

Oral Bacterial Lysate OM-85 Prevents Respiratory Tract Infections in Asthma: The OMRIA RWE Study

Maria Elpida Christopoulou^{1,2}, Lilia S Panteli¹, John A Moisidis¹, Ioannis A Christopoulos³, Maria Eleni Kasimeri⁴, Amalia S Tryphonidou¹, Antonios I Christopoulos^{1,3}

¹Asthma Clinics, Primary Care Clinics for Asthma, Allergy & Respiratory Health Athens, Patras, Kalavryta, Greece; ²Clinic of Pneumology, Medical Center-University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany; ³Department of Respiratory Medicine, University General Hospital, Faculty of Medicine, University of Patras, Patras, Greece; ⁴Mid Yorkshire Teaching NHS Trust, Pinderfields Hospital, Wakefield, West Yorkshire, UK

Correspondence: Maria Elpida Christopoulou; Antonios I Christopoulos, Email maria.elpida.christopoulou@uniklinik-freiburg.de; asthmaclinics@outlook.com

Background: OM-85 is a well-characterized bacterial lysate with antiviral properties, enhancement of airway epithelial barrier function, and tolerance induction. However, real-world evidence is needed to evaluate its effectiveness as an add-on therapy in patients with allergic asthma.

Methods: This retrospective cohort study analyzed medical records of 137 adults with moderate to severe allergic asthma over 12 months. Patients receiving standard of care (SoC) asthma therapy alone (GINA step 4, n = 67) were compared to those on SoC+OM-85 (n = 70). All symptom episodes (CEPs) indicative of respiratory tract infections (RTIs) were recorded, and a 3-scale mean severity index (mSI) was calculated. Propensity score weighting was used for Poisson and linear regression analyses.

Results: Patients on OM-85 demonstrated significant reductions in the number of CEPs (60%), asthma exacerbations (71%), unscheduled visits (72%), oral corticosteroid courses (73%), and antibiotic cycles (67%). The mSI was 1.15 points lower in the OM-85 group (p < 0.001).

Conclusion: OM-85 as an add-on to standard asthma therapy significantly reduced RTI-related episodes, exacerbations, and healthcare utilization while lowering symptom severity in adults with allergic asthma.

Keywords: OM-85, allergic asthma, human rhinovirus (HRV), HRV, bacterial lysates, asthma exacerbations, immunomodulation

Introduction

Respiratory tract infections (RTIs) represent a significant global health challenge with profound clinical and economic impacts.¹ Bronchial asthma, a long-term condition affecting over 300 million individuals worldwide, is associated with an increased vulnerability to recurrent RTIs (rRTIs).^{2–7} Nearly two-thirds of recurrent respiratory tract infections (rRTIs) in asthmatic individuals—both children and adults—are attributed to various subtypes of human rhinoviruses (HRV).^{6–9} Other common culprits include adenoviruses (HAdV), coronaviruses (eg, SARS-CoV-2), influenza viruses (IFV), and respiratory syncytial virus (RSV), which are also common across age groups. Bacterial pathogens, particularly in cases of sinusitis or pneumonia, also play a critical role in exacerbating rRTIs.¹⁰

rRTIs are closely associated with a decline in pulmonary function and a deterioration in quality of life (QoL) among asthma patients.^{2,3} These infections frequently act as triggers for asthma exacerbations (AEXs), with their management representing nearly 80% of the total direct costs associated with asthma care.^{2–4} The overuse of antibiotics in managing RTIs contributes to adverse outcomes, including antibiotic resistance and disruption of the gut microbiota, which compromises immune defense and may increase the risk of atopy.¹¹ Additionally, rRTIs often necessitate the escalation of asthma treatment, particularly with oral corticosteroids (OCS), which are associated with significant adverse events.¹² Thus, preventing rRTIs is essential for improving asthma management and reducing the associated healthcare burden.

Current strategies to mitigate RTI-related complications include eliminating environmental triggers and promoting vaccination. However, limitations such as incomplete vaccine coverage, variable efficacy, and the absence of vaccines for HRV highlight the need for alternative approaches. Insights from the “hygiene hypothesis” suggest that exposure to microbial products, such as bacterial lysates (BLs), may strengthen immune defenses and reduce the incidence of rRTIs.^{13,14}

OM-85 is an oral preparation of lyophilized bacterial lysates from eight common respiratory pathogens: *Haemophilus influenzae*, *Diplococcus pneumoniae*, *Klebsiella pneumoniae* and *Klebsiella ozaenae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans*, and *Neisseria catarrhalis*. OM-85 has demonstrated both antiviral and immunomodulatory properties across in vitro studies, animal models, and clinical trials. These findings suggest that OM-85 offers protection against a broad spectrum of respiratory viruses, including HRV, IFV, RSV, and SARS-CoV-2.^{15,16} It has shown efficacy in preventing RTIs in children^{15–18} and in vulnerable adult populations, such as those with chronic bronchitis, COPD, or undergoing hemodialysis.^{19–23} However, to date, only limited data are available regarding the effectiveness of OM-85 in preventing recurrent RTIs in adults with bronchial asthma.²²

This study aimed to evaluate the real-world effectiveness of OM-85 as an add-on therapy in adults with T2-high allergic asthma. The primary objective on reducing both the frequency and severity of these infections. Secondary outcomes included the impact on asthma exacerbations (AEXs), antibiotic and oral corticosteroid (OCS) use, unscheduled visits, and hospitalizations.

Methods

Study Design

This was a Phase IV, multicentric, observational, controlled real-world evidence (RWE) cohort study conducted across three geographically distributed asthma units in Greece. The study included patients with moderate-to-severe allergic asthma, whose medical records documented regular follow-ups every three months for at least 12 months before and after the study’s initiation. Data spanning from August 2021 to July 2023 were retrospectively collected. The objective was to assess whether adding OM-85 to standard-of-care (SoC) therapy reduced the number and severity of clinical episodes (CEPs) indicative of respiratory tract infections (RTIs) in this patient population.

