REVIEW

OM-85 in the prevention of respiratory infections: State-of-the-art and future perspectives in clinical practice

G.L. Marseglia[1], M. Benazzo[2], P. Biasci[3], F. Blasi[4], C. Cricelli[5], M. Doria[3], S. Leonardi[6], D.G. Peroni[7], F. Scaglione[8] and G. Ciprandi[9]

[1]Pediatric Clinic, Fundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [2]Otorhinolaryngoiatric Clinic, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [3]Italian Federation of Pediatricians, Rome, Italy; [4]Department of Pathophysiology and Transplant, University of Milan, Italy; [5] The Italian Society of General Medicine, Florence, Italy; [6]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; [7] Pediatric Unit, University of Pisa, Pisa, Italy; [8]Department of Oncology and Onco-Hematology, University of Milan, Milan, Italy; [9]Casa di Cura Villa Montallegro, Genoa, Italy

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Respiratory infections (RI) significantly burden patients, their families, and society. Respiratory infection recurrence (RRI) usually depends on a defect of the immune response, which can be more or less transient and/or selective. In particular, children, older people, heavy smokers, and patients with chronic diseases, characterized by an inadequate immune response, may be at risk of developing RRI. In this context, OM-85 could represent a valuable option in the management of RRI. OM-85 is a bacterial lysate containing the extracts of some common pathogens, including *Branhamella catarrhalis, Klebsiella pneumoniae, Klebsiella ozaenae, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans*, and *Staphylococcus aureus*. Methodologically rigorous studies have documented the mechanism of action, efficacy, and safety of OM-85. OM-85 enhances the natural and acquired immune response through multifaceted mechanisms. Substantial evidence has shown that OM-85 can prevent respiratory infections, reduce the number of COPD exacerbations, and shorten the disease duration at home or in hospital. OM-85 can enhance the effectiveness of the 'flu vaccination without affecting the vaccine tolerability. The preventive use of OM-85 can reduce the use of antibiotics, contributing to contrast antibiotic resistance and saving the high cost of chronic respiratory diseases. Further studies should define the ideal candidate to OM-85 treatment.

Epidemiology of respiratory infections

Respiratory infections (RI) represent a relevant public health issue, mainly concerning children and older people (1). As a result, the socio-economic burden of respiratory infections is particularly relevant.

Acute respiratory infections (ARI) affect the upper airways (rhinitis, rhinopharyngitis, rhinosinusitis, tonsillitis, laryngitis, and otitis media) and/or the lower airways (tracheitis, bronchitis, bronchiolitis, and pneumonia), with very varied clinical pictures depending on the organ(s) involved, the patient's age, and the general clinical condition (2, 3). ARI have a notable impact on morbidity and mortality and direct and indirect healthcare costs (4-

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Corresponding Author:
Prof. Giorgio Ciprandi,
Allergy Clinic,
Casa di Cura Villa Montallegro,
Genoa, Italy
e-mail: gio.cip@libero.it

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6). Respiratory infections are the second cause of death in children under five years of age, just after prematurity, as documented by the WHO report (7).

The incidence of upper airway respiratory infections is inversely proportional to age. Children usually have 6-8 episodes per year, while adults tend to have 1-2 respiratory infections yearly (4). Moreover, it was estimated that approximately 6% of Italian children under six years of age had recurrent RI (RRI), defined by the presence of at least one of the following conditions: i) ≥ six annual RI; ii) one or more monthly RI from October to February; iii) ≥ 3 RI involving lower airways (8). The prevalence of ARI reaches 25% among children under one year of age, decreasing to 18% in those between 1 and 4 years of age (9). Respiratory infections represent approximately one-third of all pediatric visits and constitute 8-18% of pediatric hospitalizations (10).

Chronic obstructive pulmonary disease (COPD) is one of the most common diseases in the elderly, such as those over 65 years. It is often associated with several comorbidities, including diabetes mellitus, cardiovascular disease, arterial hypertension, obesity, cancer, and impaired immune response (11). In addition, COPD is worsened by various unfavorable situations, namely malnutrition, prolonged hospitalization, and poor hygienic conditions (11, 12). In the US, COPD is the fourth most common cause of morbidity; it is the reason for more than 17 million medical visits per year and 13% of all hospital admissions, and the fourth cause of death (13, 14). Respiratory infections significantly affect COPD patients as they induce an exacerbation of respiratory symptoms and deterioration of the disease (15, 16). Furthermore, each COPD exacerbation irreversibly accelerates the respiratory functional decline and worsens the quality of life of patients and their families (11-13).

Etiology and pathophysiology

Viral respiratory infections are the most common cause of ARI, so much so that they represent up to 80% of all infectious forms affecting the respiratory system (17). Rhinoviruses are the most common cause of ARI in all age groups; other virus families, frequently responsible for respiratory infections, are adenoviruses, influenza viruses, and coronaviruses (17, 18). The coronavirus family has been deeply investigated in the era of the pandemic caused by the SARS-CoV-2 coronavirus (19).

As a rule, viral infections tend to resolve in a short time and, in the majority of cases, spontaneously; sometimes, however, they can be accompanied or followed by bacterial over-infections. It has been estimated that 60% of patients with upper respiratory tract infections, whose symptoms last for more than ten days, have bacterial over-infection, which is associated with additional damage to the respiratory tissues (20). In particular, the so-called "10-day" sign has been proposed: if infectious rhinitis (the common cold) lasts for more than ten days or gets worse after the first five days, acute rhinosinusitis must be suspected.

