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Primary Prevention of Acute Respiratory Tract Infections in Children Using a Bacterial Immunostimulant: A Double-Masked, Placebo-Controlled Clinical Trial

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ABSTRACT

Background: Acute respiratory tract infections (ARTIs) are among the main causes of morbidity and mortality in children. The bacterial extract OM-85 BV has shown some protective effect for ARTIs in preschool children and a reduction in exacerbations of chronic bronchitis in adults.

Objectives: This trial reports results of a double-masked, placebo-controlled, parallel-group clinical study that assessed the efficacy and tolerability of OM-85 BV in the prevention of ARTIs in school girls living in an orphanage.

Methods: Two hundred girls (age range, 6 to 13 years) living in an orphanage entered the trial. Participants were randomly allocated to receive either OM-85 BV or placebo for 10 consecutive days a month for 3 consecutive months. Patients were followed up for 6 months, including the administration period. The trial began in September 1996 and finished in March 1997. Primary end points were the type and number of infections. Secondary end points included when an infection occurred, time to clinical cure, severity of infection, absenteeism from school due to an ARTI, number of antibiotics or other drugs prescribed, and duration of concomitant drug treatment.

Results: During the trial, patients in the OM-85 BV group experienced 143 ARTIs (135 upper ARTIs and 8 otitis episodes) and patients in the placebo group experienced 299 ARTIs (273 upper ARTIs, 1 lower ARTI, and 25 otitis episodes). The median number of ARTIs was 1.0 (0.0, 3.0; 5th percentile, 95th percentile) in the OM-85 BV group compared with 3.0 (2.0, 4.0; 5th percentile, 95th percentile) in the placebo group. This difference was statistically significant ($P < 0.001$). Participants who received OM-85 BV also showed significantly better results ($P < 0.001$) than participants who received placebo in terms of median duration of illness, median number of missed school days due to an ARTI, median number of antibiotic and drug courses, and median duration of concomitant treatment. There were significant differences ($P < 0.05$) in severity of ARTIs during

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month 4 of the trial, with patients receiving OM-85 BV showing less severe ARTIs than patients receiving placebo and shorter mean time to clinical cure from the second month to the fourth month. No adverse events related to the trial medications were reported.

Conclusions: OM-85 BV had a preventive effect on ARTIs in the school girls, with a reduction in the antibiotic requirements and the duration of ARTIs. Future studies are needed to further explore the role of OM-85 BV in the prevention of ARTIs.

Key words: acute respiratory tract infection, prevention, immunostimulant, OM-85 BV. (*Clin Ther.* 2000;22:748–759)

INTRODUCTION

By the end of the 20th century, acute respiratory tract infections (ARTIs) were one of the primary causes of childhood morbidity and mortality worldwide.[1] It is estimated that ARTIs have caused 28% of all deaths in children younger than 5 years.[1] ARTIs are responsible for many missed school days[2] and much parental absenteeism from work.[3] They are also often associated with otitis, which is an important cause of hearing loss and poor school performance.[4]

Risk factors for ARTI include attendance at a day care center,[5] overcrowding at school,[3,6] having older brothers or sisters,[6] smoking at home,[7] and lack of breast-feeding.[8]

Various methods of preventing ARTIs have been studied in clinical trials; for example, general hygiene methods in children attending day care centers[9]; administration of nutritional supplements such as vitamin A to malnourished children,[10] vitamin C in normal and malnourished children,[11] and trace elements in malnourished and susceptible children[12]; antibiotics[13]; administration of gamma globulins[14]; and the use of immunostimulants from various sources, including synthetic,[15] thymic extracts or factors,[16] or biologic, such as *Klebsiella* extracts containing lipopolysaccharide[17] and mixtures of bacterial extracts.[18–21] Although the therapeutic use of immunostimulants (defined as medications that produce an enhancement of nonspecific immunity and an increased infection resistance) is common in some European countries, the efficacy of these medications in the prevention of ARTIs in children is controversial.[22,23]

OM-85 BV[*] is an immunostimulant containing the lyophilized extract of the following bacteria: *Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae, Klebsiella ozaenae, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus viridans,* and *Moraxella catarrhalis.*[24] Previous controlled clinical trials have shown that OM-85 BV reduces the incidence of ARTIs for 6 months in children prone to these infections,[25] and for 3 months in children attending day care centers.[26] The relative risk for ≥4 ARTIs in 6 months was 0.79 (95% confidence interval [CI], 0.59 to 1.06), and a relative risk for ≥3 ARTIs in the first 3 months was 0.52 (95% CI, 0.31 to 0.86).[26] The protective effects of OM-85 BV in viral ARTI were shown in a trial of children attending day care centers, a study that included viral isolation.[27] The protective effects of OM-85 BV have also been shown for exacerbations of chronic bronchitis in adults.[28,29]

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[*] Trademark: Broncho-Vaxom® (OM PHARMA Meyrin, Geneva, Switzerland; marketed in Mexico by Química Knoll de Mexico).