All patient data were anonymized to ensure confidentiality, and all information was handled in compliance with local ethical guidelines and the General Data Protection Regulations (GDPR). Informed consent for publication was included in the ICF and obtained from all individual participants.

Patient Population

Eligible patients were adults (aged 18 to 80 years) with an established diagnosis of moderate-to-severe allergic asthma, classified as “difficult to treat.” These patients were receiving conventional GINA step 4 therapy, with good symptom control (Asthma Control Test (ACT) >19). Despite good symptom control, they experienced frequent exacerbations (≥ 2 mild to moderate or ≥ 1 severe exacerbation requiring hospitalization within the previous 12 months), as evidenced by their medical records.²⁴

SoC Asthma Treatment Included

1. GINA Step 4 therapy with budesonide 200 µg plus formoterol 6 µg per inhalation as maintenance (two inhalations twice per day) and as a reliever when needed (MART);
2. Preventative vaccinations, including the annual influenza vaccine (anti-IFV), pneumococcal conjugate vaccine (PCV13), and completion of 3 doses of the COVID-19 vaccine (Pfizer-BioNTech); and
3. Management of comorbidities and modifiable risk factors to reduce exacerbations.

Some patients, based on the recommendations of their treating physicians, were additionally started on OM-85 to prevent recurrent RTIs (rRTIs) and avoid asthma exacerbations. OM-85 therapy involved one capsule of 7 mg per day for 10 days each month for 3 months, administered as two 3-month treatment courses (August–October and February–April), with two 3-month “off-treatment” periods between courses (November–January and May–July).

Table 1 Baseline and Clinical Characteristics

	Standard of Care	OM-85+Standard of Care (N=70)	Total (N=137)
Gender			
Female	36 (53.7%)	45 (64.3%)	81 (59.1%)
Male	31 (46.3%)	25 (35.7%)	56 (40.9%)
Age (years)			
Mean (Standard deviation)	51.7 (16.62)	51.4 (17.17)	51.6 (16.84)
Median (Q1, Q3)	54.0 (43.5, 67.0)	48.5 (36.2, 67.0)	49.0 (38.0, 67.0)
Min, Max	18, 80	19, 80	18, 80
Body mass index (kg/m ²)			
Mean (Standard deviation)	30.0 (5.96)	28.7 (6.02)	29.3 (6.01)
Median (Q1, Q3)	31.0 (25.0, 35.0)	26.0 (24.0, 34.0)	28.0 (24.0, 34.0)
Min, Max	16, 41	16, 41	16, 41
Packs per years			
Mean (Standard deviation)	5.2 (11.45)	4.6 (9.92)	4.9 (10.66)
Median (Q1, Q3)	0.0 (0.0, 4.0)	0.0 (0.0, 4.0)	0.0 (0.0, 4.0)
Min, Max	0, 55	0, 45	0, 55
Forced expiratory Volume in 1 sec			
Mean (Standard deviation)	2209.3 (1806.79)	2203.6 (1771.77)	2206.4 (1782.39)
Median (Q1, Q3)	2000.0 (1450.0, 2457.0)	2065.5 (1450.0, 2457.5)	2000.0 (1450, 2458.0)
Min, Max	190, 15.600	190, 15.600	190, 15600
Cardiovascular disease			
Yes	8 (11.9%)	9 (12.9%)	17 (12.4%)
No	59 (88.1%)	61 (87.1%)	120 (87.6%)
Diabetes Melitus			
Yes	6 (9.0%)	7 (10.0%)	13 (9.5%)
No	61 (91.0%)	63 (90.0%)	124 (90.5%)
Gastroesophageal reflux			
Yes	14 (20.9%)	16 (22.9%)	30 (21.9%)
No	53 (79.1%)	54 (77.1%)	107 (78.1%)
Rhinosinusitis with nasal polyps			
Yes	8 (11.9%)	10 (14.3%)	18 (13.1%)
No	59 (88.1%)	60 (85.7%)	119 (86.9%)
Prior exacerbation history			
Mean (Standard deviation)	3.4 (1.00)	3.4 (1.05)	3.4 (1.02)
Median (Q1, Q3)	3 (3.0, 4.0)	3 (3.0, 4.0)	3 (3.0, 4.0)
Min, Max	0, 5	1, 6	0, 6

Baseline and clinically important characteristics of the patients are presented in [Table 1](#). Key exclusion criteria included the maintenance use of oral corticosteroids (OCS) or other immunosuppressive medications. Full inclusion and exclusion criteria are provided in [Appendix 1](#).

Box 1 Clinical Symptoms Indicative of Respiratory Tract Infection

• Common cold symptoms: sneezing, stuffy nose, sore throat, coughing, post-nasal drip, watery eyes, low grade fever
• Bronchitis symptoms: low grade fever, chest congestion, wheezing or a whistling sound while breathing, productive cough, feeling run-down or tired and a chest-X-ray that ruled out pneumonia
• Sinusitis symptoms: green or yellow discharge from the nose, blocked nose, pain and tenderness around the cheeks, eyes or forehead, a high temperature (fever) of 38 °C or more, toothache, reduced sense of smell, bad breath (halitosis)
• Pneumonia symptoms: cough which may produce greenish, yellow mucus, fever, sweating and shaking chills, shortness of breath, rapid shallow breathing and a chest-X-ray with findings of consolidation
• Asthma symptoms: recurrent episodes of acute shortness of breath, a combination of acute onset episodes of dry cough, wheezing and/or chest tightness

Procedures

All patients with an established diagnosis of allergic asthma were retrieved to identify those fulfilling the prespecified criteria for inclusion in the current study ([Appendix 1](#)) using an analytical system (MedExpress). All reported clinical episodes (CEPs) of respiratory symptoms (see [Box 1](#)), with a physician-confirmed diagnosis of RTIs, over a 12-month period (August 2022 to July 2023), were then retrieved from their medical records. The severity of the CEPs was recorded, assessed, and scored on a 3-point scale, expressed as a mean severity index (mSI): 1 for mild (mild stuffed or runny nose, which does not affect daily activities), 2 for moderate (symptoms affecting daily activities but not sleep), and 3 for severe (sleep and breathing difficulties).

