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RESPIRATORY INFECTIONS

# Clinical and Immunological Benefits of OM-85 Bacterial Lysate in Patients with Allergic Rhinitis, Asthma, and COPD and Recurrent Respiratory Infections

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**Abstract**
*Purpose* The aim of this study was to evaluate the efficacy of OM-85 in reducing the incidence of respiratory tract infections (RTIs) in patients with allergic rhinitis, asthma, or chronic obstructive pulmonary disease (COPD), and its effect on immunological parameters, namely serum and secretory IgA levels.
*Methods* This was an open-label, prospective, sequential study which included 84 consecutive patients aged 16–65 years, who presented with recurrent (three or more) respiratory infections during the year prior to study entry. In the first year of the study, patients received standard optimized care (SOC), according to their underlying disease condition (asthma, allergic rhinitis, or COPD). In the following year, patients received treatment with OM-85 oral bacterial lysate (one 7 mg capsule daily for ten consecutive days per month, for 3 months), with a 6-month follow-up. Medical history, clinical symptoms, serum, and secretory IgA levels, and the number of infections and exacerbations were evaluated before and after treatment.
*Results* There was a decrease in the total number of RTIs before the OM-85 treatment period (SOC only) compared to the year before the study start [69/266 (corresponding to a 74 % reduction)] and an additional decrease [38/69 (corresponding to a 45 % reduction)] after OM-85 treatment; $p < 0.05$. There was also a significant reduction in the total number of exacerbations related to the patients' underlying medical conditions, which decreased from 55 to 35 during OM-85 (+SOC) treatment, corresponding to a reduction of 36 %. In addition, an increase in serum and secretory IgA levels which coincided with the administration of OM-85 was observed.
*Conclusions* Our results showed the clinical benefits of OM-85 in reducing RTIs and exacerbations of the underlying medical condition, in patients with allergic rhinitis, asthma, or COPD.

**Keywords** Respiratory tract infection · Bacterial lysate · OM-85 · Asthma · Rhinitis · COPD · Exacerbation · Re-infection

## Introduction

Recurrent respiratory tract infections (RTIs) have a significant health and socioeconomic impact. Recurrent infections of the upper and lower respiratory tract often require multiple treatment modalities, including the use of antibiotics [1–4]. The high incidence of these diseases in combination with the substantial morbidity, clinical sequelae, and associated overuse and misuse of antibiotics contribute towards the overall disease burden that includes the direct costs of healthcare and indirect economic costs to society [4, 5].

The vast majority of recurrent RTIs are triggered by viruses, but these are frequently followed by bacterial superinfections [6]. There is extensive literature on the synergistic effect between viruses and bacteria in the pathogenesis of respiratory infections [2]. Regardless of whether they are viral or bacterial, the presence of

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pathogens in the respiratory tract triggers the involvement of the innate and adaptive mucosal immune systems. Innate mucosal immunity is related to the function of the epithelial lining of the respiratory tract, including the production of antimicrobial peptides, the cytotoxic actions of NK cells, and the engulfment of pathogens by monocytes/macrophages and neutrophils. A key event among the actions of the acquired immune system is the production of IgA molecules.

Patients with impaired immunity and chronic inflammation are at greater risk of RTIs. This is especially true for those with underlying conditions such as allergic rhinitis, asthma, or chronic obstructive pulmonary disease (COPD) [7, 8]. These disorders are highly prevalent worldwide and are of great public health concern [9, 10]. Patients with these disorders have impaired immunologic response mechanisms such as a preponderance of Th2-driven responses and a reduction in protective Th1 responses [11]. Furthermore, they have increased levels of IgE antibodies which are related to a stronger inflammatory response [12–14].

From the preventive and clinical point of view, there is a need for addressing the recurrence and severity of RTIs in this large patient population. OM-85 (Broncho-Vaxom®, Broncho-Munal®, Vaxoral®, Ommunal®, Paxoral®) is an immunomodulator comprising lyophilized bacterial lysates from the eight major strains responsible for RTIs (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans*, and *Moraxella catarrhalis*). OM-85 has pleiotropic immunomodulating effects on both the innate and adaptive immune responses [15–17]. There is an extensive body of evidence showing the safety and efficacy of OM-85 in the prevention of RTIs in children and adults regardless of the etiology, including in those with impaired immunity [15, 18–24]. The use of OM-85 has been shown to have beneficial effects on the incidence, duration, and severity of RTIs [25–28].

The aim of this study was to evaluate the efficacy of OM-85 in reducing the incidence of RTIs in patients with allergic rhinitis, asthma, or COPD and its effect on immunological parameters, namely serum and secretory IgA levels.

## Methods

### Study Design

This was an open-label, prospective, sequential study conducted in 2009 and 2010. A total of 84 consecutive patients presenting with three or more respiratory infections during the previous year, eligible according to the inclusion and exclusion criteria, and who had provided written informed consent were included. Among these 84 patients, 29 had allergic rhinitis, 28 had asthma, and 27 had COPD. All patients underwent a complete medical history, as well as testing for specific serum IgE and the allergen skin prick test, serum IgA, and salivary secretory IgA. IgA levels only were tested again after 3 months. After 9 months of observation, the same group of patients was re-assessed. All patients presented with respiratory infections despite optimization of the standard care regimen (standard optimized care [SOC]) and as they did not receive prophylaxis with a bacterial lysate they were included in the second phase of the study. In 2010, the same patients received treatment with OM-85 bacterial lysate (alongside SOC) and were evaluated in the same manner as the previous year.

