Immunostimulation With OM-85 in Children With Recurrent Infections of the Upper Respiratory Tract*

A Double-Blind, Placebo-Controlled Multicenter Study

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Objective: **Recurrent upper respiratory tract infections (URTIs) are common illnesses in young children. As the immunoactive bacterial extract OM-85 has been shown to prevent these infections in both adults and children, the aim of the present trial was to investigate further its efficacy and safety in infection-prone children.**

Methods: **This is a randomized, double-blind, placebo-controlled, multicenter study with OM-85 in 232 patients aged 36 to 96 months with recurrent URTIs. Treatment was one capsule daily during month 1 and during 10 days in months 3 to 5. URTI was defined by the presence of at least two of the following: rhinitis, pharyngitis, cough, hoarseness, temperature ≥ 38.5°C, or URTI-related prescription of an antibiotic.**

Results: **OM-85–treated patients had a lower rate of URTIs ($p < 0.05$). The cumulated difference in URTIs between the two groups reached − 0.40 URTIs per patient in 6 months, corresponding to a 16% reduction in the active-treatment group with respect to placebo. The largest difference was observed in the patients having had three or more URTIs during the study period; odds ratios for three or more URTIs were 0.51 (95% confidence interval, 0.29 to 0.91) and 0.65 (95% confidence interval, 0.37 to 1.11) after 5 months and 6 months, respectively. The difference between OM-85 and placebo was independent of age but was more important in patients reporting a larger number of URTIs in the previous year. Patients' global assessment showed improvement in comparison to the previous season in the majority of the cases (OM-85, 78.4% of cases; placebo, 75.5%); however, there were more cases reporting worsening with placebo (6.4% vs 0.9%; $p = 0.05$).**

Conclusions: **OM-85 treatment significantly reduced the rate of URTIs, particularly in children with a history of frequent URTIs. Safety and tolerance of test medication were good, comparable to placebo.** ***(CHEST 2002; 122:2042–2049)***

Key words: bacterial extract; child; immunostimulation; OM-85; prevention; recurrence; upper respiratory tract infection

Abbreviations: ANOVA = analysis of variance; URTI = upper respiratory tract infection

Pediatric acute infections of the airways continue to play an important role with regard to morbidity and mortality and have significant socioeconomic implications.[1–3] They primarily affect children < 5 years old. Nearly 50% of the pediatric consultations in Switzerland are caused by infections of the respiratory tract.[4] The vast majority—80 to 90%—of these infections are caused by viruses. Uncomplicated upper respiratory tract infections (URTIs) are usually self-limiting and do not require antibiotics. However, several bacterial complications can arise, such as acute otitis media, sinusitis, and bronchitis. In a French study, overall incidence of complications

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The study was supported by a grant from OM PHARMA, CH-1217 Meyrin/Geneva, Switzerland.

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Manuscript received November 29, 2001; revision accepted July 12, 2002.

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was 16.8% (10.9% acute otitis media, 4% laryngitis or bronchitis, 1.9% pulmonary infections).[5] Simple episodes of URTIs generally have a good prognosis, but recurrence and/or bacterial superinfection may lead to numerous complications requiring various medical and surgical treatments, in particular appropriate antibiotic therapy. Furthermore, duration of pediatric URTIs is often prolonged: rhinopharyngitis lasting ≥ 14 days in 35% of children vs 20% of adults.[6]

From an epidemiologic point of view, it has been shown that 57% of children with recurrent respiratory infections (three or more episodes a year during at least 2 years) were deficient in one of the IgG subclasses and that 17% were IgA deficient.[7] IgG subclass deficiency is quite prominent in young children but rare in older children, suggesting a transient immaturity of the immune system as one of the possible pathogenic factors. Defects in the immune system such as common variable immunodeficiency and the more frequent selective IgA deficiency are known to be linked with frequent respiratory infections by bacteria and viruses.[8] As OM-85 stimulates immune defenses and in particular the production of salivary and bronchoalveolar serum IgA as well as serum IgA and IgG, it has been administered since the 1980s to adults and children in order to prevent recurrences of respiratory tract infections.

OM-85 is an immunoactive lyophilized extract from eight pathogenic bacteria of the respiratory tract. It stimulates the local immune responses, via activation of the mucosa-associated lymphoid tissue, and possibly the systemic immune responses, activates the macrophages and phagocytosis, the natural killer and cytotoxic activity, as well as increases the level of serum IgA in saliva and BAL fluid and of IgG in serum.[9–12] Summarizing, Emmerich et al[11] defined OM-85 as having pleiotropic immunomodulating effects, *ie*, activating different systems in the chain of immunologic defense reactions.