Viruses and bacteria are capable of inducing transient modifications of the immune system. In particular, a viral infection is associated with a state of relative immunodeficiency, obviously transient in the immunocompetent subject. This phenomenon explains the susceptibility to contract other infections, both viral and bacterial, occurring during and/or after a viral infection. As a consequence, the immune system requires some time to restore its normal functionality after a viral infection. Bacteria also implement mechanisms to contrast the host defenses; for example, they carry out a proteolytic activity against secretory immunoglobulin A (IgA), reduce the complement system's opsonizing capacity, and inhibit chemotaxis (20).

The extremes of life share a reduced ability of the immune system to defend the body from infectious agents. In addition, the clinical situation becomes more complicated in the elderly as numerous comorbidities worsen infectious diseases. Combining these factors explains the greater susceptibility to infections in children and the elderly (21, 22).

Children require several years to achieve adequate immunological competence, i.e., a sufficient repertoire of specific memory cells. The maturation of the immune system occurs linearly with the growth, as documented, for example, by the number of alveolar macrophages: minimal in the first years of life, but progressively increasing

over time (22). Furthermore, numerous risk factors play a pathogenetic role in children, such as certain environmental conditions ("cold" season, exposure to passive smoke, outdoor and indoor pollution, early socialization, promiscuity, and kinship groups), pathophysiological elements (reduced validity of the tussive reflex, low levels of secretory IgA, IgG2, and IgG4, inadequate antibody response to polysaccharide antigens, reduced complement activity, and granulocyte function), anatomical elements (reduced airway caliber and length as well as horizontalization of the Eustachian tube) and, obviously, the genetic predisposition of having an altered immunological function (23-25).

Older adults with COPD usually have a reduction of immunological defenses, often related to smoking and mechanical alterations of the airways due to underlying inflammation and the accumulation of endobronchial secretions (26). Moreover, in elderly subjects, a high risk of reduced immunological response is characterized by a low level of B lymphocytes, an increase in CD8+/CD28-/CD57+ cells (suppressor and cytotoxic lymphocytes), high levels of pro-inflammatory interleukins (IL-1 and IL-6), low T lymphocyte function, and cytomegalovirus seropositivity (27). This immunopathological scenario emphasizes the concept that pro-inflammatory cytokines play an important role. Healthy adults display a balance between pro-inflammatory and anti-inflammatory cytokines. On the contrary, the elderly present a series of pathogenetic factors (stress, continuous exposure to antigens, metabolic and chronic diseases) that create a situation which has been defined as "inflammaging," that is a low-level chronic inflammatory state linked to aging. Inflammaging in turn causes a predisposition to the onset of inflammatory diseases, such as atherosclerosis, type 2 diabetes, obesity, arterial hypertension, and sarcopenia (28). In addition, the incidence of autoimmune and neoplastic diseases is also increased in the elderly, again due to a defect in the immune response, particularly the so-called regulatory response. This immunopathological setting creates a vicious circle, such as a defective immune system promotes the onset of chronic diseases, which also depresses the immune function.

Treatment strategies

One of the main problems in treating respiratory infections is indirectly linked to the high rate of inappropriate antibiotic prescriptions in subjects with viral infections. In Italy, 70% of antibiotic prescriptions concern patients with ARI, mainly affecting the upper airways (mostly pharyngotonsillitis and rhinosinusitis). Italy is among the European countries in which the use of antibiotics in childhood is the highest. Indeed, 88.7% of the total number of antibiotic prescriptions are prescribed by the family pediatrician (61.2%) or by the general practitioner (27.5%); the remaining antibiotics are prescribed by various specialists (29-32). Unfortunately, this excessive use of antibiotics results in a continuous increase in resistance to the antibiotics themselves, which significantly reduces their effectiveness, especially in children and the elderly.

Different strategies are available to prevent RI in clinical practice. Vaccinations currently represent the most effective, safest, and best documented way for preventing infections. The Italian Ministry of Health has prepared a vaccination calendar that includes a series of mandatory and optional vaccinations for all ages of life. In particular, the latest ministerial newsletter recommended the flu vaccine in subjects 65 years of age or over, in children, and a number of subjects at risk. To confirm the preventive value of vaccinations, in the present phase of the SARS-CoV-2 pandemic, the Ministry of Health had issued a more stringent recommendation regarding the 2020-2021 anti-flu vaccination (33). Moreover, an immense vaccination program against COVID-19 is implementing.

The clinical response to vaccines depends on the age of subjects as it is reduced in children and older people (34-36). In particular, antibody production tends to decline over time. The degree of response to a vaccine depends on several factors, some intrinsic to the vaccine itself, its composition, while others are related to the host. In this respect, there is a very close correlation between the efficacy of the influenza vaccine and the age of the vaccinated subject. Concerning the coverage efficacy, vaccine effectiveness is detectable in approximately 70-90% of healthy people under 65 years of age, obviously depending on the type of vaccine used (37, 38).

However, a much lower efficacy is observed in the elderly, up to only 30-40% in elderly adults in assisted residences (37, 38). Seroprotection ranges from 42 to 91% one month after vaccination and from 16 to 84% five months after vaccination (38). Therefore, the problem of an adequate response to vaccinations requires adequate attention, mainly in subjects with vulnerability, such as frail patients affected by multiple debilitating chronic diseases.