As prior exacerbation history is an important factor increasing the risk for future exacerbations, all asthma exacerbations (AEXs) experienced 12 months before OM-85 initiation and 12 months after that date were recorded. A clinical significant asthma exacerbation was defined as the onset and/or worsening of already chronically existed symptoms from the upper and/or lower respiratory tract, causing clinically significant distress or impairment in social, occupational, or other important areas of functioning, and requiring any of the following: a) treatment with systemic corticosteroids for at least 3 days; b) an increase in the maintenance dose of OCS for at least three days or a single depo-injectable dose of corticosteroids; c) an ED visit that required the use of systemic corticosteroids; d) hospitalization. Prescriptions for antibiotics and/or OCS cycles (exacerbation bursts), AEXs, unscheduled visits, and hospitalizations were also retrieved from the medical records. Additionally, the e-prescription system of the National Health System was searched for prescriptions of antibiotics and/or systemic corticosteroids and any visits to the emergency department or hospitalizations not mentioned in the medical records of the patients included in the study. Such data were added to the medical records and used in the analysis of the results. Patients were then divided into two groups: the SoC-group, which included patients treated with SoC therapy as described above, and the OM-85-group, which included patients treated additionally with OM-85 ([Figure 1](#)).

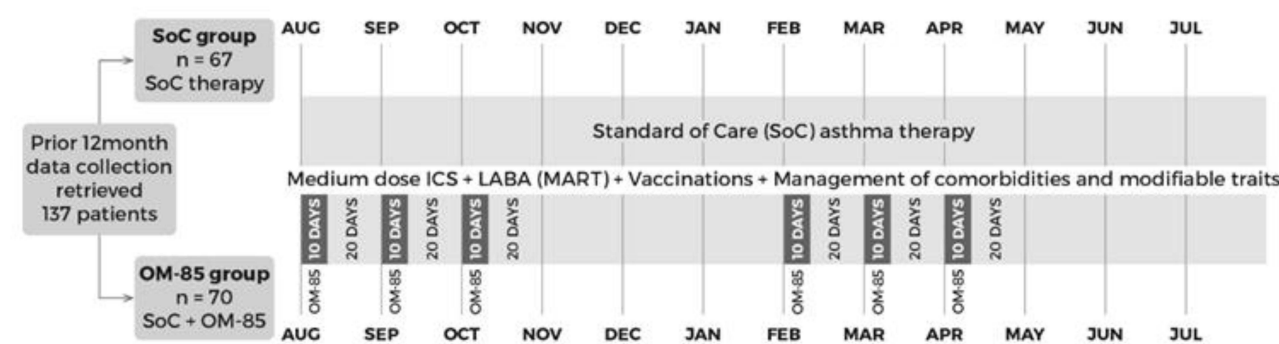


Figure 1 Therapy with oral OM-85 (one capsule of 7 mg per day for 10 days each month over 3 months) was administered in two 3-month treatment courses (August–October and February–April), with two 3-month “off-treatment” intervals in between (November–January and May–July).

Study Outcomes

Primary Study Endpoints Were

1. The total number of CEPs indicative of RTIs, and
2. The severity of CEPs in each patient group throughout the 12-month observational period.

Secondary endpoints included the total number of asthma exacerbations (AEXs), cycles of oral corticosteroids (OCS) and antibiotics, as well as the number of unscheduled visits and hospitalizations in each patient group.

Statistical Analysis

Poisson regression analysis was used to estimate the treatment effect of OM-85 on all count data, including the total number of CEPs and all secondary outcomes. Additionally, negative binomial regression analysis was applied to assess the overdispersion parameter for all count data. Large values of the overdispersion parameter indicate no significant overdispersion, suggesting that Poisson regression is adequate for estimating the treatment effect. For continuous data, such as the mean severity index (mSI) per CEP, linear regression was used.

Both the Poisson and negative binomial regression models were weighted analyses. Weights were derived from propensity scores, which were estimated using logistic regression. Covariates included gender, age (in years), body mass index (in kg/m²), pack-years of smoking, forced expiratory volume in 1 second (FEV1 in mL), prior 12-month asthma exacerbation (AEX) history, and the presence or absence of comorbidities (cardiovascular disease, diabetes mellitus, gastroesophageal reflux, and rhinosinusitis with nasal polyps). The reported treatment effect represents the average treatment effect in the population.

Results

Between August 2022 and July 2023, 137 adults met the inclusion and exclusion criteria for the study. As this was a real-world evidence (RWE) study, patients presented factors known to increase the risk of exacerbations, even when asthma symptoms were well-controlled, such as smoking, chronic rhinosinusitis with nasal polyps, and gastroesophageal reflux (Table 1). Additionally, all patients were sensitized to perennial or seasonal allergens. According to medical records, 67 patients received standard of care (SoC) therapy alone (SoC group, N=67), while 70 patients received add-on OM-85 (OM-85 group, N=70). Adherence to the treatment schedule, as reported by patients and verified in the e-prescription system, was similar between the two groups. No serious adverse events were reported, and none led to discontinuation of therapy. Mild gastrointestinal disturbances (2.3%) were the most commonly reported side effects in the OM-85 group.

Primary Outcomes

Total Number of CEPs

CEPs indicative of respiratory tract infections (RTIs) were commonly reported across all patients, with a mean (SD) of 3.6 (1.89) during the 12-month study period. Patients on SoC therapy alone had a higher mean number of CEPs (5.2 [1.23]) compared to those on add-on OM-85 (2.1 [0.84]). A statistically significant 60.1% decrease (p-value <0.0001) in the average number of CEPs was observed in the OM-85 group during the 12-month period (Table 2).