The major placebo-controlled adult studies show that OM-85 diminishes the incidence of respiratory infections and antibiotic prescriptions in patients with known immune defects (*eg*, hemodialysis) or with a chronic inflammatory and/or obstructive process of the respiratory tree, making them more susceptible to bacterial infection (chronic bronchitis, chronic sinusitis).[13–15] OM-85 proved also significantly superior to placebo with regard to the number of hospitalizations.[16] As regards children, several double-blind trials have shown its efficacy in reducing the frequency of respiratory and ear, nose, and throat infections of both bacterial and viral origin, accompanied by a reduction in antibiotics and other concomitant medications.[17–22] The rationale for performing the present study was to investigate further the therapeutic benefit of OM-85 in children with recurrent URTIs.

Materials and Methods

This study is a randomized, double-blind, placebo-controlled, multicenter study with OM-85 (Broncho-Vaxom; OM PHARMA; Meyrin/Geneva, Switzerland) in patients with acute recurrent URTIs. Two hundred twenty patients were enrolled in order to obtain 170 assessable cases (110 patients/85 assessable cases per treatment group) in 40 centers. The duration of the study was 6 months, with visits planned every 30 days, totaling seven visits and starting between mid-August and mid-December for all patients.

Patients

The patients were children of either gender, aged 36 to 96 months, with a history of recurrent URTIs and presenting with URTI at hospital admission. The definition used for recurrent URTIs was three or more such episodes during the last 12 months. The current episode required for study eligibility was defined by the presence of at least two of the following: rhinitis, pharyngitis, cough, hoarseness, temperature ≥ 38.5°C, or prescription of an antibiotic for a URTI, occurring after an asymptomatic period of at least 1 week without antibiotics.

Patients meeting any of the following criteria at entry were excluded: occurrence of otitis media and/or sinusitis and/or infection of the lower respiratory tract (*ie*, bronchitis, pneumonia) and/or proven group A streptococcal angina at the enrollment visit. Further main exclusion criteria were allergic asthma, mucoviscidosis, significant systemic disease (*eg*, hepatic and/or renal disease, malignancy), immune system disorders, suspected malabsorption, known allergy to the bacterial extract, major surgical procedure within 3 months of commencement of the study, recent immunosuppressive or immunostimulant therapy, or corticosteroids.

Patients fulfilling the inclusion/exclusion criteria and whose parents or guardians gave their informed consent were randomly assigned by blocks of four to OM-85 or placebo at initial visit. Randomized assignment to masked medication of identical appearance was accomplished by prepackaging of masked study and control medications at random sequence. The allocation of the study treatment to each patient was carried out according to the next available consecutive patient number printed on the prescription card and on the label of the box.

Medication

OM-85 contains 3.5 mg per capsule of standardized lyophilized bacterial fractions of the following: *Haemophilus influenzae*, *Diplococcus pneumoniae*, *Klebsiella pneumoniae* and *Klebsiella ozaenae*, *Staphylococcus aureus*, *Streptococcus pyogenes* and *Streptococcus viridans*, and *Moraxella (Neisseria) catarrhalis*. Patients had to take one capsule per day of OM-85 or placebo on an empty stomach, as follows: month 1, 1 capsule per day during 30 days; month 2, no therapy; months 3 to 5, 1 capsule per day during 10 days; and month 6 (follow-up), no treatment.

Assessments

The primary end point of the study was the reduction of URTIs (as defined above) during treatment and over the entire obser-

Table 1—*Demographic Characteristics of the Intent-to-Treat Population*

Variables	OM-85			Placebo			*t* Test p Value
	No.	Mean	SD	No.	Mean	SD	
Age, yr	120	5.2	1.2	100	5.3	1.4	0.59
Height, cm	120	110.2	9.3	100	111.4	10.3	0.40
Weight, kg	120	20.4	4.0	100	20.5	5.3	0.94
Infections during previous year, No.	119*	5.8	2.4	100	6.1	2.2	0.32
Days since last infection, No.	118*	66.9	67.7	100	74.1	70.1	0.44
Days of absence from school, No.	48	3.2	2.0	52	3.1	1.8	0.77

*Data were missing in one and two patients, respectively.

vation period. Presence of an URTI was reported at regular or intermediate visits, and occurrences between scheduled visits were reported even if they did not imply a supplementary visit. Secondary end points were the ratings of rhinitis, pharyngitis, cough, hoarseness, (coded as none, mild, or severe), fever (coded as 0 = absent; 1 = 38.5 to 39.4°C; 2 = ≥39.5°C), number of days of absence from school, incidence of otitis, sinusitis, or other related infections.