By the end of 1999, 9387 patients had received OM-85 BV as part of clinical trials. Only 448 (4.8%) had reported adverse events. These were mainly gastrointestinal disturbances (1.7%), exacerbation of symptoms (0.5%), skin disturbances (0.4%), and headache and dizziness (0.3%) (data on file; OM PHARMA Meyrin, Geneva, Switzerland; 1999).

Each capsule of OM-85 BV contains 3.5 mg of the lyophilized extract. The mechanism of action of OM-85 BV is partially known. OM-85 BV is free of lipopolysaccharide, and its effect is mediated by a CD14-independent pathway.[30] In macrophage and monocytic cells, OM-85 BV increases intracellular calcium levels and induces the production of glucose-regulated protein[31] and C-Fos/serum responsive element protein.[32,33] These second messengers induce the expression of proinflammatory cytokines interleukin (IL) 1-alpha, IL-6, IL-8, and tissue necrosis factor-alpha.[32–35] In addition, OM-85 BV induces phagocytic cells to produce nitric oxide and oxygen,[35] and to express adhesion molecules.[30,36]

The production of these cytokines and substances may be related to the changes observed in the immunoglobulin (Ig) levels and phagocytic activity in patients receiving OM-85 BV. These patients have shown enhancement of cellular immune responses,[37,38] and increases of secretory IgA,[39–41] serum IgA,[28,42] and serum IgG and IgM,[39,42] as well as activation of phagocytic cells.[40,41]

Because the tolerability and efficacy of OM-85 BV have been studied in children younger than 6 years and adults,[25–29] we conducted a clinical trial to investigate the tolerability and efficacy of the immunostimulant OM-85 BV in school-age girls.

PATIENTS AND METHODS

This double-masked, placebo-controlled, parallel-group clinical trial began in September 1996 and finished in March 1997. The trial was conducted during the boreal winter because this season had the highest incidence of ARTI, according to the orphanage records. The primary aim of the study was to investigate the effect of OM-85 BV on the incidence of ARTIs. Secondary aims were to investigate the effect of OM-85 BV on absenteeism from school and the use of antibiotics. The girls were informed about the aims and procedures of the trial, and told they could refuse to participate or withdraw their consent at any time, without providing a reason and without being punished or losing any rights.

All participants provided oral consent to participate in the study. In addition, written informed consent was obtained from the legal guardian for each girl (a close relative and if missing, the chairman of the institution).

The protocol and case report forms were approved by the Research and Ethics Committee of the Central Medical Committee of the National Program for the Family (formed by the chairmen and medical directors of the 3 other orphanages in the program) and were in accordance with the Mexican regulations and the Helsinki Declaration of 1975, as revised in 1983.

Based on previous trials in Mexico,[20] we expected to have a 50% reduction in the incidence of ARTIs. Using a difference of 1.5 ± 1.5 ARTIs between the groups during 6 months,[20] the calculated sample size was 23 patients per group; for a difference of 0.75 ± 1.5 (half of the previously reported efficacy), a sample size of 86 patients per group was needed. An initial sample size of 100 patients per group was used.

Patients were girls aged 6 to 13 years living in a single orphanage (Girl's Home, National Program for the Family) south of Mexico City. They had been in the orphanage for ≥2 years and stayed in 60 bedrooms with 6 beds each, without any special clustering.

Selection criteria were as follows: ≥3 ARTIs during the previous 6 months (according to the medical records in the orphanage), negative familial history of allergy, no seasonal or food-related wheezing or nose itching, and no nasal fold. Participants could not have anatomic alterations of the respiratory tract, chronic respiratory diseases (tuberculosis, cystic fibrosis), autoimmune diseases, liver or kidney failure, malnutrition, or cancer, and could not have received treatment with corticosteroids, immunosuppressants, immunostimulants, gamma globulins, or anticonvulsive drugs in the past 6 months. All the girls were between the 60th and 95th percentiles of height and body weight for their respective ages.