The study protocol was approved by the institutional Ethics Committee. Written informed consent was obtained from all participants included in the study, and the study was conducted according to the principles of the 1964 Declaration of Helsinki and its amendments.

### Main Inclusion and Exclusion Criteria

The study included male and female outpatients (aged 16–65 years) who had a confirmed history of perennial ($\geq$2 years) allergic rhinitis, asthma, or COPD and at least three RTIs in the previous year (assessed at the screening visit). Patients with allergic rhinitis or asthma had to have elevated serum IgE levels. In addition, patients with allergic rhinitis or asthma had to have a positive skin prick test against one or more of the following allergens: dermatophagoides, cat dander, alternaria, and/or *Aspergillus*. Key exclusion criteria included structural alterations of the nasal pyramid, the presence of any underlying medical condition that could interfere with the study results, pregnancy, or breastfeeding.

### Study Treatment

After 9 months of observation and SOC therapy, the patients received treatment with OM-85 (one 7 mg capsule daily for ten consecutive days per month, for 3 months), and were followed-up for 6 months after the treatment period (Fig. 1). In addition, 10 healthy subjects (with no underlying asthma, allergies, or COPD, but who occasionally visited the clinic for uncomplicated respiratory infections) were selected as normal controls for the measurement of IgA values.

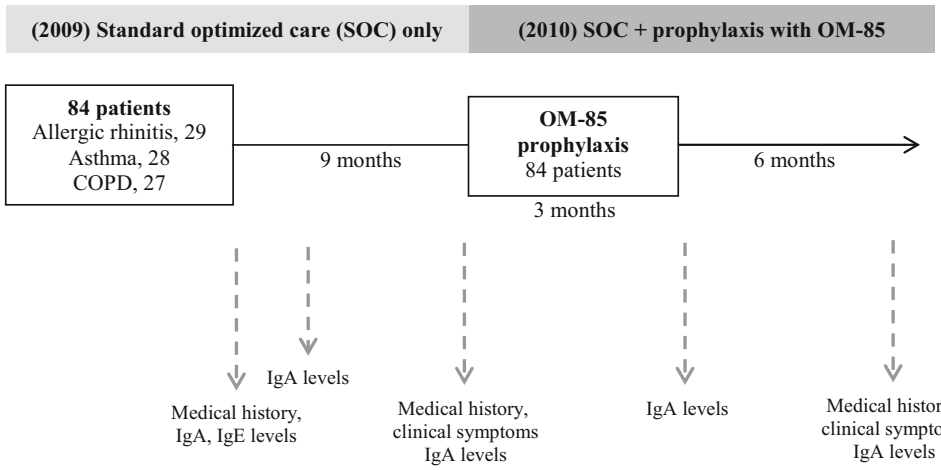



**Fig. 1** Summary of the study plan

## Study Parameters

### *Clinical Symptoms*

An RTI was defined as any viral or bacterial infection of the upper or lower respiratory tract. An exacerbation of asthma was defined as an acute or subacute episode of progressively worsening shortness of breath, cough, wheezing, and/or chest tightness, accompanied by decreases in expiratory airflow and lung function [29]. Rhinitis exacerbations were considered when there was an increase in the typical symptoms, such as inflammation of the nasal membranes accompanied by sneezing, nasal congestion, nasal itching, and/or rhinorrhea [30]. Exacerbations of COPD were defined as increased dyspnea, sputum volume, and/or sputum purulence with or without accompanying cough, wheeze, or other symptoms of an upper RTI [31].

Clinical symptoms were assessed by investigators according to a standard symptom score before the study (baseline visit), at the end of the SOC period and at the end of OM-85 prophylaxis follow-up, and in the event of a respiratory infection (in case of RTIs, patients were advised to visit the clinic). The symptom score for the underlying disease (asthma, rhinitis, or COPD) was also reported by the patients. The following scoring system was used:

0—No symptoms.

1—Mild symptoms (mild rhinitis or mild dyspnea, without nocturnal symptoms or alterations in the quality of life or daily activities, or the need for extra medication).

Peak flow: 80 % predicted; variability <20 %.

2—Moderate symptoms (moderate rhinitis, moderate dyspnea ≤3 times per week, no nocturnal symptoms, not affecting the ability to work or attend school, and disappearance of the symptoms with a single extra dose of medication).

Peak flow: 80 % predicted; variability 20–30 %.

3—Severe symptoms (severe rhinitis with obstruction, dyspnea more than three times per day, and nocturnal symptoms twice a week, i.e., sleep disturbance, asthenia. Ability to attend work or school is affected).

Peak flow: 60–80 % predicted; variability >30 %.

All patients were rigorously trained to record their score, including peak flow measurements.