Prescribed medications were also recorded. Patient (parent or guardian) and investigator assessments of the efficacy of the therapy were recorded at the end of the treatment period on a 7-point scale (from − 3 = marked worsening, to 0 = no change, to + 3 = marked improvement). No invasive diagnostic procedures were planned in order to improve study compliance.

Ethics

This study was conducted in accordance with the Declaration of Helsinki (revised 1996), the specific local laws governing clinical trials, and in accordance with good clinical practice guidelines. The study in a participating center was only started once written approval by the ethics committee and/or regulatory authorities was obtained.

Statistical Analysis

The sample size was computed to prove that a 15 to 20% decrease of the rate of URTIs in the OM-85 group compared with placebo group is statistically significant in a population with a history of recurrent URTIs. Assuming such a difference and a URTI rate of approximately 60% in the placebo group, approximately 82 analyzable patients in each group were required, with $\alpha = 0.05$ and $\alpha = 0.2$, respectively.[23]

The primary efficacy parameter, the mean rate of URTIs (per patient, per month) was computed at each visit up to visit 7 and tested by analysis of variance (ANOVA) for repeated measures. URTIs in the first 15 days of the trial were discarded, since it was estimated that they were linked to the infection already present at the initial visit. A URTI had to be preceded by an asymptomatic period of at least 7 days in order to be considered a new URTI.

Secondary efficacy variables were analyzed for descriptive purposes using adequate standard statistical tests, *eg*, χ^2 test resp. ANOVA for repeated measures for symptom scores, Mann-Whitney test for global assessments, etc. Analyses and data management were carried out using software (DataEase v0.4; DataEase International; Trumbull, CT) for the data management and SPSSPC+ release 5.0 resp. (Systat v0.9; SPSS; Chicago, IL; and NCSS release 2000; NCSS; Kaysville, UT) and TESTIMATE release 5.2 (IDV, D-82131; Gauting; Munich, Germany) for the statistical analysis.

RESULTS

Two-hundred thirty-two patients were enrolled in 40 centers (30 in Switzerland and 10 in Germany) between 1997 and 1999. Of these, 12 patients were never exposed to the test medication; therefore, 220 patients received treatment and were allotted to the intent-to-treat sample or the safety sample (OM-85, 120 patients; placebo, 100 patients).

The main demographic data that are summarized in Table 1 show that the two therapeutic groups were fairly homogeneous (all variables $p \geq 0.3$) and therefore comparable. Distribution by sex was also comparable (OM-85, 69 male and 51 female patients; placebo, 61 male and 38 female patients, 1 missing data). A small percentage of children presented alterations in other body systems (neurologic, GI, urogenital, dermatologic, or endocrinologic), slightly but not significantly higher in the OM-85 group. The symptom ratings at hospital admission were also comparable in the two groups, as shown in Table 2 (all variables $p \geq 0.11$).

URTIs

Table 3 shows the mean rate of URTIs per month and per patient in the two treatment groups, which was consistently lower in the patients treated with OM-85, except in the last month (follow-up).

Table 2—*Symptom Score of URTI at Hospital Admission*

Variables	OM-85			Placebo			χ^2 Test p Value
	None	Mild	Severe	Normal	Mild	Severe	
Rhinitis*	6	68	45	1	61	38	0.23
Pharyngitis	27	72	21	14	69	17	0.25
Cough†	7	71	41	12	57	30	0.25
Hoarseness‡	59	56	2	40	54	6	0.11
Fever	75	43	2	57	40	3	0.62

*Data were missing in one OM-85–treated patient.
†Data were missing in one patient in each group.
‡Data were missing in three OM-85–treated patients.