There were 450 girls within the age range in the orphanage at the beginning of the trial. We included 200 girls who met the selection criteria and had the highest number of ARTIs.

The names of the participants were sorted alphabetically, and patients were assigned to receive either OM-85 BV or placebo according to a random number list in blocks of 10. The treatment for each patient number was prepared in advance. The boxes, blisters, and capsules for the active treatment and placebo had the same appearance, and the tastes of the powders were similar. A.B. prepared the randomization list and the rest of the materials but did not see the patient list. The capsules were administered by nurses, and the empty blisters were kept to determine compliance (ie, to count the possible missing capsules).

For each patient number there was an opaque sealed envelope with a sheet of paper stating whether the trial medication was OM-85 BV or placebo. All the envelopes were kept available for the investigators in the study center. The envelopes could be opened in the case of serious adverse events. Closed envelopes were recovered by A.B. at the end of the trial.

Patients received 1 capsule orally—OM-85 BV (3.5 mg) or placebo—per day for the first 10 consecutive days of each month for 3 consecutive months. All patients started the trial medication at the same time of day. The trial participants were examined daily by the nurse and medical teams, and the characteristics of ARTIs were recorded on the case report form as they occurred. The following variables were assessed: type and number of infections (main end point), when a girl had an infection, time to clinical cure, severity of the infection, absenteeism (days out of school) due to an ARTI, number of antibiotics or other drugs prescribed, and duration of treatment in days (secondary end points). Severity of infection was assessed using a 114-mm visual analog scale with 3 ratings (very mild, moderate, very severe). Only J.J.-P. marked the scale. In addition, J.J.-P. examined and questioned participants with ARTIs daily up to the end of the episode and completed the case report forms.

An upper ARTI was defined as the presence of ≥1 of the following signs: rhinorrhea, sore throat, or cough without signs of a lower ARTI for ≥48 hours. A lower ARTI was defined as the presence of ≥1 of the following signs: rales or crepitations, wheezing, stridor, respiratory rate >50 per minute, cyanosis, or chest indrawing (depression of intercostal spaces) for ≥48 hours. Otitis was defined as earache with erythema and limited mobility of the tympanic membrane determined by pneumatic otoscopy. Similar upper and lower ARTI definitions have been used in epidemiologic studies in developing countries.[6] Two infections were counted as such only when the patient was without symptoms for ≥72 hours between the end of 1 ARTI and the beginning of another. A treatment course was defined as completion of ≥1 day of drug treatment. Clinical cure was defined as complete resolution of all symptoms.

Adverse events were recorded on case report forms as they occurred and reported monthly on an adverse event report form provided with the case report form.

Statistical Analysis

The end point differences between the groups were analyzed using the Mann-Whitney *U* test. In addition, the rate of patients suffering <3 ARTIs throughout the 6-month period were analyzed by Kaplan-Meier statistics defining the event as the occurrence of 3 ARTIs, and the relative risk for ≥1 ARTI, ≥2 ARTIs, ≥3 ARTIs, and ≥1 otitis episode were calculated. The SPSS statistics program (SPSS Inc., Chicago, Illinois) was used for all analyses.

RESULTS

No significant differences were observed between the groups at the beginning of the trial. Baseline demographics are shown in Table I. All participants completed the trial. However, data for 1 girl in the OM-85 BV group were lost. Thus, statistical analysis of results is based on 99 patients who received OM-85 BV and 100 patients who received placebo.

During the trial, patients in the OM-85 BV group had 143 ARTIs (135 upper ARTIs and 8 otitis episodes) and patients in the placebo group had 299 ARTIs (273 upper ARTIs, 1 lower ARTI, and 25 otitis episodes). When the number of ARTIs in each group was compared with the number recorded in clinical files during the 6 months (March 1996 to August 1996) before the trial (494 and 509, respectively), significant differences were detected for both groups ($P < 0.001$ by Mann-Whitney *U* test).

Table I. Baseline patient characteristics.

	OM-85 BV (n = 99)	Placebo (n = 100)
Age (y)*	9.8 ± 1.9	9.6 ± 1.9
Body weight (kg)*	32.8 ± 8.5	33.3 ± 9.5
Height (cm)*	134.7 ± 11.6	134.0 ± 11.9
No. of ARTIs in past 6 months†	5 (4;6)	5 (4;6)

ARTIs = acute respiratory tract infections.
*Mean ± SD.
†Median values (percentiles 5;95).