Apart from vaccines, many other products have been tested, but the outcomes rarely were reliable because of methodological drawbacks that arose in the study design or during the study conduction. Nevertheless, a long list of substances is commonly used in daily clinical practice to stimulate the immune system to prevent infections and enhance the response to vaccinations. In this regard, probiotics have been used to bolster the response to vaccines. The definition of probiotic is a live microorganism that confers a benefit to the health of the host when administered in adequate quantities. A meta-analysis has shown that probiotics (and prebiotics, i.e., the metabolic substrate of probiotics) effectively increased the immunogenicity of influenza vaccination in healthy adult subjects by increasing seroconversion rates and seroprotection (39). The effectiveness of probiotics depends on the gut-lung axis, such as the cross-talk between the intestinal tube and the respiratory tract, mainly concerning the activation of the immune system (40). From a conceptual point of view, the existence of this gut-lung axis also allows us to understand how an oral immunomodulator can act on the airways (41). A microorganism taken orally, after coming into contact with the immunocompetent cells of the enteric mucosa, initiates a cascade of phenomena at this level which, also thanks to the bloodstream and lymphatic vessels, allows the passage of cells, mediators, and cytokines from one organ to another, thus also determining effects “at a distance”.

In the broad class of substances with presumed adjuvant activity on the immune system, bacterial lysates are the most commonly used in daily practice (41). Different mixtures of purified bacterial antigens, derived from various inactivated pathogens, are available in the market. The antigens are obtained by chemical or mechanical lysis, after which the extract is lyophilized to be stored for a long time. In this context, OM-85 has been deeply investigated.

OM-85 is obtained by the chemical lysis of a series of common Gram-positive and Gram-negative respiratory pathogens (42). The list of pathogens contained in OM-85, therefore, includes extracts of *Branhamella catarrhalis*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus viridans*, and *Staphylococcus aureus*. All these pathogens are suitably inactivated and purified. The lyophilized extract is administered orally and contains proteins, peptides, and traces of sugars, fatty acids, lipoiteic acids, and inactivated lipopolysaccharides (43). The pediatric formulation of OM-85 contains 3.5 mg of bacterial extracts, while the adult formulation contains 7 mg.

OM-85: mechanism of action

OM-85 has a multifaceted and complex mechanism of action (Fig. 1) that can play an important role in preventing recurrent bacterial and viral respiratory infections in the pediatric and adult populations and elderly subjects. OM-85 activates both the innate and adaptive immune responses through the gut-lung axis (41, 42). In detail, OM-85 induces an upregulation of the antiviral cytokine interferon-gamma (IFN-γ), associated with the type 1 immune response and, at the same time, a downregulation of type 2 cytokines, including IL-4, IL-5, and IL-13, produced by specific Th2 cells. This rebalancing of the immunological response also leads to a reduction in IgE levels in allergic subjects, as documented by several studies (44-51).

OM-85 induces the homing of immune cells in the so-called bronchus-associated lymphoid tissue (BALT) and their subsequent activation against viral and bacterial agents (44-46). OM-85 promotes interferon-α and interferon-β and has a dual effect on IL-1 (47). OM-85 reduces IL-1β during the inflammatory response, dampening the inflammation, whereas it induces IL-1β expression in the absence of inflammation, thus ensuring prompt immune response in case of need (48). OM-85 stimulates IL-6 and tumor necrosis factor-alpha (TNF-α) production, allowing a greater macrophage capacity to eliminate

invading bacteria (49, 50). OM-85 promotes the development of $CD4^+/CD25^+/Foxp3^+$ regulatory cells in the respiratory mucosa, exerting an anti-inflammatory activity and mitigating the airway hyperreactivity (51). OM-85 selectively induces nuclear transcription factor NF-κβ and mitogen-associated protein kinases (MAPKs) in dendritic cells, thus increasing the release of the chemokines involved in the migration of macrophages and neutrophils, and of cytokines activating B cells, such as IL-10 and TGF-β, which can control the excessive expression of the pro-inflammatory mediators involved in the tissue damage observed in COPD patients (47). OM-85 downregulates the expression of ICOSL (Inducible T Cell Co-stimulator Ligand), connected to the Th2-mediated immune response, thus diminishing allergic reaction (49, 52). In addition, OM-85 increases nitric oxide production (NO) with a consequent increase in ciliary beating, a crucial element of the physiological mucociliary clearance, which serves to eliminate all harmful agents from the mucous membranes (53). The NO-mediated antibacterial activity is a very intriguing issue. The NO receptors are highly represented in children and are involved in pathogen recognition mechanisms, thus triggering an immune response. These receptors are also involved in the recognition of taste which in turn is connected to the cough receptors. This scenario could open new interesting pathophysiological consequences.