Table 3—*Mean Monthly URTI Rate and SEM Per Patient ($p < 0.05$)*

Treatment*	Month					
	1	2	3	4	5	6
OM-85 (n = 118)*						
Mean	0.31	0.47	0.43	0.30	0.24	0.31
SEM	0.05	0.05	0.06	0.05	0.04	0.05
Placebo (n = 99)*						
Mean	0.37	0.54	0.54	0.41	0.31	0.29
SEM	0.05	0.06	0.06	0.06	0.05	0.06
ΔOM-85-PL†	0.06	0.07	0.11	0.11	0.07	− 0.02
Cumulative ΔOM-85-PL	0.06	0.13	0.24	0.35	0.42	0.40

*Three patients had missing data (two receiving OM-85 and one receiving placebo).

†ΔOM-85-PL = difference of monthly URTI rate between OM-85 and placebo.

ANOVA for repeated measures confirmed a significantly lower rate of URTIs in the OM-85–treated patients ($p < 0.05$). Calculating the cumulated mean rate of URTIs, the difference between the two groups builds up progressively during active therapy (at end of treatment, the mean cumulated difference was of 0.42 URTIs per patient in 5 months) and diminishes very slightly in the month of follow-up, as can be seen in Figure 1. Thus, over the 6 months of the study, OM-85 treatment significantly reduced the mean incidence of URTIs by 16% (ratio of 0.40 on 2.5). In fact, the largest reduction observed in the OM-85 group is in the number of children with three or more URTIs in the observation period, as shown in Figure 2, revealing a difference in favor of OM-85 of 22% at month 4 and of 15% at month 3 and month 5; the odds ratios for three or more URTIs with OM-85 were 0.51 (95% confidence interval, 0.29 to 0.91) and 0.65 (95% confidence interval, 0.37 to 1.11) after 5 months and 6 months, respectively.

An explorative analysis by multiple stepwise regression analysis was performed, with the cumulated rate of URTIs at month 5 as a dependent variable, and considering age, treatment, time in study, number of URTIs in the previous year, sex, year of participation in trial, and history of allergy as independent variables. There were higher rates of URTIs

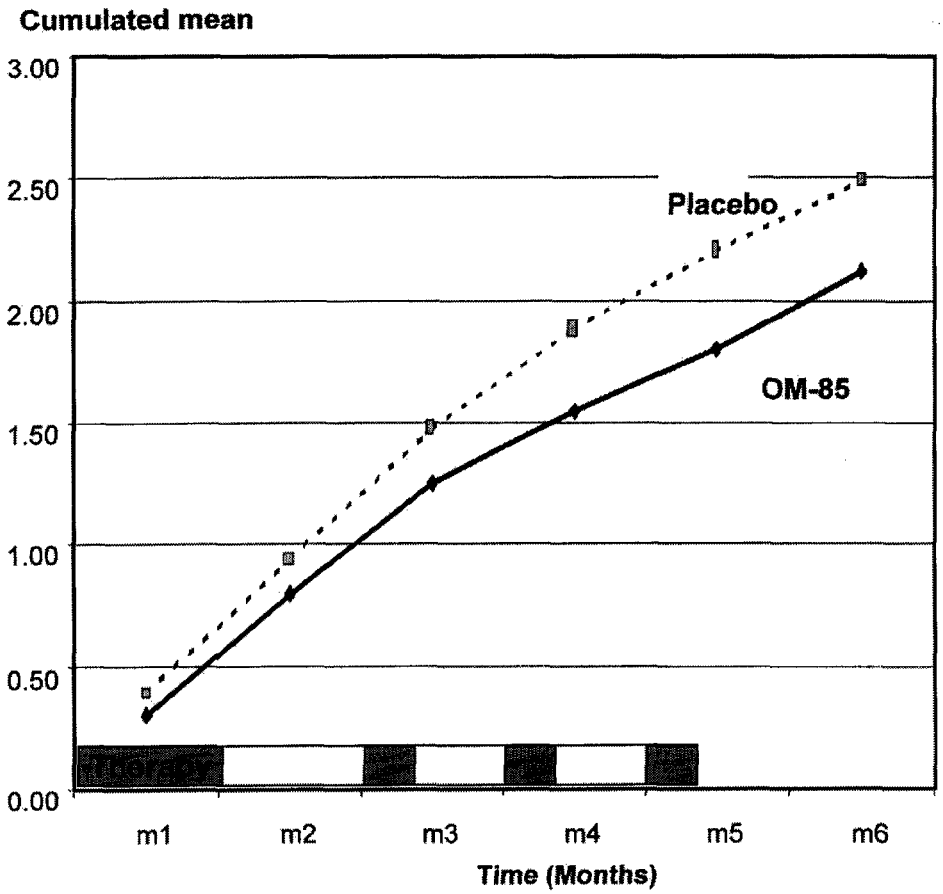

FIGURE 1. Mean cumulated rate of URTIs. m1 = month 1; m2 = month 2; m3 = month 3; m4 = month 4; m5 = month 5; m6 = month 6.

