bacterial infections (12, 16). Thus, BV may be used as a preventive agent in patients susceptible to recurrent exacerbations of COPD. As already noted by other authors (17), BV did not change the normal immunoglobulin levels which remained in both groups within normal ranges during the whole trial.

Conclusions

Broncho-Vaxom is endowed with evident clinical efficacy in the management of patients with chronic obstructive pulmonary disease and may play a crucial role in the recovery of these patients.

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References

(1) Fletcher C.M., Pride N.B. *Definition of emphysema, chronic bronchitis, asthma and airflow obstruction.* (Editorial) Thorax, **39**, 81, 1984.

(2) Fraser R.G., Parre J.A.P., Parre P.D., Fraser R.S., Generaux G.P. (eds.). *Diseases of the airways.* In: "Diagnosis of diseases of the chest". Vol. III, W.B. Saunders Co., Philadelphia, 1990, p. 2087.

(3) Gurvitz D. et al. *Pulmonary function and bronchial reactivity in children after croup.* Am. Rev. Respir. Dis., **122**, 95, 1980.

(4) Green G.M. et al. *Defence mechanisms of the respiratory membrane.* Am. Rev. Respir. Dis., **115**, 479, 1977.

(5) Bienenstock J., Clancy R. *A framework for immunization strategy.* In: Bienenstock J. (ed.) "Immunology of the lung and upper respiratory tract." McGraw-Hill Co., New York, 1984.

(6) Bessler W.G. et al. *Biological activity of bacterial surface components: Bacterial extract and defined bacterial cell wall components as immunomodulators.* Lung (Suppl.), 707–715, 1990.

(7) Messerli C. et al. *A bacterial lysate (Broncho-Vaxom) in chronic bronchitis: A multicentre double blind, clinical trial.* Rev. Med. Suisse Romande, **101**, 143–146, 1981.

(8) Palma-Carlos A.G., Palma-Carlos M.L. *Immunomodulation with bacterial extracts in respiratory diseases.* Lung (Suppl), 732–736, 1990.

(9) Djuric O., Mihailovic-Vucinic V., Stojcic V. *Effect of Broncho-Vaxom on clinical and immunological parameters in patients with chronic obstructive bronchitis. A double-blind, placebo-controlled study.* Int. J. Immunother., **III**, 139–143, 1989.

(10) Emmerich B. et al. *Effects of a bacterial extract on local immunity in patients with chronic bronchitis.* Lung (Suppl.), 726–731, 1990.

(11) Cvorisec B. et al. *Oral immunotherapy of chronic bronchitis: A double-blind placebo-controlled multicentre study.* Respiration, **55**, 129–135, 1989.

(12) Maestroni G.J.M., Losa G.A. *Clinical and immunobiological effects of an orally administered bacterial extract.* Int. J. Immuno-pharmacol., **6**, 111–117, 1984.

(13) Debbas N., Derenne J.P. *Preventive effects of an immuno-stimulating product on recurrent infections of chronic bronchitis in the elderly.* Lung, 737–740, 1990.

(14) Keller R., Hinz G. *Effect of an oral polyvalent bacterial lysate (Broncho-Vaxom) in chronic bronchitis.* Prax. Klin. Pneumol., **38**, 225–228, 1984.

(15) Zagar S., Löfler -Badzek D. *Broncho-Vaxom in children with rhinosinusitis: A double-blind clinical trial.* ORL, **50**, 397–404, 1988.

(16) Emmerich B. et al. *Local immunity in patients with chronic bronchitis and the effects of a bacterial extract, Broncho-Vaxom, on T-lymphocytes, macrophages, gamma-interferon and slgA in bronchoalveolar lavage fluid and other variables.* Respiration, **57**, 90–99, 1990.

(17) Copova M., Tomasova M., Sukova B. *Effect of Broncho-Vaxom on some immunologic indices in children with recurrent respiratory diseases. Possibilities of immunomodulation for prevention and therapy of respiratory tract infection.* Proc. 7th Congr. European Society of Pneumology (SEP), Budapest, Sept. 7 1988, p. 11.