Another intriguing aspect is the transplacental immune modulation; two animal studies, conducted

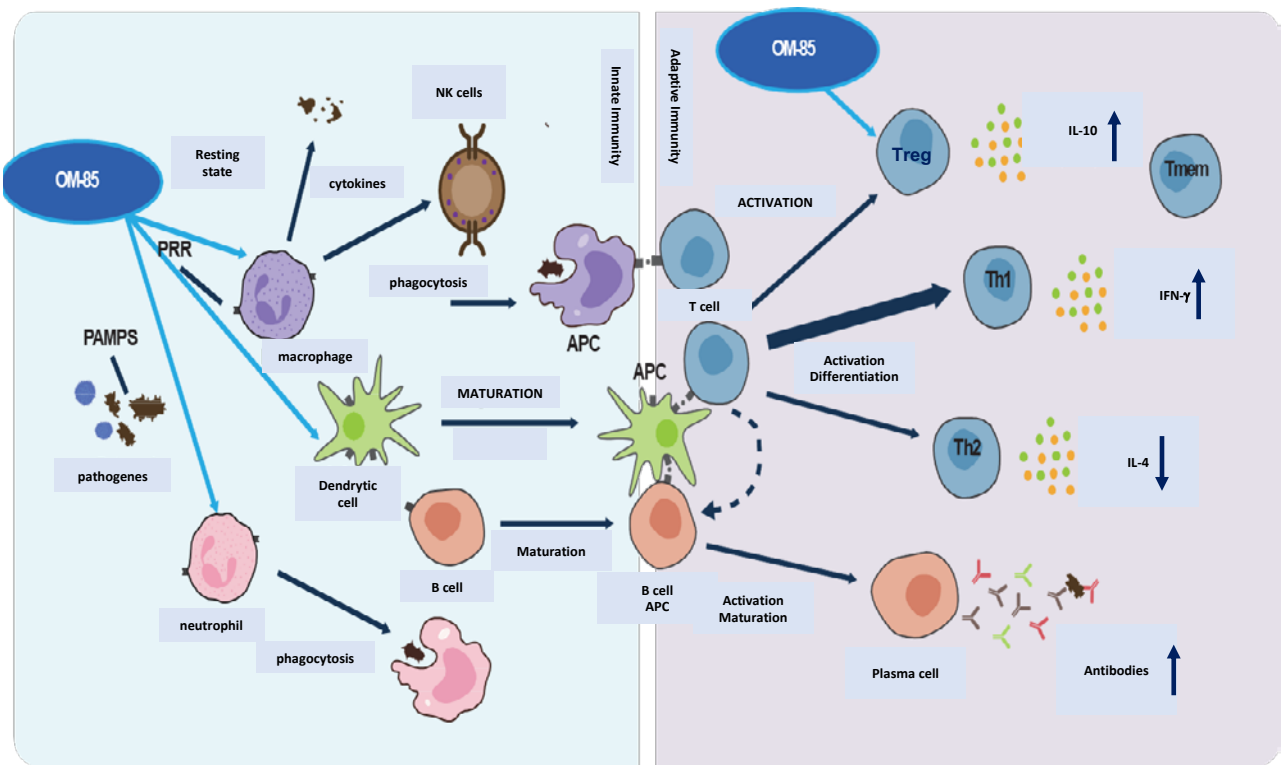

Fig. 1. *Schematic representation of the mechanism of action of OM-85 (Adapted from Scaglione, ref 45). Left panel: effect on innate immunity; Right panel: effect on acquired immunity. PAMPS: pathogen associated molecular patterns; PRR: pattern recognition receptors; NK: natural killer; APC: antigen presenting cell; Tmem: T memory cell; Th: T helper cells; Treg: T regulatory cell; IFN: interferon; IL: interleukin. OM-85 exerts direct effects (blue arrows) on macrophages, dendritic cells, and neutrophils. These cells send signals to NK cells, APC, B cells that activate maturation of APC and macrophages. These effects promote the specific immunity acting on T effector cells, including memory cells, and plasma cells. OM-85 stimulates (dotted arrow) T helper 1 to release of IFN-gamma, plasma cells to produce antibodies (mainly the A class), and T regulatory cells to release IL-10. OM-85 suppresses Th2 reducing IL-4 release.*

by the same research team, provided promising results. The first study demonstrated that OM-85, supplemented to pregnant mice, prevented the development of experimental allergic inflammation (54). Offspring presented an enhanced dendritic cell-dependent mechanism of respiratory surveillance function resulting in more efficient T regulatory activity, preventing induced allergic inflammation. Further study explored the pathways involved in the transplacental innate immunity training (55). OM-85 administration to the mother enhanced the offspring's XBP1-ERN1 signaling axis, fundamental for the survival and maturation of dendritic cells.

Post-viral bacterial co-infections are a common challenge in clinical practice, as a bacterial superinfection frequently occurs after acute viral respiratory infection. In this regard, OM-85 pretreatment in mice prevented *S pneumoniae* co-infection after experimental influenza (56). OM-85 induced a significant increase of $CD8^+$ cells that