Table 2 Number of Clinical Episodes (CEPs) Indicative of RTIs and Mean Severity Index per CEP

	Standard of Care (N = 67)	OM-85 + Standard of Care (N = 70)	Total (N = 137)
Number of CEPs			
Mean (Standard deviation)	5.2 (1.23)	2.1 (0.84)	3.6 (1.89)
Median (Q1, Q3)	5.0 (4.5, 6.0)	2 (2.0, 3.0)	3.0 (2.0, 5.0)
Min, Max	2, 8	0, 4	0, 8

(Continued)

Table 2 (Continued).

	Standard of Care (N = 67)	OM-85 + Standard of Care (N = 70)	Total (N = 137)
Number of CEPs (Categories)			
0	0 (0.0%)	2 (2.9%)	2 (1.5%)
1	0 (0.0%)	14 (20.0%)	14 (10.29%)
2	2 (3.0%)	29 (41.4%)	31 (22.6%)
3	2 (3.0%)	24 (34.3%)	26 (19.0%)
4	13 (19.4%)	1 (1.4%)	14 (10.2%)
5	22 (32.8%)	0 (0.0%)	22 (16.1%)
6	19 (28.4%)	0 (0.0%)	19 (13.9%)
7	7 (10.4%)	0 (0.0%)	7 (5.1%)
8	2 (3.0%)	0 (0.0%)	2 (1.5%)
Mean of severity index per CEP			
Mean (Standard deviation)	2.64 (0.261)	1.48 (0.432)	2.05 (0.679)
Median (Q1, Q3)	2.66 (2.54, 2.75)	1.50 (1.33, 1.66)	2.00 (1.50, 2.266)
Min, Max	2.0, 3.2	0.0, 2.5	0.0, 3.2

Severity of CEPs

The severity of symptoms varied across the study population. Patients receiving SoC therapy alone had more severe upper and lower respiratory tract symptoms, with a mean (SD) severity index of 2.64 (0.261). In contrast, those on add-on OM-85 experienced less severe symptoms, with a mean (SD) severity index of 1.48 (0.432). A statistically significant reduction of 1.17 units (p -value <0.0001) in the mean severity index was observed in patients treated with OM-85 (Table 2). Figure 2 displays the distribution of CEP severity across both treatment groups, further illustrating this difference.

Secondary Outcomes

Asthma Exacerbations (AEXs)

As shown in Table 4, the included patients were frequent exacerbators, with a mean (SD) of 2.1 (1.48) AEXs per patient. However, those on add-on OM-85 experienced fewer AEXs (mean [SD] 1.0 [0.71]) compared to those on SoC therapy alone (mean [SD] 3.3 [1.05]). A statistically significant 71% decrease (p -value <0.0001) in the average number of AEXs was observed in the OM-85 group during the 12-month period, despite no significant difference in prior AEX history between the groups (Table 3).

Unscheduled Visits and Hospitalizations

Patients on OM-85 had fewer unscheduled visits, with a mean (SD) of 1.0 (0.63), compared to 3.5 (0.99) in the SoC group. This represents a statistically significant 72.4% decrease (p -value <0.0001) in the average number of unscheduled visits during the study period (Table 3). There were few hospitalizations recorded in both treatment groups ($N=8$, 5.8%), with 98.6% ($N=69/70$) of patients in the OM-85 group being free of hospitalization, compared to 89.6% ($N=60/67$) in the SoC group. A non-statistically significant 91.6% decrease (p -value: 0.05806) in the average number of hospitalizations was observed in the OM-85 group during the study period (Table 3).

Oral Corticosteroid (OCS) and Antibiotic Cycles

Based on medical records and the e-prescription system, patients treated with add-on OM-85 had fewer prescriptions for OCS and antibiotics (mean [SD] 1.0 [0.71] and 1.0 [0.66], respectively) compared to those receiving SoC therapy alone (mean [SD] 3.6 [1.03] and 2.8 [1.00], respectively). Statistically significant reductions of 73% and 66.6% (p -value <0.0001) in the average number of OCS and antibiotic cycles were observed in the OM-85 group during the 12-month study period (Table 4).

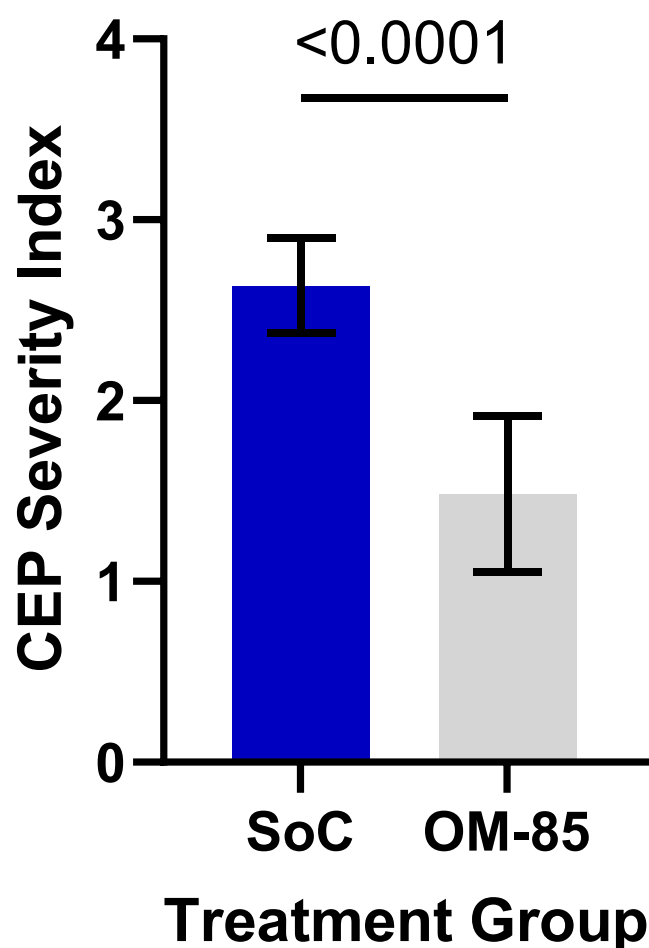


Figure 2 Distribution of clinical episode (CEP) severity index across treatment groups. Patients receiving standard of care (SoC) therapy had significantly higher severity indices than those on add-on OM-85. Bars represent mean $\pm$ SD. $p < 0.0001$ (unpaired t-test).

