The immunostimulant OM-85 BV prevents wheezing attacks in preschool children

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Background: No reagents have been shown to be effective in preventing wheezing attacks provoked by acute respiratory tract illnesses (ARTIs) in preschool children. New therapeutic agents and preventive strategies are needed.
Objectives: We assessed the effect of OM-85 BV (Broncho-Vaxom; OM Pharma, Geneva, Switzerland) in preventing ARTI-provoked wheezing attacks in preschool children with recurrent wheezing.
Methods: A randomized, double-blind, placebo-controlled, parallel-group study was carried out between August 2007 and September 2008. The study included 75 children with recurrent wheezing who were 1 to 6 years old. Participants were randomly assigned to groups given either OM-85 BV or a placebo (1 capsule per day for 10 days each month for 3 consecutive months) at the start of the trial. Participants were followed for 12 months, which included the administration period of the test article.
Results: Subjects given OM-85 BV had a lower rate of wheezing attacks. The cumulative difference in wheezing attacks between the 2 groups was 2.18 wheezing attacks per patient in 12 months; there was a 37.9% reduction in the group given OM-85 BV compared with the group given placebo ($P < .001$). Stepwise multiple (linear) regression analysis showed that the main difference between the OM-85 BV and placebo groups was a reduction the number of ARTIs ($R = -0.805$, $P < .001$). The duration of each wheezing attack was 2 days shorter in the group given OM-85 BV than in the group given placebo ($P = .001$).
Conclusion: Administration of OM-85 BV significantly reduced the rate and duration of wheezing attacks in preschool children with ARTIs. (J Allergy Clin Immunol 2010;126:763-9.)

Key words: *Wheezing, OM-85 BV, children*

Abbreviations used
ARTI: Acute respiratory tract illness
ICS: Inhaled corticosteroid

The prevalence of asthma has increased over the last 20 to 30 years.[1] Most preschool children have episodic asthma exacerbated by viral colds, with few or no interval symptoms, such as activity-induced coughing or wheezing.[2,3]

Inhaled steroids are the mainstay of treatment for persistent asthma; their use is associated with reduced risk of exacerbation.[4] The Physical Exercise and Activity in Kids study reported that daily use of inhaled corticosteroids (ICSs) reduced exacerbations in preschool children.[5] However, in a subgroup of young children with intermittent wheezing induced by only respiratory tract viral infections, symptoms improved modestly after episodic use of relatively high-dose ICSs[6,7]; these attacks could not be prevented with a maintenance dose of ICSs.[8-10] A Cochrane meta-analysis showed no benefit from continuous use of preventative anti-inflammatory medications among children of any age in this subgroup.[11] Montelukast, an antagonist of the cysteinyl leukotriene receptor, significantly reduced the rate of asthma exacerbations in young children (by 32%).[12] The data on montelukast are promising but require replication in a large independent trial.

Current therapies have limited efficacy in preventing virus-provoked wheezing attacks; new therapeutic agents and primary or secondary preventative strategies need to be developed.[13] Because infants and preschool children catch an average of 6 to 8 colds per year and respiratory tract viral infections are detected in most children with asthma exacerbations (80% to 85%),[14] secondary approaches to prevent wheezing attacks in preschool-ages children should focus on preventing acute respiratory tract illnesses (ARTIs).[15]

OM-85 BV (Broncho-Vaxom; OM Pharma, Meyrin/Geneva, Switzerland) is an immunostimulant extracted from 8 bacterial pathogens of the upper respiratory tract. Several randomized clinical trials[16-22] have shown that OM-85 BV can reduce the number of ARTIs by 25% to 50% compared with placebo in adults and children with a history of recurrence. However, these studies were designed to demonstrate the preventive effect of OM-85 BV on ARTIs in children with recurrent infections; recurrent wheezing and asthma were among the exclusion criteria.

We propose that ARTIs are the main cause of recurrent wheezing attacks in preschool-aged children and that ARTI-induced wheezing attacks could be reduced by OM-85 BV.

METHODS

Patients

The study included children who were 1 to 6 years old with 3 or more acute wheezing attacks induced by respiratory tract illness in the previous 6 months (according to medical records from outpatient clinics). Exclusion criteria were as follows: anatomic alterations of the respiratory tract; chronic respiratory diseases (tuberculosis and cystic fibrosis); autoimmune disease; liver or kidney failure; malnutrition; cancer; treatment with inhaled or systemic corticosteroids within the previous month; and treatment with

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immunosuppressants, immunostimulants, gamma globulins, or anticonvulsive drugs within the previous 6 months.

Study design

This study was a randomized, double-blind, placebo-controlled, parallel-group study with OM-85 BV in patients with recurrent wheezing. It was carried out from August 2007 to September 2008 at the outpatient Department of Pediatric Allergy of Kecioren Education and Research Hospital in Ankara, Turkey.

The primary aim of the study was to investigate the effect of OM-85 BV on the total number of wheezing attacks induced by ARTIs over a 12-month period (excluding the first 15 days' randomized assignment to study groups). The secondary aims were to investigate the effect of OM-85 BV on (1) duration of wheezing episodes, (2) the number and duration of β_2-agonist and steroid uses during the attacks, (3) the rate of hospitalization, (4) the number of ARTIs, and (5) the number of cases of acute nasopharyngitis over the 12-month period.