### *IgA Levels*

Measurement of IgA levels was performed during the period of the SOC treatment as well as during the period of OM-85 prophylaxis. IgA levels obtained from a separate group of healthy adults were used as controls. Unstimulated parotid saliva samples (1 mL) were collected with a Salivette sampling device composed of a cotton roll impregnated with saliva and then centrifuged to obtain a transparent saliva sample to be analyzed. All samples were stored at −20 °C until analysis.

Secretory IgA was measured by means of Mancini radial immunodiffusion in agar (Diffu-Plate®, Biocientífica S.A.) at 2.5 % and Heremans buffer (pH 8.6) using monospecific anti-serum. Human colostrum was used as a standard (48 mg %).

### *IgE Levels*

Specific IgE was measured to confirm the involvement of an allergic component in patients with rhinitis and asthma, and to rule out allergic involvement in COPD patients.

A radioallergosorbent test (RAST) consisted of incubation of a patient serum sample with the allergen covalently bound to a paper disk. Any antibodies in the sample against the allergen will bind to the solid phase. After incubation for 3–4 h, the solid phase was washed three times with wash solution to remove the nonspecifically bound

antibodies. Immediately after, the sample was incubated with anti-IgE anti-serum labeled with $I^{125}$, for 18–24 h at room temperature. Afterwards, disks were washed and the remaining radioactivity was measured using a Wistar-38 gamma counter.

Allergen-specific IgE levels were determined by comparing the sample counts per minute with the standard counts per minute according to the following qualitative classification: undetectable, low, moderate, high, very high, and extremely high. Of note, normal specific IgE levels are expressed in kU/L or U/mL (same numeric value for both), and in classes (positive or negative). A non-sensitized person has undetectable levels of specific IgE. If IgE is absent, the IgE is said to be negative; and if it is present, it is said to be positive. Table 1 depicts the most frequently used threshold values. The specific IgE levels found in patients with asthma and rhinitis (without COPD) are shown in Table 2.

### Statistical Analysis

An initial sample of 90 patients was deemed necessary in order to detect potential trends in nasal immunological responses and to detect potential differences in exacerbations between healthy controls and patients, attributed to study treatment and/or underlying medical condition (with a type I error of 5 % and statistical power of 80 %).

Pre- and post-treatment differences were evaluated for the variables of interest and described for each study group (i.e., allergic rhinitis, asthma, COPD). The changes in serum and salivary secretory IgA levels were assessed. The symptoms score of the underlying pathology were determined descriptively.

## Results

A total of 84 patients who suffered from recurrent RTIs were followed-up for a 9-month period, during which they only received SOC and no preventative treatment with OM-85. The following year, all the patients received prophylaxis with OM-85 (one 7 mg capsule daily for the first 10 days each month, for three consecutive months) plus SOC. SOC administered to patients during the study was unchanged throughout the 2-year study period.

The results presented below reflect the data obtained during the OM-85 + SOC study period, which were compared to the data from the SOC study period.

**Table 1** Specific IgE threshold levels [42]

| kU/L or U/mL | Class | Interpretation |
|---|---|---|
| <0.35 | 0 | Normal or negative |
| 0.35–0.70 | 1 | Positive, minimum |
| 0.70–3.5 | 2 | Positive, low to intermediate |
| 3.5–17.5 | 3 | Positive, intermediate to high |
| 17.5–50 | 4 | Positive, high |
| 50–100 | 5 | Positive, very high |
| >100 | 6 | Positive, maximum |

### Respiratory Infections

The total number of RTIs experienced by the patients in 2009 and 2010 are depicted in Table 3 and Fig. 2. In 2008 (the year prior to study start), the 84 patients reported a total of 266 RTIs (Table 3). In 2009, after the adjustment of the concurrent background medication (SOC) the same patient cohort reported a total of 69 RTIs, corresponding to a reduction of 74 %. In 2010, with the added OM-85 prophylaxis, the patients reported 38 RTIs, corresponding to a further reduction of 45 % compared to the previous year ($p < 0.05$; Fig. 2a).

The number of RTIs was further sub-divided into those reported by patients with COPD, asthma, or allergic rhinitis (Fig. 2b).

In COPD patients, the number of infections was 24/48 (50 % reduction), and in the asthma/rhinitis groups this was 14/21 (33 % reduction), with OM-85 treatment compared to the previous study year (Table 3).

### Exacerbations of the Underlying Pathology

In 2009, there were 55 exacerbations of the underlying disease pathology, compared to 183 reported in 2008 (Table 3). This corresponds to a reduction of 70 % (Fig. 3).

In 2010, all patients were treated with OM-85 alongside SOC. During this time, there were 35 exacerbations, compared to the 55 exacerbations reported in 2009 (corresponding to an additional reduction of 36.4 % compared to 2009) ($p < 0.05$; Fig. 3a).

The number of exacerbations was further sub-divided into those reported by patients with COPD, asthma, or allergic rhinitis (Fig. 3b). COPD patients showed a reduction in the number of exacerbations corresponding to 25/38 (34 % reduction), and those with asthma and allergic rhinitis showed a 10/17 (41.2 %) reduction during the OM-85 treatment year (Table 3).