Discussion

All patients included in this study were vaccinated against influenza, pneumococcus, and SARS-CoV-2. However, CEPs indicative of RTIs were commonly reported, with only a minority of patients (1.5%) experiencing no episodes during the study period (Table 2).

The inflammation present in the airways of patients with allergic asthma makes them more susceptible to airborne infections, as pathogens find a favorable microenvironment in the swollen and narrow airways. There is extensive evidence of an abnormal innate immune response, which makes asthma patients potentially slower at clearing infections and more susceptible to both.^{3,25} The primary defect appears to be in the first step of inducing anti-viral protective cytokines, such as interferons (IFNs) β and λ , after viral components (like double-stranded viral RNA) are detected by pattern recognition receptors (PAMPs). Additionally, the airways of asthmatics are more susceptible to injury, with delayed healing following environmental insults.^{26–28}

Furthermore, patients with asthma exhibit inadequate epithelium tight-junction assembly. Increased permeability is enhanced by T-cell interactions within the epithelium, as well as by the actions of allergens (eg, proteases), pollutants, and viral infections, all of which disrupt tight junction functions.^{14,28}

Most authors agree that RTIs in patients with asthma cause an extended duration of illness and increase the severity of lower respiratory tract symptoms.^{3,25,29} In this study, the mean (SD) severity index estimated per CEP was 2.05 (0.679), indicative of moderate to severe symptomatic episodes that caused significant day and night disturbances (Table 2).

Table 3 Number of Asthma Exacerbations, Unscheduled Visits and Hospitalizations

	Standard of Care (N = 67)	OM-85 + Standard of Care (N = 70)	Total (N = 137)
Number of asthma exacerbations			
Mean (Standard deviation)	3.3 (1.05)	1.0 (0.71)	2.1 (1.48)
Median (Q1, Q3)	3.0 (3.0, 4.0)	1.0 (1.0, 1.0)	2.0 (1.0, 3.0)
Min, Max	0.5	0.3	0.5
Number of asthma exacerbations (Categories)			
0	1 (1.5%)	17 (24.3%)	18 (13.1%)
1	1 (1.5%)	38 (54.3%)	39 (28.5%)
2	12 (17.9%)	14 (20.0%)	26 (19.0%)
3	21 (31.3%)	1 (1.4%)	22 (16.1%)
4	24 (35.8%)	0 (0.0%)	24 (17.5%)
5	8 (11.9%)	0 (0.0%)	8 (5.8%)
Number of unscheduled visits			
Mean (Standard deviation)	3.5 (0.99)	1.0 (0.63)	2.2 (1.49)
Median (Q1, Q3)	4.0 (3.0, 4.0)	1.0 (1.0, 1.0)	2.0 (1.0, 4.0)
Min, Max	0.5	0.2	0.5
Number of unscheduled visits (Categories)			
0	1 (1.5%)	13 (18.6%)	14 (10.2%)
1	0 (0.0%)	43 (61.4%)	43 (31.4%)
2	9 (13.4%)	14 (20.0%)	23 (16.8%)
3	21 (31.3%)	0 (0.0%)	21 (15.3%)
4	27 (40.3%)	0 (0.0%)	27 (19.7%)
5	9 (13.4%)	0 (0.0%)	9 (6.6%)
Number of hospitalisations			
Mean (Standard deviation)	0.1 (0.31)	0.0 (0.12)	0.1 (1.24)
Median (Q1, Q3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Min, Max	0.1	0.1	0.1
Number of hospitalisations (Categories)			
0	60 (89.6%)	69 (98.6%)	129 (94.2%)
1	7 (10.4%)	1 (1.4%)	8 (5.8%)

Olenec et al suggested that allergic asthma is associated with more severe illness than non-allergic asthma after infection with respiratory viruses.³⁰ Message et al, assessing responses to HRV infection in asthmatic patients, found that virological and clinical outcomes were strongly related to deficient IFN- γ and IL-10 responses and to the augmented generation of Th2 cytokines like IL-4, IL-5, and IL-13.³¹ This suggests a link between allergic sensitization, T2-high inflammation, and susceptibility to viral infections.

The rationale behind the oral administration of immunomodulators for the prevention of recurrent RTIs (rRTIs) is based on the concept of the gut-lung immune axis, a topic that has been extensively reviewed.³² Multiple components of the innate and adaptive immune responses have been shown to be targeted by OM-85, resulting in a reduced incidence and severity of RTIs.^{15,33–36}

In the study by Dagg AT et al, wild-type mice bone marrow dendritic cells (BMDCs) were pretreated with OM-85, which acts as a PAMP, potentiating antiviral type 1 signaling and inducing the secretion of IFN- β , a well-known antiviral cytokine. OM-85 also acted as a priming signal for the NLRP3 and AIM2 inflammasomes, which are crucial platforms for detecting and protecting against viral infections. These inflammasomes help keep innate immune cells in an alert

