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Immunotherapy with an Oral Bacterial Extract (OM-85 BV) for Upper Respiratory Infections

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Key Words. Immunotherapy · Bacterial extract · Respiratory infections, children · Infections, ear, nose and throat

Abstract. The efficacy of Broncho-Vaxom®/Imocur® (OM-85 BV), an orally administered lyophilized bacterial extract, for recurrent respiratory and ear, nose and throat (ENT) infections was evaluated in 116 children aged 6 months to 19 years by comparing its activity in 61 children with that of a placebo in 55 children. The study was randomized, double-blind, and comprised a 90-day treatment period followed by a 90-day follow-up period without test drugs. Over the 180 days, 39.5% of patients taking OM-85 BV remained free from infection compared with 16.5% on placebo ($p < 0.01$). 44% on OM-85 BV did not need antibiotics compared with 23.5% on placebo ($p < 0.05$). These differences were even greater in the subgroup of children aged 6 years and less (34 vs. 3.5% for the absence of infections, $p < 0.01$ and 37 vs. 10% for the need of antibiotics, $p < 0.05$). Tolerance to OM-85 BV was excellent, and laboratory investigations showed no abnormalities attributable to this product. This work confirms that the immunomodulator OM-85 BV is an effective immunotherapy for recurrent respiratory and ENT infections in children.

Introduction

Recurrent ear, nose and throat (ENT) and respiratory tract infections can represent a considerable problem in children. These conditions may lead to repeated absenteeism from school and therefore affect educational achievement.

Although antibiotics and other medications generally cause remission of the immediate infection, they do not always prevent recurrences and may even be associated with adverse effects. Oral immunotherapy may be a more rational approach for recurrent respiratory and ENT infections.

The immunomodulator Broncho-Vaxom®/Imocur® (OM-85 BV) is a bacterial extract prepared from species commonly responsible for respiratory diseases. It has been shown, for example, to reduce the incidence of exacerbations in adult chronic bronchitis [1]. In children, three double-blind placebo-controlled studies have demonstrated the therapeutic efficacy of OM-85 BV against different ENT and respiratory tract infections [2–4].

The purpose of the present randomized, placebo-controlled, double-blind trial was to assess the effectiveness of OM-85 BV in preventing recurrent respiratory and ENT infections in children in clinical practice and to monitor its tolerance.

Patients and Methods

This was a multicenter study conducted in 10 clinics throughout France. A total of 127 patients were recruited for this study. 64 of them received OM-85 BV (OM Laboratories, Geneva, Switzerland; in France OM-85 BV is marketed under the trade name

Imocur® by Laboratoires Fournier, Dijon, in other countries under the trade name Broncho-Vaxom® or Broncho-Munal®) and 63 a placebo.

One patient in the OM-85 BV group and 2 in the placebo group were excluded from the statistical analysis of efficacy parameters because they were in contradiction with the inclusion criteria as they took other immunoactive agents. Two other patients in the placebo group were excluded because they missed the visits after 3 months, the whole study lasting 6 months. Further excluded were 6 patients who prematurely dropped out of the study for a known reason unrelated to the treatment, thus leaving 116 patients for the analysis of efficacy parameters. An additional analysis of efficacy parameters was performed for the children aged 6 years and less. All the 127 recruited patients were monitored to evaluate OM-85 BV's clinical tolerance while its biological safety was evaluated in the 116 patients selected for efficacy analysis.

In the 116 assessed subjects the age ranged from 6 months to 19 years. They had suffered three or more respiratory or ENT infections in the previous autumn and winter or in the 6 months immediately preceding the trial. No patients were included who were known to be allergic to products of bacterial origin, to be receiving corticosteroids, to be suffering from severe immune deficiency or systemic disease, to be unlikely to comply with the trial protocol, or to be unsuitable on ethical grounds for the administration of placebo. The study was approved by the local ethical committee, and the parents or legal guardians gave informed consent.

The patients were assigned by randomization to receive OM-85 BV (61 patients) or a placebo (55 patients) under double-blind conditions. There were no statistically significant differences between the 2 groups in the total collective as regards sex, age or pretrial characteristics or in the children aged 6 years and less (table 1).

OM-85 BV is presented in capsules for oral administration. A capsule contains 3.5 mg of a lyophilized extract of the following bacteria: *Diplococcus pneumoniae, Klebsiella pneumoniae, Klebsiella ozaenae, Haemophilus influenzae, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus viridans* and *Neisseria catarrhalis.*

Each patient in the treated group was given one OM-85 BV capsule daily in the fasting state, on the first 10 days of each of 3 consecutive 30-day periods. Patients in the control group received placebo capsules of identical appearance according to the same time schedule. The capsules were dispensed in boxes of 10 on days 0, 30 and 60. The 90-day treatment period was followed by a 90-day observation period.