The results for the overall study period (2009 and 2010) are summarized in Table 3.

**Table 2** Specific IgE levels in patients with asthma and/or rhinitis (but without COPD)

| Allergens | Asthma patients | | Rhinitis patients | | COPD |
|---|---|---|---|---|---|
| | *N* | Media (U/mL) | *N* | Media (U/mL) | *N* |
| Dermatophagoides | 27 | 7.572 | 25 | 25.04 | 0 |
| Cat dander | 12 | 13.25 | 14 | 9.428 | 0 |
| Alternaria | 1 | 0.45 | 5 | 0.64 | 0 |
| *Aspergillus* | 3 | 1.3 | 2 | 24.5 | 0 |

**Table 3** Differences in the number of RTIs and exacerbations of the patients' underlying medical condition over the 2-year study period

| Year | Total number of patients | Patients and underlying pathology | Total number of respiratory infections | Number of respiratory infections in each patient group | Total number of exacerbations | Number of exacerbations of the underlying pathology |
|---|---|---|---|---|---|---|
| 2008 (patients selection) | 84 | COPD, 27 | 266 | 88 | 183 | 68 |
| | | Rhinitis, 29 | | 91 | | 54 |
| | | Asthma, 28 | | 87 | | 61 |
| 2009 (no treatment with OM-85, SOC only) | 84 | COPD, 27 | 69 | 48 | 55 | 38 |
| | | Asthma, 28 | | 9 | | 11 |
| | | Rhinitis, 29 | | 12 | | 6 |
| 2010 (treatment with OM-85 + SOC) | 84 | COPD, 27 | 38 | 24 | 35 | 25 |
| | | Rhinitis, 29 | | 8 | | 6 |
| | | Asthma, 28 | | 6 | | 4 |

## Symptoms of the Patients' Underlying Medical Condition

Table 4 shows the patients' symptom scores during the year they received only SOC, compared to the following year when they received treatment with OM-85 and SOC. The table indicates the numbers of patients who reported scores of 0, 1, 2, or 3 in 2009 (treatment with SOC only) and 2010 (SOC plus OM-85 prophylaxis). Within each category of symptom severity (ranging from one [1]—severe symptoms [3]), a lower proportion of patients reported these scores during the year they received OM-85 preventative treatment. In addition, fewer patients reported severe symptoms during the OM-85 treatment period. Overall, the reduction in the proportion of patients who reported each symptom ranged from 48.29 % (for nasal congestion) to 79.42 % (for cough; Table 4).

## Severity of Respiratory Tract Infections and Exacerbations

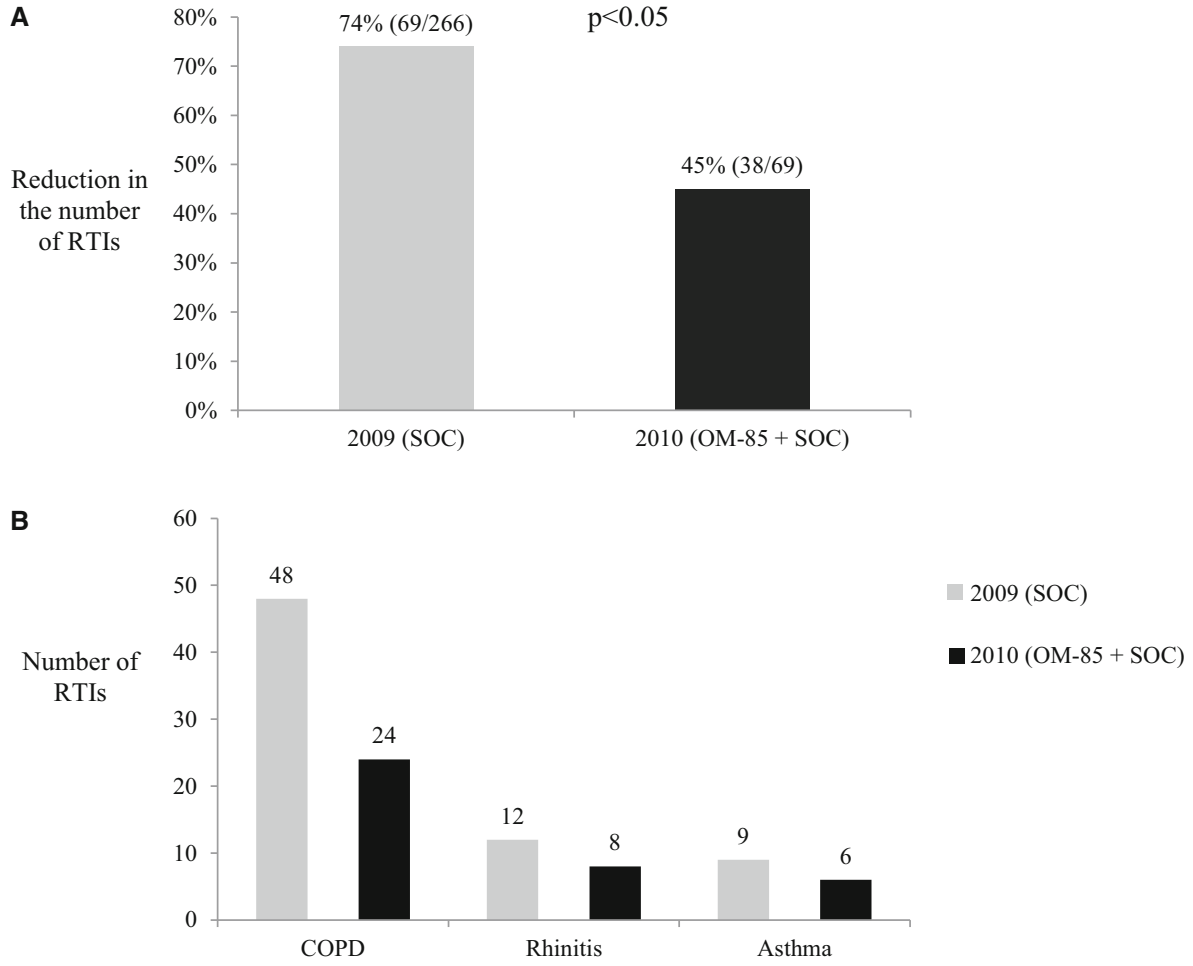
There were fewer incidences of severe viral infections during the year patients received treatment with OM-85 and SOC, compared to the previous year when patients received only SOC. There were two counts of hospitalization in asthma patients due to severe viral infections during the year before OM-85 treatment; no hospitalizations occurred during the year patients were treated with OM-85 plus SOC.