Table 4 Number of OCS and Antibiotic Cycles

	Standard of Care (N = 67)	OM-85 + Standard of Care (N = 70)	Total (N = 137)
Number of OCS cycles prescribed			
Mean (Standard deviation)	3.6 (1.03)	1.0 (0.71)	2.2 (1.56)
Median (Q1, Q3)	4.0 (3.0, 4.0)	1.0 (1.0, 1.0)	2.0 (1.0, 4.0)
Min, Max	0.6	0.3	0.6
Number of OCS cycles prescribed(Categories)			
0	1 (1.5%)	17 (24.3%)	18 (13.1%)
1	0 (0.0%)	38 (54.3%)	38 (27.7%)
2	8 (11.9%)	14 (20.0%)	22 (16.1%)
3	22 (32.8%)	1 (1.4%)	23 (16.8%)
4	25 (37.3%)	0 (0.0%)	25 (18.2%)
5	10 (14.9%)	0 (0.0%)	10 (7.3%)
6	1 (1.5%)	0 (0.0%)	1 (0.7%)
Number of antibiotics cycles prescriber(Categories)			
0	2 (3.0%)	14 (20.0%)	16 (11.7%)
1	3 (4.5%)	42 (60.0%)	45 (32.8%)
2	17 (25.4%)	12 (17.1%)	29 (21.2%)
3	32 (47.8%)	1 (1.4%)	33 (24.1%)
4	10 (10.9%)	0 (0.0%)	10 (7.3%)
5	3 (4.5%)	0 (0.0%)	3 (2.2%)
NA	0 (0.0%)	1 (1.4%)	1 (0.7%)

state, capable of releasing large amounts of IL-1 β upon sensing inflammatory triggers, thereby reducing selected infections. However, OM-85 does not directly lead to IL-1 release, which is important considering the detrimental effect of the NLRP3/IL-1 axis in chronic inflammatory diseases.³⁴

It is worth noting that following intranasal administration of OM-85, a gene coding for the tight-junction protein Claudin 1, critical for epithelial barrier function, was upregulated in treated mice, indicating direct barrier-enhancing effects.³⁵ In addition, data suggest that OM-85 induces a tolerance-promoting landscape in the lungs, associated with the suppression of experimental asthma.³⁶

In the current study, treatment with additional OM-85 was associated with significant reductions in the total number of CEPs indicative of RTIs. Moreover, patients on add-on OM-85 experienced a milder disease course, as evidenced by the significantly lower average mSI per CEP.

Combined administration of OM-85 and vaccines for common respiratory pathogens was well tolerated, with no evidence in the medical records indicating any increase in local or systemic adverse events or the occurrence of severe adverse events. The contemporaneous administration of OM-85 and the influenza vaccine to optimize the efficacy of prevention strategies has already been evaluated and recommended. However, specific studies are needed to extend such a recommendation for COVID-19 and pneumococcal vaccines.³²

As the first study to assess the effectiveness of OM-85 administration in reducing RTIs in an adult population with difficult-to-treat T2-high asthma in real-world practices, this study provides valuable insights. The underlying mechanisms involved deserve further investigation to fully validate the merit of OM-85 administration as an addition to conventional asthma therapy. One of the most consistent findings in clinical studies is that allergy and viral infections synergistically increase the risk of acute exacerbations.^{3,25,29} In this study, potential immune modifications induced by OM-85 inhibited the provocation of exacerbations, resulting in subsequent reductions in unscheduled visits, hospitalizations, oral corticosteroid (OCS) use, and antibiotic cycles.

Our findings align with those of Koatz et al (37), who reported a significant reduction in the total number of recurrent RTIs (rRTIs) and exacerbations in adults with allergic rhinitis, asthma, and COPD treated with OM-85 as an add-on to

standard of care (SoC) therapy.³⁷ However, it is important to note that their study was an open-label, prospective, sequential design, which included 84 consecutive patients aged 16–65 years, who had experienced three or more respiratory infections during the year prior to study entry.

Autumn and spring are peak seasons for asthma flare-ups. During autumn, RTIs are frequently detected in September, a phenomenon referred to as the “September epidemic”, mainly associated with the return of children to school, exposure to viruses, and airborne allergens. RTIs then spread to other family members, particularly the elderly and most vulnerable individuals. During spring, we continue to see a high incidence of RTIs, exacerbated by the influx of pollen.

In our clinical practice, OM-85 is administered twice a year, typically a few weeks before peak respiratory infection seasons, with the goal of priming the immune system and reducing both the frequency and severity of recurrent RTIs. This approach has shown to be particularly effective in patients sensitized to perennial allergens.³⁸ The positive outcomes of this practice are likely explained by the findings of Roth M et al, who explored the effects of OM-85 on isolated human airway epithelial cells (BECs) from asthma patients. In that study, OM-85 was found to activate two signaling pathways, Erk1/2MAPK and cAMP, improving cell survival of BECs infected with human rhinovirus (HRV). However, this preventive effect of OM-85 became significant only when the cells had been pre-incubated with OM-85 for 48 hours, indicating that the protective effect is time-dependent.³⁹

In line with the above, prophylactic treatment with OM-85 is effective against both infectious and allergen-induced insults. Treatment should be offered a few weeks before the high season for RTIs and/or allergen exposure. This approach should be seriously considered when designing future OM-85 studies.

This study has a few limitations, mainly due to its retrospective design. While the results indicate a strong association between OM-85 and reduced RTIs/exacerbations, the retrospective nature of the study limits the ability to make causal inferences. Future prospective studies are needed to confirm these findings and assess the long-term effectiveness of OM-85. Additionally, although the study did not include laboratory data, the identification of RTIs was based on a strict clinical categorization, reflecting everyday practices in primary care. The limitations outlined above are offset by the study’s provision of real-world evidence derived from data collected in routine clinical practice, ensuring greater representativeness of the target clinical population.

In summary, the findings of the current study demonstrate significant clinical benefits of OM-85 when added to SoC therapy in patients with moderate-to-severe allergic asthma. Contemporaneous treatment with add-on OM-85 complemented the effects of vaccinations, optimizing the efficacy of prevention strategies. Further investigations are needed to explore the potential clinical benefits of OM-85 in non-allergic asthma phenotypes.

Take-Home Message

Patients with allergic asthma who took OM-85 in real-world settings experienced fewer and less severe respiratory infections. They also had fewer asthma flare-ups, unplanned doctor visits, and needed fewer courses of antibiotics or oral corticosteroids (OCS).