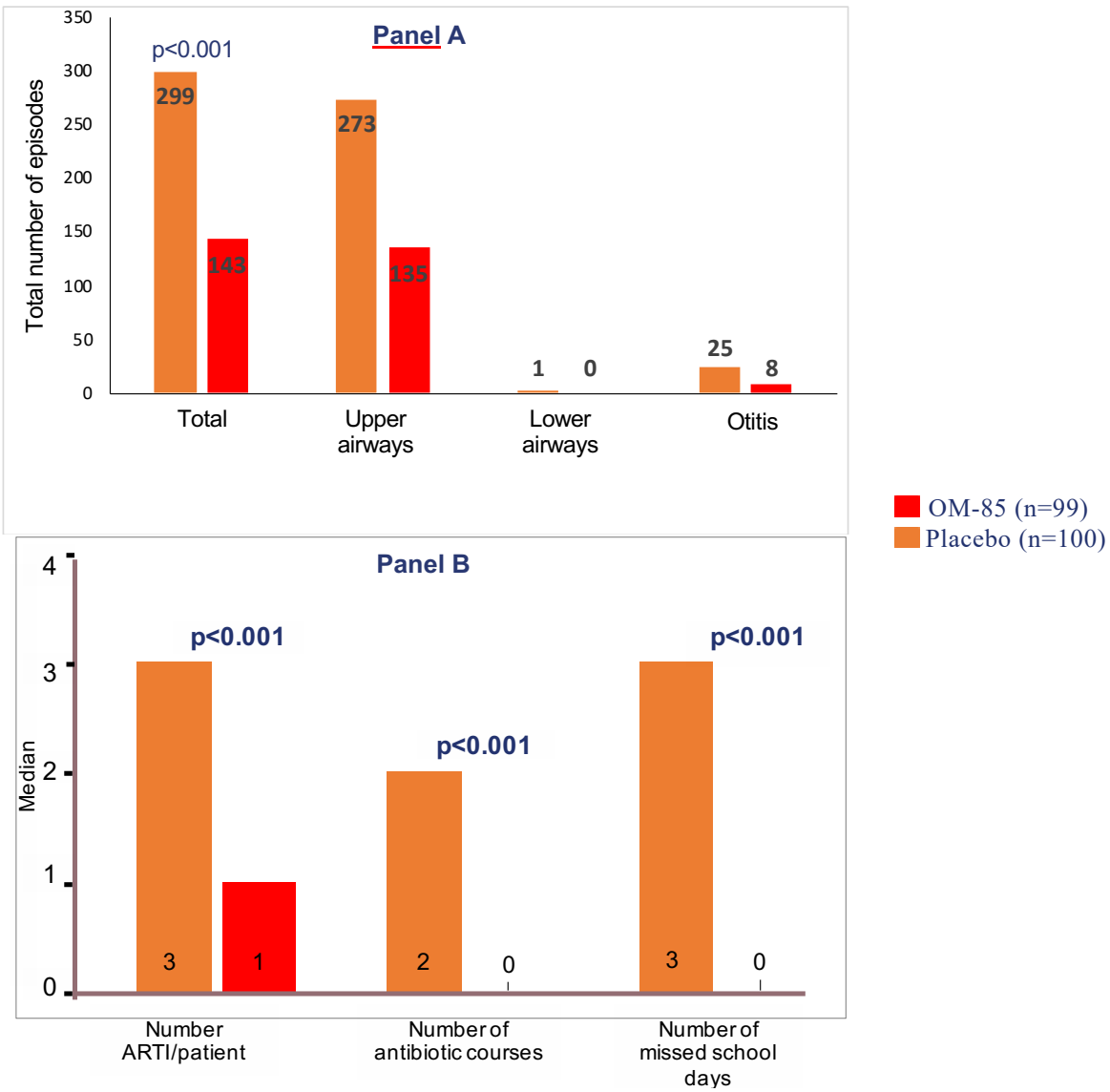

Fig. 2. *Rate of episodes of total acute respiratory infections according to type (Panel A), the median rate of episodes of infection per patient, the median number of days of antibiotic treatment, and median number of days of absence from school (Panel B) in female children of school age living with foster families, and treated with OM-85 or a placebo (Adapted from Jara-Pèrez, ref. 59).*

provided the reduced susceptibility to the secondary bacterial infection. These findings were supported by an *in vitro* study demonstrating that OM-85 pretreatment reduced the viral load and increased dendritic cell maturation and activation (57).

OM-85: clinical efficacy

The clinical development program of OM-85 has included more than 8,000 patients, of whom approximately 2,000 were enrolled in more than 40 randomized controlled clinical trials. These studies demonstrated that OM-85 reduced the number and duration of ARI and antibiotics use.

Evidence in childhood

One of the first studies involved 116 children over six months of age with recurrent respiratory infections (58). The study considered a three-month OM-85 treatment (3.5 mg/day) or placebo for ten days per month for three consecutive months, followed by a

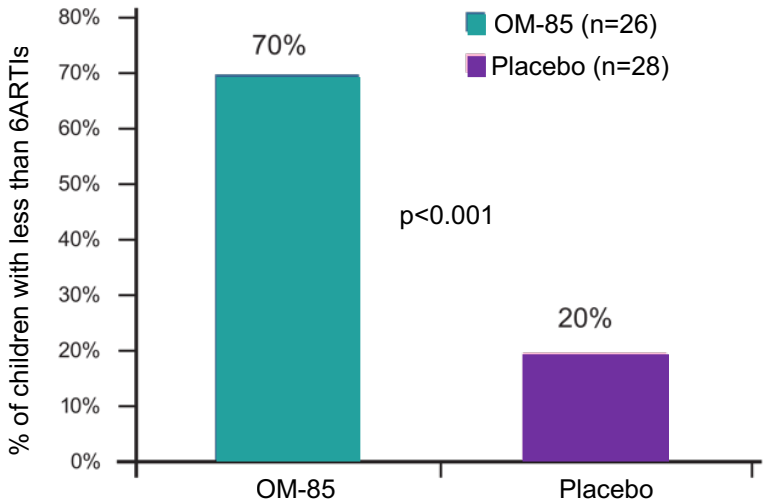

Fig. 3. *Percentage of patients experiencing fewer than 6 acute respiratory infections (RIs) over the 12-month study period of OM-85 treatment vs a placebo (Adapted from Gutiérrez-Tarango, ref. 60)*

