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Oral Immunotherapy of Chronic Bronchitis: a Double-Blind Placebo-Controlled Multicentre Study

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Abstract. 104 patients with chronic bronchitis were treated under randomized double-blind conditions with either Broncho-Vaxom® (BV) or a placebo over a period of 6 consecutive months. The beneficial effect of BV was manifested by a statistically significant reduction in the duration of acute episodes and of fever ($p < 0.001$) with respect to the placebo group. The consumption of antibiotics dropped significantly in the BV group ($p < 0.05$) but not in the placebo group. The serum IgA levels increased in the BV group and the difference with the placebo group was statistically significant ($p < 0.05$) from the 3rd month onwards. In the patients with bronchitic exacerbations during the trial, T-lymphocyte counts increased steadily under BV therapy until 3 months after the exacerbation ($p < 0.05$), but not under the placebo. BV was generally well tolerated with the exception of 1 patient who reported nausea and upper abdominal pain. In their assessment of the overall therapeutic effect, the physician judged BV to be significantly superior ($p < 0.001$) to the placebo as regards both the curative and prophylactic efficacy.

Introduction

Infections of the respiratory system, particularly in immunocompromised hosts, represent a major health problem because of the large number of potentially infectious agents in contact with this system. The oral administration of bacterial preparations, in order to activate the body's natural defence mechanisms against pathogens was already recommended more than a hundred years ago [14]. With such an oral therapy, the intestinal lymphoid tissues hold a key role in the development of local and distant immune responses [16].

Broncho-Vaxom® (BV; a product of OM Laboratories Ltd., Geneva, Switzerland, marketed in Yugoslavia under the trade mark of Broncho-Munal®) is an oral nonspecific immunobiotherapeutic drug whose immunostimulating properties and

therapeutic efficacy have been documented in pharmacological and clinical investigations [1–13, 15, 17]. BV for adults is presented as capsules containing 7 mg of a lyophilized bacterial lysate of *Haemophilus influenzae, Diplococcus pneumoniae, Klebsiella pneumoniae* and *ozaenae, Staphylococcus aureus, Streptococcus pyogenes* and *viridans* and *Neisseria catarrhalis.*

The purpose of the present study was to evaluate the curative and prophylactic efficacy of BV on acute episodes of chronic bronchitis and to investigate its influence on various immunological parameters, particularly serum IgA levels and T-lymphocyte counts. The incidence of adverse reactions occurring during the study was also carefully monitored.

Patients and Methods

One hundred-and-four patients with chronic bronchitis in the age range of 20–69 years and suffering from an acute bronchitic episode were randomly treated over 6 consecutive autumn-winter months with 1 capsule of either BV for adults (52 patients) or placebo (52 patients) according to the following schedule:

1st month: 1 capsule daily of either BV or placebo for 30 days; 2nd month: no BV or placebo; 3rd, 4th and 5th month: 1 capsule daily of either BV or placebo on each of the first 10 days of each month; 6th month: no BV or placebo.

Patients suffering from diseases other than mild chronic obstructive bronchitis were excluded as well as those treated concomitantly with corticosteroids or other immunotherapeutics.

Laboratory Investigations

The following investigations were performed: determination of the forced expiratory volume in the first second (FEV_1), erythrocyte sedimentation rate (ESR), determination of serum IgA concentrations by laser nephelometry and radial immunodiffusion (results expressed as changes in percent with respect to baseline values designated as 100%), identification and counting of T-lymphocyte population by the E-rosette technique (results expressed as percentages of rosette-forming T-lymphocytes), sputum bacteriology using blood agar cultures and Gram staining technique.

These parameters were evaluated at baseline and then monthly till the end of the 6-month trial.

Clinical Parameters

Cough, expectoration, dyspnea at rest and effort, fever and the need for concomitant therapy (antibiotics, chemotherapy or others) were recorded on a daily symptom chart. The symptoms of cough, expectoration and dyspnea at rest and effort were rated separately each month using a 3-point scale: 1 = absent, 2 = moderately frequent (weekly), 3 = frequent (daily). The daily cigarette consumption was also noted and the overall therapeutic effect was assessed by the physician at the end of the 6-month study.

Statistical Analysis

The results were analyzed using the following statistical methods: mean values (arithmetic and geometric) and standard deviations, t test for the significance of differences in mean values, Pearson's variability coefficient, correlation coefficient, analysis of variance.

Results

At the beginning of the trial, the two groups were well matched with respect to age, sex, type of chronic bronchitis, previous duration of the disease, mean recurrence rate, smoking habits (duration and average cigarette consumption) and concomitant diseases (table 1).