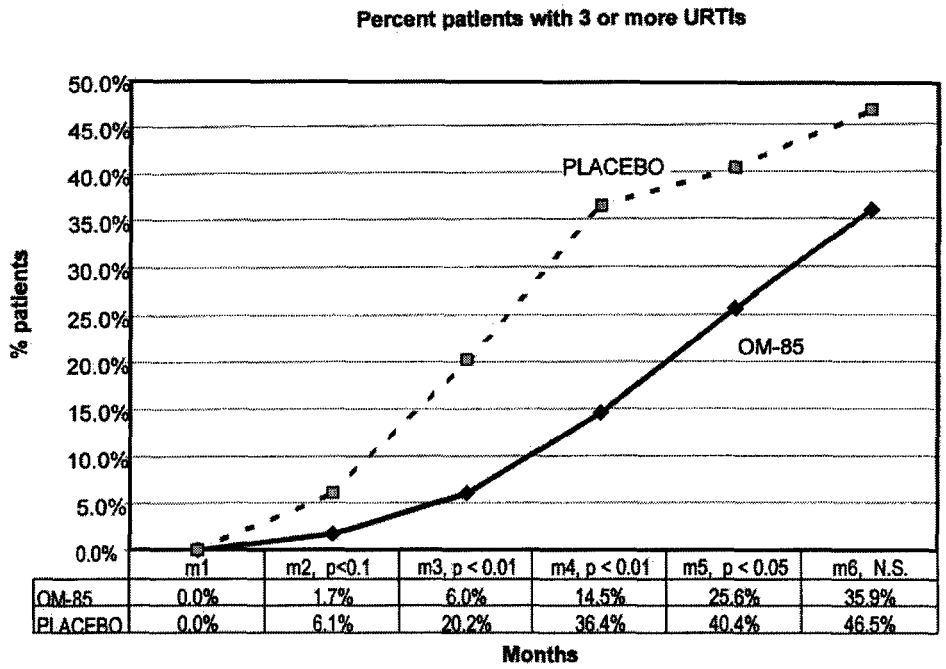

FIGURE 2. Cumulated percentage of patients reporting three or more URTIs during the study period. N.S. = not significant; see Figure 1 legend for expansion of abbreviations.

in patients treated with placebo ($p = 0.06$), in younger children ($p = 0.006$), in those who reported more URTIs in the previous year ($p = 0.06$), and, as expected, in those remaining the longer time in the study ($p = 0.0001$). The difference between OM-85 and placebo was independent of age but was more important in patients reporting a larger number of URTIs in the previous year. Stratification by number of URTIs reported in the previous year (cutoff was median of 5 URTIs) shows that the cumulated rate of URTIs was reduced in the OM-85 group by 14% (− 0.28 URTIs) in those reporting 2 to 5 URTIs in the previous year (not significant), and by 22% (− 0.56 URTIs) in those reporting 6 to 15 URTIs in the previous year ($p < 0.05$). It may be concluded that OM-85 treatment significantly reduced the incidence of URTIs in children with a history of frequent URTIs.

Secondary Variables

Of the target variables recorded, the main differences between treatments, favoring OM-85, were observed in the frequency and severity of rhinitis ($p = 0.06$) and, to a lesser extent, in the frequency and severity of pharyngitis ($p = 0.16$) and of fever ($p = 0.2$). No difference was observed as far as cough and hoarseness were concerned.

In the first 2 months of treatment, there were more cases of otitis reported in the OM-85–treated group (13 episodes vs 4 episodes in the placebo group), although not reaching the threshold of significance. In the later visits, the percentage of patients with otitis was similarly low (2 to 4%) in both groups. This finding is likely to reflect a difference between the two groups at baseline. The reported incidence of sinusitis was very low (mean monthly percentage < 1%) and comparable in both groups.