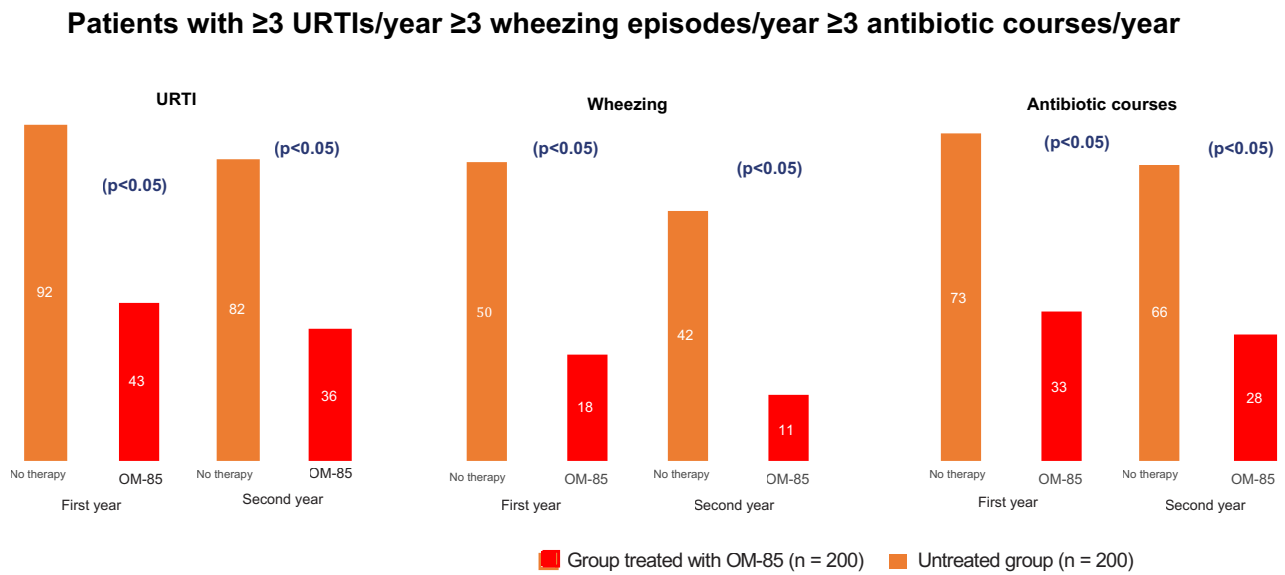

Fig. 4. *Percentage of patients with recurrent respiratory infections (RRIs (treated for two years with OM-85 or a placebo. (Adapted from Esposito, ref. 62).*

3-month follow-up (58). This study showed that OM-85 significantly ($p < 0.01$) prevented RI: 39.5% of the subjects taking OM-85 and 16.5% of subjects treated with placebo remained free from respiratory infections. Furthermore, 44% of children treated with OM-85 did not require antibiotic therapy as compared to 23.5% of the placebo group ($p < 0.05$). The differences were even more pronounced in the subgroup of children six years of age and younger [34% *vs* 3.5% for the absence of infections ($p < 0.01$) and 37% *vs* 10% for the need for antibiotics, respectively ($p < 0.05$)].

Jara-Pèrez and colleagues evaluated a population of 200 girls, between 6 and 13 years of age, living in an orphanage and with RRI (59). The OM-85-treated group (3.5 mg/day for ten days per month for three consecutive months, followed by three months of follow-up) had 143 episodes of ARI as compared to 299 infections observed in the placebo group ($p < 0.001$) at the end of the 6-month study. The median number of RI episodes per patient was 1 in the OM-85 group and 3 in the placebo group ($p < 0.001$). The study also showed statistically significant benefits in terms of the reduction in antibiotic prescriptions (2 in the placebo group *vs* 0 in the OM-85 group; $p < 0.001$), days with disease (19 in the placebo group *vs* 5 in the OM-85 group; $p < 0.001$), and days of school absence (3 in the placebo group *vs* 0 in the OM-85 group; $p < 0.001$), as shown in Fig. 2.

The study of Gutiérrez-Tarango included 54 children, 1 to 12 years of age, with a high number of respiratory infection recurrences in the 12 months preceding the start of the study: mean RRI = 12 (60). Over 12 months, the enrolled subjects received two cycles of OM-85 (3.5 mg) or placebo, both taken for ten days per month, for three consecutive months, with a first cycle at the start of the study and a second cycle after six months. The results showed that the median number of RIs per patient was 5.04 in the OM-85 group compared to 8 in the placebo group ($p < 0.001$). The proportion of patients experiencing less than six acute RI episodes during the study period was also significantly higher in the OM-85 group than the placebo group (70% *vs* 20%, respectively; $p < 0.001$), as shown in Fig. 3. Treatment with two courses of OM-85 also significantly reduced the number of days with the disease as compared to the placebo (35.23 days *vs* 60.75 days, respectively; $p < 0.001$) as well as the mean number of antibiotic courses (2.46 *vs* 4.46, respectively; $p < 0.001$).