In patients with asthma, viral infections have been shown to be an important risk factor for wheezing. The patients experienced concomitant worsening of cough and secretions, particularly those patients who were exposed to more antigens to which they tested positive in the allergy screen, exhibiting a late response to the antigens that could be observed even 1–3 weeks after recovery from the initial viral infection.

Recovery from wheezing, cough, and secretions took more time (at least 7 days longer) compared to those patients who had wheezing episodes that were not triggered by viral infection (recovery from symptoms was observed in 48 h in these patients).

Of note, we detected the presence of viruses in nearly 60 % of the patients with severe asthma crises who required intensive care support, despite optimization of the appropriate medication. In these patients, the symptoms of respiratory infections included spasms, secretions, coughing, dyspnea, decrease in $O_2$ saturation, and chest tightness. There was no need for antibiotic administration in any of these cases. All the patients with asthma and viral infections had chest X-ray findings that showed distinct interstitial infiltration and hyperventilation. The most frequently arising complications were atelectasis and bronchopneumonia.

In those patients with asthma who had bacterial infections, we identified the strains *H. influenza* and *C.*




SOC = standard optimized care.

**Fig. 2** **a** Reduction in the total number of RTIs in 2009 (versus 2008) and 2010 (versus 2009). **b** Number of RTIs reported in each patient subgroup (COPD, rhinitis, asthma) in 2009 and 2010

*pneumoniae*. Symptoms included sudden fever (≥38 °C), significant exacerbation of the underlying conditions (asthma, mainly with dyspnea) accompanied by headache, cough, tachypnea, intercostal retraction, wheezing, rales, general malaise, myalgias, and loss of appetite. Other clinical symptoms that were frequently observed included nasal congestion and odynophagia, which was in some cases accompanied by hoarseness, ocular congestion with tears, retrosternal cough pain, and gastrointestinal symptoms (including nausea, vomiting, or diarrhea). A few patients presented with speech difficulties and alteration of consciousness. Patients who exhibited signs of imminent acute respiratory claudication, including bradycardia, absence of wheezing, paradoxical thoracicoabdominal respiratory movement, cyanosis, and sensory depression were hospitalized immediately in intensive care units.

In patients with rhinitis, exacerbations are triggered by the common cold caused by rhinoviruses; other viruses such as the adenovirus, coronavirus, parainfluenza virus, and respiratory syncytial virus may also play a role. Clinical symptoms included nasal congestion with pharyngeal irritation and cough, watery rhinorrhea, and sneezing. All these symptoms are consistent with the underlying allergic rhinitis, although there was an increase in their intensity and these were frequently accompanied by fever. The amount of post-nasal mucus and the transformation from pale to erythematous nasal mucosa are indicators of a stronger inflammatory process, such as that triggered by respiratory infections. There were no cases of acute bacterial rhinitis in our study.

The symptoms of COPD included dyspnea and chronic coughing accompanied by a history of exposure to known risk factors. The most frequent trigger of exacerbations that worsen the condition are bacterial or viral infections. Although the use of spirometry is necessary to confirm a clinical diagnosis of COPD, spirometry is not