Clinical examination, including blood pressure and heart rate, was performed on day 0 and every 30 days until day 180 inclusive. On days 90 and 180 the supervising physician recorded the number of respiratory or ENT infections and the number of concomitant treatments (including antibiotics) given for these infections in the preceding 90 days. The following investigations were carried out: full blood count; erythrocyte sedimentation rate; serum activities of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and γ-glutamyltransferase; serum concentrations of creatinine, glucose, urea, nitrogen, IgA, IgG and IgM, and urinary concentrations of glucose and protein. Respiratory and ENT infections were diagnosed on the basis of clinical manifestations such as cough, dyspnea, expectoration, nasal discharge, inflammation and auscultatory rales. All concomitant illnesses and drug therapies were recorded. Side effects, detected by direct observation and indirect questioning, were also recorded, and their severity, duration and relation to treatment noted. Statistical comparisons were performed by the χ^2 test, and the level of significance was set at $p < 0.05$.

Table 1. Characteristics of the total patient collective (61 treated with OM-85 BV and 55 with placebo) and the subgroup of children aged 6 years and less (35 treated with OM-85 BV and 29 with placebo)

Characteristics	Group	Total collective	6 years and under
Sex (M/F)	OM-85 BV	37/24	20/15
	Placebo	24/31	11/18
Age, years, Mean ± SD	OM-85 BV	6.6 ± 5.3	2.8 ± 1.5
	Placebo	7.6 ± 5.3	3.5 ± 1.7
Patients under antibiotics at entry, n	OM-85 BV	35 (57%)	17 (49%)
	Placebo	40 (73%)	20 (69%)
Patients with respiratory or ENT infections during pretrial period, n	≤4 OM-85 BV	28 (46%)	18 (51%)
	Placebo	23 (42%)	12 (41%)
	>4 OM-85 BV	33 (54%)	17 (49%)
	Placebo	32 (58%)	17 (59%)
Infections during pretrial period, n			
Total number	OM-85 BV	107 (100%)	63 (100%)
	Placebo	101 (100%)	55 (100%)
Rhinopharyngitis	OM-85 BV	43 (40%)	23 (37%)
	Placebo	44 (43%)	22 (40%)
Bronchitis	OM-85 BV	32 (30%)	20 (32%)
	Placebo	25 (25%)	16 (29%)
Otitis	OM-85 BV	26 (24%)	19 (30%)
	Placebo	19 (19%)	12 (22%)
Sinusitis	OM-85 BV	4 (4%)	1 (2%)
	Placebo	7 (7%)	3 (5%)
Tonsillitis	OM-85 BV	2 (2%)	0 (0%)
	Placebo	6 (6%)	2 (4%)

Results

The principal criteria of efficacy were the numbers of patients without respiratory and ENT infections appearing in the treated and the placebo groups, during the total 180-day period (90-day treatment period plus 90-day follow-up period without test drugs), as well as the numbers of patients who did not require concomitant treatments, in particular antibiotics.

In the total patient collective, the findings were more favorable in the OM-85 BV group than in the placebo group, and all the intergroup differences were statistically significant except for the patients

Table 2. Total patient collective with respiratory and ENT infections, 61 treated with OM-85 BV and 55 treated with placebo: status during treatment and follow-up

	Days 0–90[1]		Days 90–180[2]		Days 0–180	
	OM-85 BV	placebo	OM-85 BV	placebo	OM-85 BV	placebo
Number of patients without infection	28 (46%)	13 (23.5%) $p < 0.05$	43 (70.5%)	18 (33%) $p < 0.001$	24 (39.5%)	9 (16.5%) $p < 0.01$
Number of patients without concomitant treatments	29 (47.5%)	15 (27%) $p < 0.05$	43 (70.5%)	21 (38%) $p < 0.001$	25 (41%)	10 (18%) $p < 0.01$
Number of patients without concomitant antibiotics	32 (52.5%)	21 (38%) n.s.	47 (77%)	26 (47%) $p < 0.001$	27 (44%)	13 (23.5%) $p < 0.05$

[1] Treatment period.
[2] Follow-up period without test drugs.

Table 3. Children aged 6 years or less, with respiratory and ENT infections, 35 treated with OM-85 BV and 29 treated with placebo: status during treatment and follow-up

	Days 0–90[1]		Days 90–180[2]		Days 0–180	
	OM-85 BV	placebo	OM-85 BV	placebo	OM-85 BV	placebo
Number of patients without infection	12 (34%)	1 (3.5%) $p < 0.01$	23 (66%)	5 (17%) $p < 0.001$	12 (34%)	1 (3.5%) $p < 0.01$
Number of patients without concomitant treatments	12 (34%)	1 (3.5%) $p < 0.01$	23 (66%)	6 (21%) $p < 0.001$	12 (34%)	1 (3.5%) $p < 0.01$
Number of patients without concomitant antibiotics	13 (37%)	4 (14%) $p < 0.05$	27 (77%)	10 (34.5%) $p < 0.001$	13 (37%)	3 (10%) $p < 0.05$

[1] Treatment period.
[2] Follow-up period without test drugs.

without concomitant antibiotics during the 90-day treatment period (table 2). Over the 180 days of the study, 39.5% of the OM-85 BV patients had no infection, 41% needed no concomitant treatments and 44% no antibiotics. The corresponding figures for the placebo group were 16.5, 18 and 23.5%. The total number of infections was 35% less in the OM-85 BV group (n = 126) than in the placebo group (n = 193).