Symptoms

The frequency of symptoms (cough, expectoration, dyspnea at rest and effort) during the trial decreased in a statistically significant manner in both groups with respect to the initial values. The decrease of

Table 1. Patients characteristics at trial entry

Characteristic	BV (n = 52)	Placebo (n = 52)	p
Mean age and range, years	48.12 ± 3.49 20-64	48.37 ± 3.10 21-69	n.s.
Sex (male/female)	28/24	31/21	n.s.
Type of chronic bronchitis, n (%)			
- Simple	14 (26.9)	14 (26.9)	n.s.
- Mucopurulent	23 (44.2)	20 (38.5)	n.s.
- Obstructive	15 (28.9)	18 (34.6)	n.s.
Previous mean duration of disease, years	11.46 ± 2.47	12.40 ± 2.68	n.s.
Mean annual recurrence rate	3.92 ± 0.88	3.64 ± 0.38	n.s.
Smoking (yes/no)	23/29	16/36	n.s.
- Mean duration, years	24.91 ± 6.36	22.88 ± 5.90	n.s.
- Mean daily cigarette consumption	14.33 ± 3.11	12.41 ± 3.05	n.s.
Concomitant diseases (yes/no)	34/18	28/24	n.s.

The concomitant diseases were not related to pulmonary diseases such as hypertension, diabetes, rheumatoid arthritis, gastric or duodenal ulcers, prostatitis.

these subjective parameters was greater in the BV group than in the placebo group except for the dyspnea at effort, but it did not reach the level of statistical significance. The incidence of febrile episodes during the trial was more or less comparable for the 2 groups, but their mean duration was shorter in the BV group (5.87 ± 2.51 days) than in the placebo group (8.67 ± 3.42 days) as well as their overall duration (229 respectively 373 days, $p < 0.001$).

Acute Episodes

The overall duration of acute exacerbations during the 6 months of the trial was significantly ($p < 0.001$) shorter in the BV group (239 days) than in the placebo group (347 days), as well as their mean duration as shown in figure 1.

Concomitant Therapy

At trial entry, the incidence of patients treated with antibiotics was slightly lower in the placebo group than in the BV group, without a statistically significant difference. During the trial it was significantly reduced in the BV group with respect to entry ($p < 0.05$), but not in the placebo group (fig. 2). On the other hand, the incidence of patients receiving β_2-agonist aerosols was lower at the beginning in the BV group than in the placebo group and remained lower (fig. 3), with a statistically

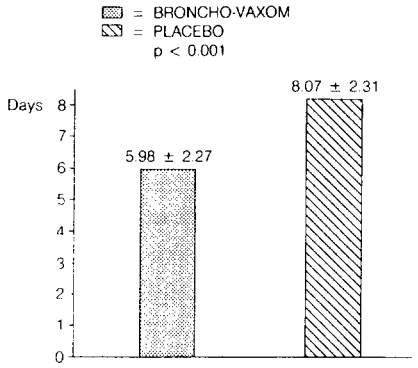

Fig. 1. Mean duration of acute episodes in the BV (52 patients) and placebo groups (52 patients).

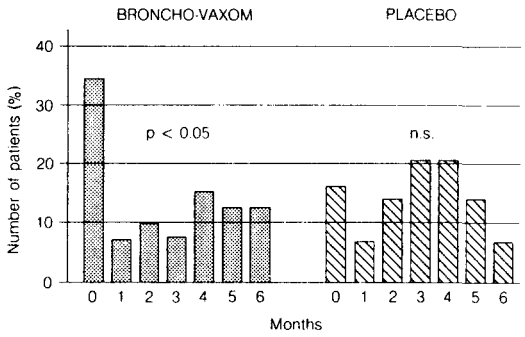

Fig. 2. Percentages of patients in both groups treated concomitantly with antibiotics during the trial.

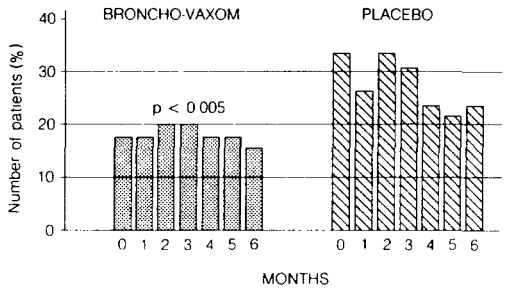

Fig. 3. Percentages of patients in both groups treated concomitantly with β_2-agonist aerosols during the trial.

significant difference in favour of BV as regards the total number of treatment courses with β_2-agonists ($p < 0.005$).

Assessment of the Clinical Response

According to the physician, the overall curative and prophylactic effects of BV were both assessed as significantly ($p < 0.001$) superior to those of the placebo (table 2).

FEV_1

The mean FEV_1 values remained practically unchanged in both groups throughout the trial and within normal limits, i.e. initially $84.06 \pm 26.8\%$ in the BV group and $78.64 \pm 25.9\%$ in the placebo group as compared to $84.31 \pm 24.4\%$ and $81.71 \pm 24.2\%$, respectively, at the end of the trial.