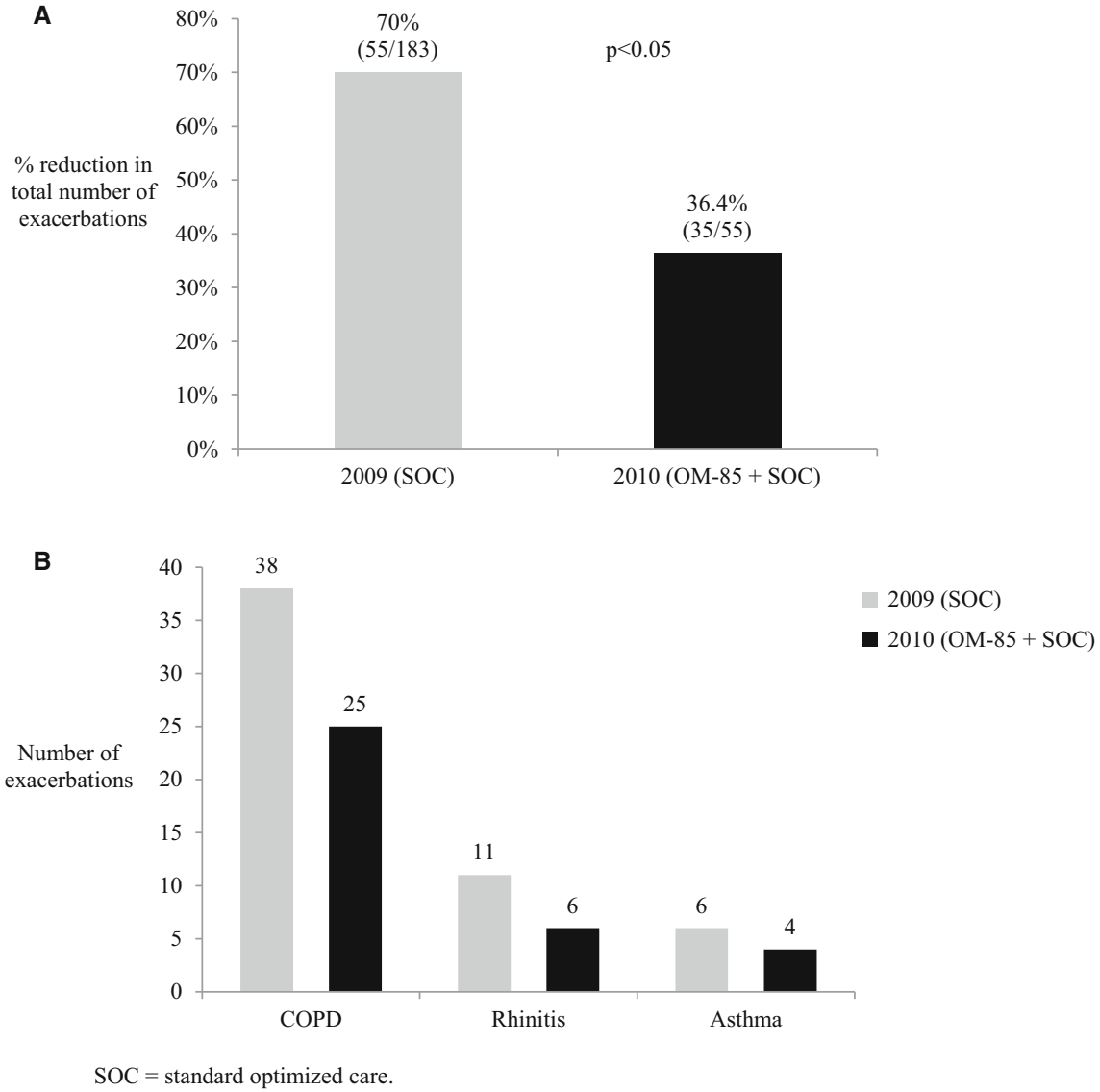



**Fig. 3** **a** Reduction in the total number of exacerbations in 2009 (versus 2008) and 2010 (versus 2009). **b** Number of exacerbations in each patient subgroup (COPD, rhinitis, asthma) in 2009 and 2010

recommended during exacerbations since exacerbations increase the difficulty of performing this technique and affect the reliability of the results [32]. In order to classify the degree of severity of COPD, we used the modified Dyspnea scale of the British Medical Research Council [33]. Overall, there were fewer exacerbations during the year of treatment with OM-85 (Table 3), and the number of severe exacerbations was markedly lower. There were 20 exacerbations of severity level 4 and 8 counts of hospitalization in 2009, compared to 4 exacerbations of severity levels 4 and 2 counts of hospitalization in 2010 when patients received OM-85 plus SOC.

## IgA Levels

Serum IgA levels were measured over the 3-month OM-85 treatment period (Group A). The same measurements had been taken over a 3-month period during the previous year, when the patients received SOC only (Group B). As a comparator, serum IgA levels were measured in a separate group of healthy volunteers (Group C); (Table 5). In the healthy adults, serum IgA levels were 217 ± 75 mg % (Group C), compared to 190 ± 84 mg % in patients who received SOC only in the year prior to treatment with OM-85 (Group B), and 296 ± 63 mg % ($p < 0.001$) in patients