The characteristics of wheezing attacks were recorded in case report forms as they were observed. As patients were enrolled in the study, consecutive numbers were assigned (double-blind code). The numbers were randomly assigned to the treatment groups in balanced blocks of 10 by using a random allocation software computer program. The treatment for each patient number was prepared in advance. K. H. prepared the randomization list and the rest of the materials but was blind to the patient list. The double-blind code for the treatment numbers were enclosed in opaque sealed envelopes and kept available for the researcher in the study center to be opened in case of a serious adverse event. Sealed envelopes were recovered by the primary investigator (C. H. R) at the end of the trial. All investigators were blind to the allocation of treatment until data analysis was completed.

The study was approved by the Ethics Committee of the Turkish Ministry of Health, and written informed consent was obtained from parents of patients on entry into the study.

Study protocol

OM-85 BV contains 3.5 mg of standardized lyophilized fractions per capsule from the following bacteria: *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans*, and *Neisseria catarrhalis*.

The children received 1 capsule of OM-85 BV (3.5 mg) or placebo per day for 10 consecutive days in each of 3 months. The test articles were given to parents by the training nurse, who was not involved in the study design or analysis. The boxes, blisters, and capsules had the same appearance, and the tastes of the powders were similar. Children less than 5 years old received powder from open capsules, and children older than 5 years received capsules. The capsules or powder were administered by the parents, and the empty blisters were kept from control compliance (to count any missing capsules).

Patients were assessed monthly and every time they had respiratory tract symptoms. If the patients had a wheezing attack, the number of days to clinical cure, the number of days that β_2-agonists and oral steroids were used, and the number and duration of hospitalizations were recorded. All the physical examinations and data collection were performed by the primary investigator (C. H. R.), who also wrote all prescriptions.

An acute wheezing attack was defined as an episode of progressively increasing shortness of breath, cough, wheezing, chest retraction or tightness, or any combination of these symptoms that lasted at least 6 hours with normal results on chest radiographic examinations. When repeated symptoms were observed, attacks were counted separately only if the patient had been without symptoms for at least 1 week between the end of one episode and the beginning of another. All the wheezing attacks were followed until a complete disappearance of all the symptoms was observed; clinical cure was defined as the complete resolution of all symptoms.

ARTIs (acute nasopharyngitis, sinusitis, acute otitis, tonsillitis, viral croup, or pneumonia) were defined by the presence of diagnostic symptoms for at least 48 hours. Multiple illnesses were counted only if the patient was without symptoms for at least 72 hours between the end of one episode and the beginning of another.[20]

Adverse events were recorded on the case report forms as soon as they were detected. Afterward, they were noted in the monthly adverse event report form and case report form.

Treatment of asthma symptoms during the study period

Based on the child's asthma symptoms, the need for hospitalization, and the number of wheezing attacks or the number of prednisolone courses required (for acute exacerbations), children were treated with ICSs or montelukast as the baseline therapy. Additions or reductions of asthma medications and treatment of wheezing attacks were performed according to the National Asthma Education and Prevention Program's Expert Panel Report 3.[4]

Statistical analysis

The primary efficacy parameter was based on the total number of wheezing attacks per patient induced by ARTIs over the 12-month period. Virus-provoked wheezing attacks in the first 15 days of the trial were disregarded because they were probably associated with wheezing present during the initial visit. All analyses were performed with a commercially available software program (SPSS Statistical Software, version 11.5; SPSS, Inc, Chicago, Ill). The Shapiro-Wilks test was used to evaluate normality of the distributions collected. When variables were normally distributed, they were expressed as means (SDs); otherwise, they were expressed as medians and interquartile ranges (25th-75th percentiles). The χ^2 test was used for categorical variables and expressed as observation counts (in percentages). Because the variables of wheezing episodes and ARTIs were not distributed normally, they were expressed as medians and interquartile ranges (25th-75th percentiles). This study was powered to demonstrate a 30% reduction of wheezing episodes compared with placebo, and therefore data were expressed as means $\pm$ SDs to demonstrate percentage differences between the groups. A Bonferroni multiple comparison test was used to compared paired intervals (0-3, 0-6, 0-9, and 0-12 months). All *P* values were 2-tailed; a *P* value of less than .05 was considered statistically significant.

Power and sample size

Based on a pilot study and clinical experience, we expected to observe a 30% decrease in the rate of virus-provoked wheezing attacks in the OM-85 BV group compared with the placebo group. During the 6-month pilot study, the number of virus-provoked wheezing attacks was 2.4 $\pm$ 1.3 in the placebo group. Using a difference of 0.8 $\pm$ 1.1 virus-provoked wheezing attacks between the groups with an α value of .05 and a β value of .10 (ie, with a power of 90%), the required sample size was calculated to be 29 patients per group. Sample size estimation was performed by using the NCSS and PASS 2000 software.

RESULTS

Eighty of 100 children were selected to participate in the trial. All participants in the placebo group completed the trial, but 5 patients in the OM-85 BV group did not. In the OM-85 BV group 1 patient refused to take the drug at the beginning of the study and was excluded from the study, 2 patients moved to another city (within the first 3 months of the study), and 2 patients did not attend any follow-up visits. The remaining 75 subjects (35 in the OM-85 BV group and 40 in the placebo group) completed all the follow-up visits (Fig 1). All the envelopes that contained the double-blind code for the treatment numbers were collected on completion of the study. Based on the empty blisters, compliance was greater than 90% for all patients. In the OM-85 BV group 32 children received powder, and 3 children received capsules; in the placebo group 36 children received powder, and 4 children received capsules. Analysis of the main demographic