Erythrocyte Sedimentation Rate

ESR, which was initially high but within normal range, decreased significantly in the BV group ($p < 0.05$) but not in the placebo group, while remaining within normal limits in both groups.

Serum IgA Levels

The relative serum IgA values increased significantly ($p < 0.05$) from the 3rd month on in the BV group with respect to the placebo group as shown in figure 4. In the placebo group, the IgA values decreased significantly during the first month ($p < 0.001$) and remained at a low level throughout the study.

T-Lymphocytes

In those patients suffering from bronchitic exacerbations during the trial a drop in the T-lymphocyte counts was found in

Table 2. Physician's assessment of overall therapeutic effect

	BV				Placebo			
	curative		prophylactic		curative		prophylactic	
Effect	n	%	n	%	n	%	n	%
Positive[a]	38*	74.5	39*	76.5	17	33.3	23	45.1
Questionable	8	15.7	7	13.7	22	43.1	13	25.5
Nil	5	9.8	5	9.8	12	23.6	15	29.4

[a] Sum of evident and possible effects.

* The differences between BV group and placebo group were statistically significant ($p < 0.001$) for both curative and prophylactic effect.

both groups at the time of the exacerbation. Then these counts increased steadily in the BV-treated patients, reaching statistical significance ($p < 0.05$) 3 months after the exacerbation, while in the placebo group these counts showed a tendency to decrease (fig. 5).

Bacterial Findings

The most frequent pathogens isolated in the sputum of our patients were *Haemophilus influenzae, Haemophilus parainfluenzae* and *Streptococcus pneumoniae.* Bacterial findings were somewhat higher in the BV group than in the placebo group except in the 6th month, without statistically significant differences.

Tolerance

Only 1 patient receiving BV complained of nausea and upper abdominal pain. In the BV group, none of the 5 patients with a known history of drug hypersensitivity and the one with chronic urticaria showed any allergic reactions to BV.

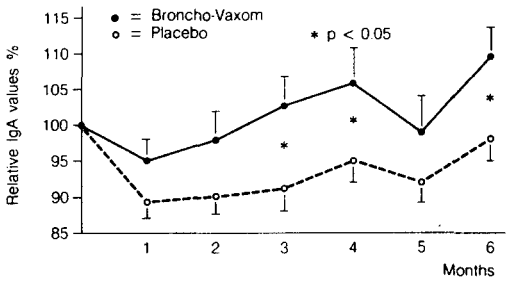

Fig. 4. Evolution of serum IgA values in both groups during the trial.

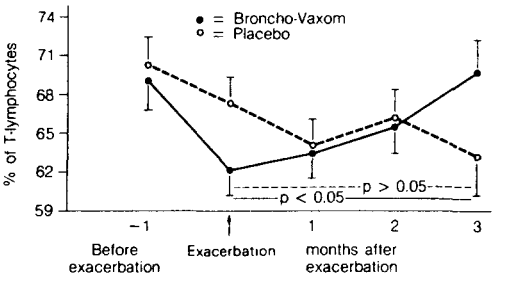

Fig. 5. Evolution of T-lymphocyte counts (%) in patients with bronchitic exacerbations during the trial (n = 29 in BV group and n = 34 in placebo group).

Discussion

The results of this double-blind placebo-controlled multicentre study in 104 patients with chronic bronchitis clearly show that this bacterial lysate is active in recurrent respiratory infections. Indeed, both objective and subjective parameters characteristic of bronchitic exacerbations were favourably influenced by BV. This was expressed in particular by the significant enhancement of serum IgA levels and T-lymphocyte counts, as well as by the decrease in the ESR values, in the duration of exacerbations, in the febrile episodes and in the concomitant consumption of antibiotics or β_2-agonists. These positive results are in line with those of other clinical double-blind placebo-controlled studies also conducted with patients suffering from chronic bronchitis [7, 9, 10, 18].

The beneficial evolution of the clinical parameters certainly reflects the stimulating effects of BV on the different cellular and humoral components of the immune system as observed in our trial (T-lymphocytes, IgA) and by other investigators. They have for instance shown that this lysate activates macrophages, lymphocytes, secretory IgA and interferon biosynthesis and confers active protection against bacterial infections [2, 4, 8, 13, 19]. It is hypothesized that through its effects on the body's immune system, BV may prevent bronchitic episodes by favourably influencing some of the risk factors generally associated with chronic bronchitis, i.e. bacterial superinfections and immunodeficiencies [20, 21], and also bring about a direct therapeutic effect in the course of the disease. Such prophylactic and curative efficacy is precisely what we observed with BV in our patients and we can conclude that immunostimulating lysates of bacterial origin constitute a valuable therapeutic approach in chronic bronchitis.

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