Abbreviations

CEPs, clinical episodes; mSI, mean Severity Index; OCS, oral corticosteroids; RTIs, respiratory tract infections; AEXs, asthma exacerbations; TLR, Toll-like receptor; PAMP, Pathogen -associated molecular pattern; PRRs, Pathogen recognition receptors; BMDCs, Bone Marrow dendritic cells; NLRP3, NOD-like receptor protein 3; MyD88, Myeloid differentiation factor 88; AIM2, absent in melanoma 2 inflammasome; Cldn1, Claudin 1; Erk1/2, extracellular signal-regulated kinase1/2; MAPK, mitogen-activated protein kinase.

Ethics Statement

This observational study was conducted in line with the principles of the Declaration of Helsinki and Order SAS/3470/2009 of 16 December.⁴⁰ All investigators were accredited and strictly followed the International Conference on Harmonization Good Clinical Practice Guidelines. The study protocol was approved by the Ethics Committee of University General Hospital of Rion, Patras, on 25 June 2021, prior to the commencement of the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

A.I. Christopoulos has received consultancy fees, speaker honoraria, advisory board fees, and research grants from AstraZeneca, GlaxoSmithKline, Chiesi, and Novartis. His institution has also received research support from OM Pharma; this funding was provided directly to the research foundation and not to him personally. OM Pharma had no role in the design of the study, analysis and interpretation of the data, or in the writing of the manuscript. The other authors declare no conflicts of interest in this work.

References

1. Gradisteanu Pircalabioru G, Iliescu FS, Mihaescu G, et al. Advances in the rapid diagnostic of viral respiratory tract infections. *Front Cell Infect Microbiol.* **2022**;12:807253. doi:10.3389/fcimb.2022.807253
2. Dubin S, Patak P, Jung D. Update on Asthma Management Guidelines. *Mo Med.* **2024**;121(5):364–367. doi:10.1378/chest.130.1_suppl.4s
3. Busse WW, Lemanske RF Jr, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet.* **2010**;376(9743):826–834. doi:10.1016/s0140-6736(10)61380-3
4. Dulek DE, Peebles RS Jr. Viruses and asthma. *Biochim Biophys Acta.* **2011**;1810(11):1080–1090. doi:10.1016/j.bbagen.2011.01.012
5. Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. *BMJ.* **1993**;307(6910):982–986. doi:10.1136/bmj.307.6910.982
6. Silva RC, Couceiro JN, Câmara FP, Valle S, Santos N. Asthma exacerbation and viral infection in adult patients, Brazil. *Braz J Infect Dis.* **2015**;19(4):446–448. doi:10.1016/j.bjid.2015.03.004
7. Horn MEC, Gregg I. Role of viral infection and host factors in acute episodes of asthma and chronic bronchitis. *CHEST.* **1973**;63(4):44S–48S. doi:10.1378/chest.63.4_Supplement.44S-a
8. Novak N, Cabanillas B. Viruses and asthma: the role of common respiratory viruses in asthma and its potential meaning for SARS-CoV-2. *Immunology.* **2020**;161(2):83–93. doi:10.1111/imm.13240
9. Pattemore PK, Johnston SL, Bardin PG. Viruses as precipitants of asthma symptoms. I. Epidemiology. *Clin Exp Allergy.* **1992**;22(3):325–336. doi:10.1111/j.1365-2222.1992.tb03094.x
10. Kraft M. The role of bacterial infections in asthma. *Clin Chest Med.* **2000**;21(2):301–313. doi:10.1016/s0272-5231(05)70268-9
11. Dethlefsen L, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biol.* **6**(11):e280. doi:10.1371/journal.pbio.0060280
12. Van Matre ET, Satyanarayana G, Page II RL, Levi ME, Lindenfeld J, Mueller SW. Pharmacokinetic Drug-drug interactions between immunosuppressant and anti-infective agents: antimetabolites and corticosteroids. *Ann Transplant.* **2018**;23:66–74. doi:10.12659/aot.906164
13. Feleszko W, Ruszczyński M, Zalewski BM. Non-specific immune stimulation in respiratory tract infections. Separating the wheat from the chaff. *Paediatr Respir Rev.* **2014**;15(2):200–206. doi:10.1016/j.prrv.2013.10.006
14. Cardinale F, Lombardi E, Rossi O, Bagnasco D, Bellocchi A, Menzella F. Epithelial dysfunction, respiratory infections and asthma: the importance of immunomodulation. A focus on OM-85. *Expert Rev Respir Med.* **2020**;14(10):1019–1026. doi:10.1080/17476348.2020.1793673
15. Ballarini S, Arduoso L, Ortega Martell JA, Sacco O, Feleszko W, Rossi GA. Can bacterial lysates be useful in prevention of viral respiratory infections in childhood? The results of experimental OM-85 studies. *Front Pediatr.* **2022**;10:1051079. doi:10.3389/fped.2022.1051079
16. Yin J, Xu B, Zeng X, Shen K. Broncho-Vaxom in pediatric recurrent respiratory tract infections: a systematic review and meta-analysis. *Int Immunopharmacol.* **2018**;54:198–209. doi:10.1016/j.intimp.2017.10.032
17. Esposito S, Soto-Martinez ME, Feleszko W, Jones MH, Shen KL, Schaad UB. Nonspecific immunomodulators for recurrent respiratory tract infections, wheezing and asthma in children: a systematic review of mechanistic and clinical evidence. *Curr Opin Allergy Clin Immunol.* **2018**;18(3):198–209. doi:10.1097/aci.0000000000000433
18. Esposito S, Bianchini S, Bosis S, et al. A randomized, placebo-controlled, double-blinded, single-centre, Phase IV trial to assess the efficacy and safety of OM-85 in children suffering from recurrent respiratory tract infections. *J Transl Med.* **2019**;17(1):284. doi:10.1186/s12967-019-2040-y
19. Orcel B, Delclaux B, Baud M, Derenne JP. Oral immunization with bacterial extracts for protection against acute bronchitis in elderly institutionalized patients with chronic bronchitis. *Eur Respir J.* **1994**;7(3):446–452. doi:10.1183/09031936.94.07030446
20. Collet JP, Shapiro P, Ernst P, Renzi T, Ducruet T, Robinson A. Effects of an immunostimulating agent on acute exacerbations and hospitalizations in patients with chronic obstructive pulmonary disease. the PARI-IS study steering committee and research group. prevention of acute respiratory infection by an immunostimulant. *Am J Respir Crit Care Med.* **1997**;156(6):1719–1724. doi:10.1164/ajrccm.156.6.9612096
21. Soler M, Mütterlein R, Cozma G. Double-blind study of OM-85 in patients with chronic bronchitis or mild chronic obstructive pulmonary disease. *Respiration.* **2007**;74(1):26–32. doi:10.1159/000093933
22. Tielemans C, Gastaldello K, Husson C, et al. Efficacy of oral immunotherapy on respiratory infections in hemodialysis patients: a double-blind, placebo-controlled study. *Clin Nephrol.* **1999**;51(3):153–160.
23. Huang Y, Pei Y, Qian Y, et al. A meta-analysis on the efficacy and safety of bacterial lysates in chronic obstructive pulmonary disease. *Front Med.* **2022**;9:877124. doi:10.3389/fmed.2022.877124