Anti-infectives

The mean monthly percentage of patients treated with antibiotics was similar in both groups (OM-85, 15.0%; placebo, 14.2%) and in the large majority of cases related to lower respiratory tract infection (OM-85, 11.9%; placebo, 12.2%). However, it has to be noted that less than half of the URTIs received antibiotic therapy with no clear-cut pattern of prescription. This finding contrasts with the prescriptions of local antiseptic, anti-inflammatory, antitussive, or mucolytic products, which were significantly less frequently used in the OM-85–treated group (mean monthly prescription of 5.2%) than in the placebo group (9.0%, $p < 0.05$).

Absenteeism

The number of patients with absenteeism from school diminished from approximately 50% at hospital admission to 10% during the first month and to

approximately 3% in the last 2 months, without significant differences between groups. It is not clear whether this absenteeism is specifically URTI related, since it was recorded independently of the occurrence of a URTI at the same visit. The mean ± SD duration of an episode of absenteeism was similar in both groups (approximately 3.5 ± 1.5 days) and did not change significantly over time.

Global Assessment

In comparison to the previous season, the majority of the patients and/or their parents or guardians reported some degree of improvement (OM-85, 78.4% of cases; placebo, 75.5% of cases); however, the distribution of answers was significantly different ($p < 0.05$) and there were more cases reporting worsening with placebo (6.4% vs 0.9%; Fisher test, $p < 0.05$). The investigators also reported an improvement in the majority of patients, with no significant differences between OM-85 and placebo.

Influence of Season

Distributing patients on treatment along the year (*ie*, mean URTIs of all patients treated in the months of November, December, etc.) showed in the placebo group a rapid increase in mean number of URTIs from September to November, followed by a plateau until February, and falling off thereafter. OM-85–treated patients showed a flat pattern, and the mean number of URTIs was lower. As a consequence, the benefit of the active treatment was largest in the period of November to February.

Safety

After active questioning, 164 patients (88 receiving OM-85 and 76 receiving placebo) complained about 835 adverse events (OM-85, 456 events; placebo, 379 events), of which approximately 40% were manifestations of the studied respiratory indications. The events were of different type, duration, and estimated relationship with the test medication, and constituted in most cases mild digestive troubles or respiratory symptoms (the latter already rated as such in the clinical part). Multiple events in the same patient were detected with as many as 20 events for OM-85 and 19 events for placebo. The average duration of the adverse events was 5.3 ± 9.0 days for OM-85 and 5.1 ± 6.8 days for placebo. There were a few reports of serious adverse events (10 events in nine patients), none of which were estimated to be related to the study medication, as follows:

OM-85–Treated Group: One case each of operation for appendicitis, acquired intestinal obstruction (in same patient), concussion of the brain, adenoidectomy, diagnostic procedure for epigastric pain (not specified), accidental burning, and tonsillectomy (n = 6).

Placebo-Treated Group: One case of pneumonia and otitis media and two cases of tonsillectomy/adenoidectomy (n = 3).

Only seven patients (six patients receiving OM-85, and one patient receiving placebo) reported nine adverse reactions (OM-85, eight reactions; placebo, one reaction) considered to be in possible or probable relationship to the trial medication. These were diarrhea (two patients), abdominal pain (two patients), fatigue, urinary frequency (twice in same the patient), and exanthem (in the same patient) in the OM-85 group. In the placebo group, there was an allergic reaction assessed as in possible relationship. All these adverse events were minor and transient, and they did not prompt any treatment discontinuation.

Discussion

This study was aimed at reducing the rate of URTIs in children with a history of frequent URTIs, starting from a current episode. Using an algorithm for diagnosing a URTI, ANOVA for repeated measures showed that treatment with OM-85 significantly reduced the incidence of URTIs by 16%, corresponding to a mean reduction by 0.40 URTIs per patient in 6 months with respect to placebo in the intent-to-treat population. It is worthwhile mentioning that the ANOVA concerning the per protocol population (excluding protocol violators) confirmed the main analysis, *ie*, a significantly lower rate of URTIs in the OM-85–treated patients ($p = 0.05$).