**Table 4** Reduction in the patients' symptom score during the year they received prophylactic treatment with OM-85, compared to the previous year (when they received standard optimized care only)

| Symptom severity Score | Total patients *n* (%) | Absent 0 | | Mild 1 | | Moderate 2 | | Severe 3 | | Total reduction (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment | |
| Nasal secretion | 29 (100 %) | – | – | – | – | 18 (62.07 %) | 6 (20.68 %) | 11 (37.931 %) | 4 (13.79 %) | 65.53 |
| Nasal/retrotracheal pruritus | 29 (100 %) | – | – | 1 (3.44 %) | 1 (3.44 %) | 20 (68.96 %) | 8 (27.58 %) | 8 (27.58 %) | 3 (10.34) | 58.64 |
| Palatine pruritus | 29 (100 %) | – | – | 5 (17.24 %) | 1 (3.44 %) | 19 (65.51 %) | 4 (13.79 %) | 5 (17.24 %) | 1 (3.44 %) | 79.33 |
| Ear pruritus | 29 (100 %) | 1 (3.44 %) | 1 (3.44 %) | 18 (62.06 %) | 6 (20.68 %) | 9 (31.03 %) | 3 (10.34 %) | 1 (3.44 %) | 1 (3.44 %) | 62.1 |
| Eye pruritus | 29 (100 %) | 2 (6.89 %) | 1 (3.44 %) | 11 (37.93 %) | 5 (17.24 %) | 9 (31.03 %) | 2 (6.89 %) | 7 (24.13 %) | – | 72.43 |
| Sneezing | 29 (100 %) | – | – | 9 (31.03 %) | 5 (17.24 %) | 15 (51.72 %) | 6 (20.68 %) | 5 (17.24 %) | 1 (3.44 %) | 58.64 |
| Nasal congestion | 29 (100 %) | – | – | 8 (27.58 %) | 4 (13.79 %) | 11 (37.93 %) | 5 (17.24 %) | 10 (34.48 %) | 6 (20.68 %) | 48.29 |
| Bronchospasms | 48 (100 %) | – | – | 3 (6.25 %) | – | 18 (37.5 %) | 3 (6.25 %) | 27 (56.25 %) | 6 (12.5) | 81.25 |
| Cough | 68 (100 %) | – | – | 9 (13.23 %) | (2.94 %) | 35 (51.47 %) | 8 (11.76 %) | 24 (35.29 %) | 4 (5.88 %) | 79.42 |

Definition of symptoms Absent (0): No symptoms. Mild (1): Only mild symptoms that do not affect quality of life. Moderate (2): Symptoms are present, but do not interfere with daily activities, such as work or school. Severe (3): Symptoms are severe and interfere with the patient's daily activities, and affect work or school attendance

after prophylactic treatment with OM-85 (Group A). Moreover, the rate of increase in IgA levels in Group A paralleled the three cycles of OM-85 therapy as shown in Fig. 4.

The levels of salivary secretory IgA followed a similar pattern as serum IgA, although with a less pronounced increase (Fig. 5). The reference standard used in this case was colostrum IgA (48 mg %), taking into account the fact that the normal level of salivary secretory IgA is 3–25 mg %.

In the group of patients who did not receive bacterial lysate (during the previous year when they received SOC only; Group B), secretory IgA values were 2–27 mg %. In the patients receiving OM-85 the following year (Group A) average initial values were 25 mg %, increasing to $125 \pm 27$ mg % ($p < 0.001$) after the last 10 days of sequential OM-85 treatment (Fig. 5).

## Discussion

The aim of our study was to assess the incidence of respiratory infections as well as the symptoms and exacerbations of the underlying medical condition in patients with allergic rhinitis, asthma, or COPD.

This is the first study to include patients who were thoroughly characterized before the administration of OM-85. These patients were followed-up in 2009 and 2010. This is also the first study that considered the reduction in the recurrence of respiratory infections as well as reduction in exacerbations of the patients' underlying medical condition, namely allergic rhinitis, asthma and COPD.

It is well known that respiratory infections in children with asthma are more frequently caused by the respiratory syncytial virus (RSV) and parainfluenza virus, but that rhinovirus is the main trigger in adolescents and adults. There is a large body of literature supporting the association between viral infections and asthma, independently of age, phenotype, and asthma stage during which the viral infection occurs [34]. The role of bacterial infections, however, is controversial and is less well-established compared to that of viruses. Of note, we detected the presence of viruses in nearly 60 % of the patients with severe asthma who required intensive care support. Among our patients with asthma who had bacterial infections, we identified the strains *H. influenza* and *C. pneumoniae*. Our clinical observations are in agreement with those reported in the literature, indicating that in patients with asthma, viral infections are more frequently associated with asthma crises, regardless of the phenotype, asthma duration, and natural history of the disease, but bacterial infections lead to an increase in inflammation and a worsening of the disease [35, 36].