24. Denlinger LC, Phillips BR, Ramratnam S, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. *Am J Respir Crit Care Med*. 2017;195(3):302–313. doi:10.1164/rccm.201602-0419OC
25. Sharma S, Tasnim N, Agadi K, Asfeen U, Kanda J. Vulnerability for respiratory infections in asthma patients: a systematic review. *Cureus*. 2022;14(9):e28839. doi:10.7759/cureus.28839
26. Holgate ST, Lackie P, Wilson S, Roche W, Davies D. Bronchial epithelium as a key regulator of airway allergen sensitization and remodeling in asthma. *Am J Respir Crit Care Med*. 2000;162(3 Pt 2):S113–7. doi:10.1164/ajrccm.162.supplement_2.ras-12
27. Holgate ST. Innate and adaptive immune responses in asthma. *Nature Med*. 2012;18(5):673–683. doi:10.1038/nm.2731
28. Xiao C, Puddicombe SM, Field S, et al. Defective epithelial barrier function in asthma. *J Allergy Clin Immunol*. 2011;128(3):549–56.e1–12. doi:10.1016/j.jaci.2011.05.038
29. Corne JM, Marshall C, Smith S, et al. Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet*. 359:9309:831–4. doi:10.1016/s0140-6736(02)07953-9
30. Olenec JP, Kim WK, Lee WM, et al. Weekly monitoring of children with asthma for infections and illness during common cold seasons. *J Allergy Clin Immunol*. 2010;125(5):1001–1006.e1. doi:10.1016/j.jaci.2010.01.059
31. Message SD, Laza-Stanca V, Mallia P, et al. Rhinovirus-induced lower respiratory illness is increased in asthma and related to virus load and Th1/2 cytokine and IL-10 production. *Proc Natl Acad Sci U S A*. 2008;105(36):13562–13567. doi:10.1073/pnas.0804181105
32. Esposito S, Cassano M, Cutrera R, Menzella F, Varricchio A, Uberti M. Expert consensus on the role of OM-85 in the management of recurrent respiratory infections: a Delphi study. *Hum Vaccin Immunother*. 2022;18(6):2106720. doi:10.1080/21645515.2022.2106720
33. Kearney SC, Dziekiewicz M, Feleszko W. Immunoregulatory and immunostimulatory responses of bacterial lysates in respiratory infections and asthma. *Ann Allergy Asthma Immunol*. 2015;114(5):364–369. doi:10.1016/j.anai.2015.02.008
34. Dang AT, Pasquali C, Ludigs K, Guarda G. OM-85 is an immunomodulator of interferon- β production and inflammasome activity. *Sci Rep*. 2017;7(1):43844. doi:10.1038/srep43844
35. Pivniouk V, Gimenes-Junior JA, Ezech P, et al. Airway administration of OM-85, a bacterial lysate, blocks experimental asthma by targeting dendritic cells and the epithelium/IL-33/ILC2 axis. *J Allergy Clin Immunol*. 2022;149(3):943–956. doi:10.1016/j.jaci.2021.09.013
36. Strickland DH, Judd S, Thomas JA, Larcombe AN, Sly PD, Holt PG. Boosting airway T-regulatory cells by gastrointestinal stimulation as a strategy for asthma control. *Mucosal Immunology*. 2011;4(1):43–52. doi:10.1038/mi.2010.43
37. Koatz AM, Coe NA, Cicerán A, Alter AJ. Clinical and immunological benefits of OM-85 bacterial lysate in patients with allergic rhinitis, asthma, and COPD and recurrent respiratory infections. *Lung*. 2016;194(4):687–697. doi:10.1007/s00408-016-9880-5
38. Lu Y, Li Y, Xu L, Xia M, Cao L. Bacterial lysate increases the percentage of natural killer T cells in peripheral blood and alleviates asthma in children. *Pharmacology*. 2015;95(3–4):139–144. doi:10.1159/000377683
39. Roth M, Pasquali C, Stolz D, Tamm M. Broncho Vaxom (OM-85) modulates rhinovirus docking proteins on human airway epithelial cells via Erk1/2 mitogen activated protein kinase and cAMP. *PLoS One*. 2017;12(11):e0188010. doi:10.1371/journal.pone.0188010
40. Claudot F, Alla F, Fresson J, Calvez T, Coudane H, Bonaiti-Pellie C. Ethics and observational studies in medical research: various rules in a common framework. *Int J Epidemiol*. 2009;38(4):1104–1108. doi:10.1093/ije/dyp164