Among children aged 6 years or less, those who remained free from infection thoughout the trial or who needed no concomitant treatments, in particular no antibiotics, were also more numerous in the OM-85 BV group than in the placebo group, and the intergroup differences were all statistically significant (table 3). Over the 180 days, 34% of the OM-85 BV patients had no infection or needed no concomitant

Table 4. Total WBC counts and ESR in the total population and in children aged 6 and less at time periods 0, 90 and 180 days

Parameter	Group		Total population			6 years and under		
			0	90	180	0	90	180
WBC, $10^3/mm^3$	OM-85 BV	Mean	9.71	9.62	8.15	10.35	10.69	8.45
		SD	3.52	3.26	2.54	3.98	3.46	2.87
		n	51	46	42	28	24	23
	placebo	Mean	8.95	8.92	8.78	9.31	9.96	8.88
		SD	2.14	2.37	2.17	2.35	2.47	1.71
		n	49	44	41	27	23	22
ESR, mm/1st h	OM-85 BV	Mean	9.6	8.6	7.7	9.3	1.1	5.7
		SD	6.8	8.3	8.0	4.6	12.1	3.6
		n	35	31	28	16	11	11
	placebo	Mean	9.0	8.6	15.5	11.3	9.2	18.9
		SD	9.4	6.5	16.0	12.4	7.1	22.1
		n	34	30	26	15	12	9

treatments, and 37% needed no antibiotics. The corresponding figures for the placebo patients were 3.5 and 10%. The total number of infections was 28% less in the OM-85 BV (n = 101) than in the placebo group (n = 141).

The white blood cell (WBC) counts and erythrocyte sedimentation rate (ESR) results are shown in table 4. The mean WBC counts decreased more in patients treated with OM-85 BV than in those treated with the placebo, both in the total collective and in the subgroup of 6 years and under. WBC counts started higher and finished lower in the active treatment groups. Similarly ESR finished lower (mean 7.7 and 5.7 mm/h in the total collective and in the subgroup of 6 years and under, respectively) under OM-85 BV than under placebo (mean 15.5 and 18.9). These observations indicate a reduced level of activity of infection in the active treatment groups.

No treatment-related abnormalities were noted in the results of the various laboratory investigations for either group.

No patients were withdrawn from the trial because of adverse events. In fact, there were no clinically important side effects. One OM-85 BV-treated patient reported diarrhea and 2 placebo-treated patients presented with diarrhea, respectively with gastrointestinal troubles and bad breath. The symptoms were mild and transient and not necessarily related to treatment.

Discussion

The principal finding in this study of 116 assessable children is the statistically significant reduction produced by OM-85 BV in comparison with placebo in the number of respiratory and ENT infections and the number of infected patients, both in the initial 90-day period of administration as well as in the 90-day treatment-free follow-up. A natural consequence of this fall in the incidence of infections was a decreased use of concomitant treatments, in particular of antibiotics.

The reduction in the number of infections as well as in the number of patients with infections is found in the entire patient population and in the subgroup of those aged 6 years or under. This subgroup analysis is important since it is the younger age group which is more prone to recurrent respiratory and ENT problems.

The results of this study show that OM-85 BV is valuable in several clinical situations. These include in particular early treatment in younger children with a history of recurrent infections, repeated exposure to siblings and at times of greatest exposure, e.g. during the first year at school.

As far as the mode of action of OM-85 BV is concerned, the available evidence shows that it increases resistance to infection by stimulating the body's natural defence mechanisms. In particular, it potentiates

in vitro the mitogen-induced nonspecific lymphocyte response of healthy subjects [5, 6], restores defective surface membrane properties of T lymphocytes in IgA-deficient subjects [6], and raises concentrations of secretory IgA in human saliva and of IgG and IgM in human serum [7]. It proved more effective than levamisole in enhancing humoral immune responses in mice, and increased IgA both in gut and respiratory tract secretions in these animals [8]. In double-blind studies in children it increased interferon production by T lymphocytes and their blastogenic transformation [9]. The decrease in the number of infectious episodes that follows its administration correlated positively with an increase in the allogeneic mixed lymphocyte reaction, suggesting that it restores depressed immune functions by stimulating the gut-associated lymphoid tissue [2].

The clinical results reported here are in line with those of other trials that have shown diminished frequency of infections and associated symptoms in children treated with OM-85 BV [2–4]. This immunotherapy has the advantages of once-a-day oral administration, good tolerance, and restriction of the use of antibiotics. The present study confirms that OM-85 BV is an effective therapy for recurrent respiratory tract and ENT infections in children.

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