A recent study enrolled 288 children, 1-6 years of age, with a history of RRIs (61). The children were treated with OM-85 (3.5 mg/day) or placebo for ten consecutive days per month for three months, after which the children were followed up for a further three months. The treatment started in October. The results demonstrated the effectiveness of OM-85 in reducing the number of RI. OM-85 treated children experienced less RI than placebo-treated ones (33% *vs* 65.1%, respectively; $p < 0.0001$). The percentage of patients with antibiotic prescriptions was also lower in the actively-treated group than the placebo group (25% *vs* 50.5%, respectively; $p = 0.0002$). In addition, the mean number of upper respiratory tract infections and acute otitis media, was approximately lower in the OM-85 group than in placebo group (0.33 ± 0.61 *vs* 0.65 ± 0.55, $p < 0.0001$, and 0.24 ± 0.41 *vs* 0.78 ± 0.73, $p = 0.006$, respectively). The sub-analysis of subjects with at least three episodes of upper respiratory tract RRI or acute otitis media showed a significant effect of OM-85 (21% with OM-85 *vs* 52% with placebo; $p < 0.05$). A further study, conducted by the same authors, investigated the long-term efficacy of OM-85 (62). The study lasted two years, during which OM-85 (3.5 mg/day) was administered for ten days per month for three consecutive months each year. The inclusion criterion was a clinical history of at least six episodes of RI/year. The subjects treated with OM-85 had significantly fewer respiratory infections, wheezing episodes, and antibiotic prescriptions than the control subjects ($p < 0.05$ for all parameters), as shown in Fig. 4. Furthermore, the proportion of children without infections during the study was significantly higher in the OM-85 group. Interestingly, there was no difference between the first and second years of treatment.

The same study group investigated the possible "adjuvant" effect of OM-85 on influenza vaccination (63). This randomized trial recruited 68 preschool children with RRI. The children must have received at least one dose of inactivated influenza vaccine. The study aimed to identify the correct timing

of the administration of OM-85, such as prior to vaccination or at the same time. In addition to vaccination, a group of children also took a course of OM-85 (3.5 mg/day for ten days per month for three consecutive months). Children treated with OM-85 had a significant reduction of RI episodes and antibiotic courses compared to the group of subjects who received only the inactivated influenza vaccine ($p < 0.05$ for both).

Razi and colleagues evaluated the post-viral wheezing in 75 preschool children with RRI (64). This randomized, placebo-controlled study demonstrated that a course of OM-85 (3.5 mg/day for ten days per month for three consecutive months) reduced both RI and wheezing episodes by 38% in 12 months. The mean cumulative frequency of wheezing episodes was also statistically lower in OM-85-treated children than a placebo (-22.4 days/year; $p < 0.001$), as reported in Fig. 5.

There is evidence that OM-85 is effective even in infants at risk of respiratory infections. A randomized placebo-controlled study recruited 59 infants (3 to 9 months of age); the primary endpoint was the development of severe respiratory tract infections (65). The study, despite being undersized, documented the OM-85 safety in infants and demonstrated a reduction of respiratory infections.

Another interesting application of the OM-85 prophylaxis could be the recurrent tonsillitis model. Children suffering from recurrent tonsillitis undergo tonsillectomy surgery, exposing them to the risks and costs associated with this invasive procedure. In this regard, a long-term retrospective observational study collected 5-year data from a population of 131 children (1 to 15 years of age) with recurrent tonsillitis (66). OM-85 (3.5 mg/day) was prescribed ten days per month for three consecutive months. The results documented either a total (defined as a > 50% reduction in acute tonsillitis episodes) or partial (i.e., a ≤ 50% reduction) response in 67 and 32 children, respectively. The total or partial response resulted in a significant reduction in tonsillectomy: none of the 67 patients with total response underwent tonsillectomy, while only 4 of the 32 patients with a partial response required tonsillectomy. A clinical report concerned a child with pulmonary arterial sling presenting as pneumonia by inhalation of a foreign body, the child was successfully treated