**Table 5** Variation in serum IgA values throughout the study period (Group A = OM-85 + SOC; Group B = SOC only; Group C = healthy group, $n = 10$)

| Serum IgA (mg %) | Baseline | 10 days | 30 days | 40 days | 60 days | 70 days |
|---|---|---|---|---|---|---|
| Group A | | | | | | |
| Maximum | 263 | 295 | 301 | 315 | 317 | 359 |
| Minimum | 137 | 169 | 175 | 189 | 191 | 233 |
| Median | 200 | 232 | 238 | 252 | 254 | 296 |
| Group B | | | | | | |
| Maximum | 274 | 269 | 281 | 282 | 289 | 284 |
| Minimum | 106 | 100 | 112 | 114 | 121 | 116 |
| Median | 190 | 185 | 196 | 198 | 205 | 200 |
| Group C | | | | | | |
| Maximum | 292 | 273 | 275 | 273 | 285 | 292 |
| Minimum | 142 | 123 | 125 | 123 | 135 | 142 |
| Median | 217 | 198 | 200 | 198 | 210 | 217 |

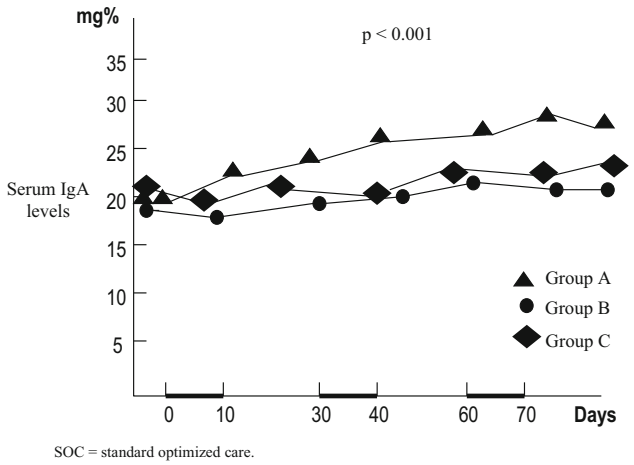



**Fig. 4** Increase in serum IgA levels over the 3-month OM-85 treatment period (Group A), compared to three months in the previous year when the same patients received only SOC (Group B). Group C represents a separate cohort of healthy patients, whose IgA levels were used as a comparator. The *black bars* shown on the *X*-axis indicate the ten consecutive days when patients received one daily capsule of OM-85

Treatment with OM-85 induced a clinical improvement in patients affected by asthma, allergic rhinitis, and COPD, not only in terms of respiratory infections, but also with respect to the underlying pathologies. Our results showed that in patients affected by asthma, allergic rhinitis, and COPD, OM-85 reduced the number of respiratory infections by 45 % and the number of exacerbations of the underlying pathologies by 36 %; the patients reporting symptoms related to the underlying medical condition was reduced by up to 80 %.

Recent studies have demonstrated that the use of immunomodulators can shift Th2 responses to Th1 responses [37, 38], thereby reducing hypersensitivity-associated responses in predisposed patients. Reductions in recurrent infections induced by OM-85 may be attributed to increased secretory IgA levels [21, 39, 40]. There are studies showing that secretory IgA may compensate for IgG immunodeficiencies [41].

An important finding of this study is the increase in serum and secretory IgA levels that coincided with the cycles of OM-85 treatment. The pattern of this increase

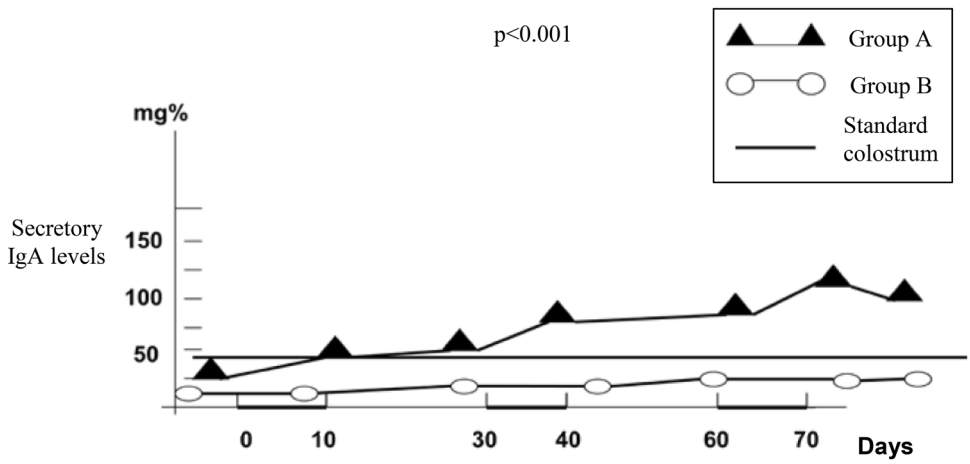



**Fig. 5** Increase in salivary secretory IgA levels during the treatment period with OM-85. The *black bars* shown on the *X*-axis indicate the ten consecutive days when patients received one daily capsule of OM-85

suggests that this is due to OM-85 treatment that induces a local immunological response in the mucosa, thereby reducing the risk of viral and bacterial infection against a background of respiratory allergic diseases and COPD.

## Conclusions

The results from this study show that OM-85 reduces the number of respiratory tract infections, as well as the number of exacerbations of the patients' underlying medical condition (allergic rhinitis, asthma, or COPD). As expected, increased concentrations of serum and secretory IgA were seen alongside the improvement in the incidence of respiratory infections and in the underlying medical condition.

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**Compliance with Ethical Standard**

**Conflict of interest** The authors declare no conflicts of interest with any companies whose products or services may be discussed in this article.

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