Rather than increasing the number of patients without any URTI, OM-85 treatment appeared to reduce the number of patients with frequent URTIs (three or more URTIs in 5 months), which represent almost half the patient population. The difference between the two treatment groups builds up during active treatment (months 1 to 5) and has a tendency to wear off thereafter (although this trial has a follow-up of only 1 month, too short to expect a significant detrition curve). These findings correspond fairly well with those reported by Collet et al[17] if the same criteria are applied. These authors, who addressed the question of the efficacy of OM-85 in the primary prevention of recurrent respiratory infections in young children in day-care centers, found a 48% reduction of the relative risk of having three or more respiratory infections after 3 months of

treatment. The efficacy of OM-85 in breaking the cycle of recurrent infections was also demonstrated by Paupe[18] in a double-blind, placebo-controlled trial including 116 children, aged 6 months to 19 years who had a history of at least three episodes of respiratory or ear, nose, and throat infections in the previous 6-month period. At the end of the prospective study period (3 months of treatment plus 3 months of follow-up), the incidence of all infections in the active group was 35% ($p < 0.01$) lower than in the placebo group. This effect was more pronounced in children < 6 years old, a finding that could not be confirmed in the study reported herein.

Even greater reductions of URTIs—by, respectively, 52% and 38%—have recently been reported with this bacterial extract in comparison to placebo during two double-blind studies.[21,22] These more marked findings with respect to those presented here may be linked to differences in settings. Indeed, the first trial included only girls aged 6 to 13 years living in a single fairly crowded center favoring microbial contamination (an orphanage), located in a region with high air pollution (Mexico City), and who were all highly susceptible to respiratory infections (a median of five infections per child over the previous 6 months, approximately double the value recorded here).[21] Overall, the same comments may address the other Mexican trial, in particular air pollution and highly susceptible children aged 1 to 12 years with a past mean rate of URTIs twice as high as the one of the present trial, but living at home and followed up for 1 year with two intermittent treatment periods of 3 months.[22]

In one of our previous multicenter studies,[24] 94 children with frequent URTIs were treated intermittently with either OM-85 or placebo, under double-blind conditions for 3 months followed by 3 months of observation. The preventive action of OM-85 was rated as "unequivocal" or "likely" in 77.3% of the cases vs 57.2% of those treated with placebo without statistically significant differences.

The findings in the present study contrast somewhat with those of the above-mentioned studies, probably conducted in more homogeneous settings[18,19,21] or in more air-polluted environments[21,22], but are more favorable for the OM-85 treatment than our previous results,[24] recorded in a heterogeneous multicentric practice-based setting, similar in fact to the one herein. Furthermore, explorative analysis strongly suggests that the efficacy of OM-85 is more evident, both in absolute and relative terms, in patients reporting frequent URTIs in the previous year (more than the median of five URTIs in the previous year), as clearly demonstrated in the above-mentioned two studies conducted in children who had an average of five acute respiratory tract infections per 6 months before inclusion.[21,22] Patients reporting "very frequent URTIs" were also likely to have more URTIs in the study period and constitute the subgroup that benefited most from the therapy with OM-85.

However, the findings concerning URTIs were not fully confirmed for the activity of the test medication on secondary variables such as the number of patients with pharyngitis, cough, hoarseness, temperature > 38.5°C, or antibiotic consumption. Some degree of masking of symptoms through prescribed or self-prescribed medication cannot be excluded. Nevertheless, intensity of rhinitis over the observation period was decreased under OM-85 with reference to placebo ($p = 0.06$), as was the consumption of local antitussive, anti-inflammatory, systemic antitussive, or mucolytic agents ($p < 0.05$). As URTIs tend to improve as children grow older, the global assessments comparing with the previous year were positive with both active treatment and placebo; however, a small but significantly larger proportion of placebo-treated patients reported a worsening of the condition.

In conclusion, confirming earlier studies, OM-85 reduced significantly the rate of URTIs in children with a history of frequent URTIs. This effect was proportional to the number of URTIs in the history of the patients. Safety and tolerance of test medication were good, comparable to placebo.

Appendix

We wish to thank the members of the BV-Child Study Group: J. F. Babel, J. Ballaman, R. Bardelli, G. Beguin, C. Bernasconi, L. Bianchetti, U. Bollag, E. Busser-Knusel, R. Christen, G. Ferrazzini, A. Frank, M. Good, P. Gordon, H. Hafliger, C. Hanggi, J. Holx, J. P. Kapp, U. Keller, R. Pancaldi, M. Renggli, U. B. Schaad, T. J. Von Kanel, Ch. Zeller, and A. Zimmerman, Switzerland; and G. Berzel, U. Brendel, J. Disselhoff, H. Gutzeit, O. Muller, R. Mütterlein, F. Panzer, S. Schneider, J. Tessmar, and F. Thanbichler, Germany.

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