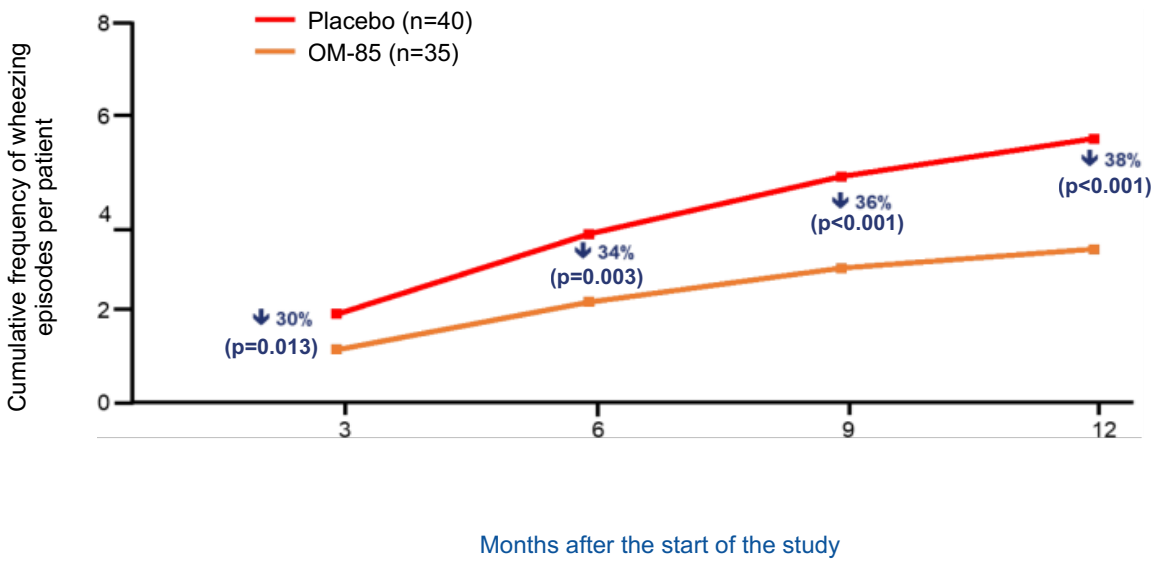

Fig. 5. *Benefits of OM-85 on the average cumulative frequency of wheezing episodes (Adapted from Razi, ref. 64).*

with a preventive 3-month OM-85 course (67). On the contrary, a pilot study showed that OM-85 did not prevent respiratory infections in 54 children (six months to five years old) with no past history of RRI attending a daycare center in Brazil (68). However, the study had some limitations, including the small size, uncertainty about treatment adherence, and the lack of the identification of risk factors associated with the explored outcomes. Moreover, some narrative reviews and meta-analyses have confirmed the efficacy and safety of OM-85 in childhood. A meta-analysis selected eight randomized, placebo-controlled studies which evaluated the impact of 1 or 2 courses of OM-85 on preventing respiratory infections in children (69). The duration of the studies lasted up to 12 months. Globally, 851 children (between 1 month and 12 years of age, mean age six years) with at least three infectious episodes in the six months preceding each study were evaluated. This meta-analysis documented a significant difference in the onset of respiratory infections between the children treated with OM-85 and the children treated with placebo. Only 32% of the children treated with OM-85 developed an RI compared with 58.2% of the children in the placebo group ($p < 0.001$). There was also a 35.5% reduction in the mean total number of acute RI compared to a placebo. A further meta-analysis confirmed the OM-85 preventive effect of RI (70). This meta-analysis included 35 studies, nine placebo-controlled and 4 with high methodological quality. The analysis included 437 children treated with OM-85 and 415 children treated with placebo. The OM-85-treated group reported a 35.9% reduction of RI episodes compared to the control group; in absolute terms, the children treated with OM-85 developed 1.12 RI less than the children treated with placebo. Another meta-analysis examined 53 studies concerning 1 or 2 OM-85 cycles and compared with placebo; the observation time lasted up to 12 months (71). A total of 4,851 patients up to 16 years of age were analyzed. This meta-analysis documented a 52% reduction in acute RI episodes (on average 2.33 episodes less), a 42% reduction in the duration of the antibiotic therapy (on average 4.1 days shorter), a 45% reduction in the duration of infection (on average 3.13 days less), and a 49% reduction in fever (2.91 days less with fever). A recent review pointed out the preventive effect

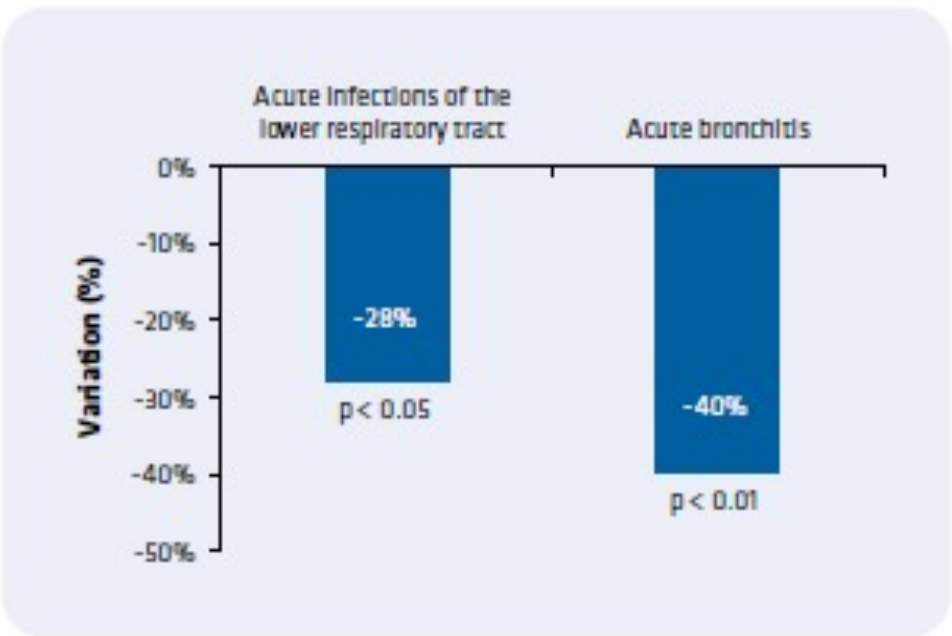

Fig. 6. *Frequency of lower respiratory tract infections with OM-85 vs placebo in elderly adults with chronic bronchitis (Adapted from Orcel, ref. 77).*

of OM-85 in respiratory infections in childhood (72). Consistently, a pharmacoeconomic study has shown that the use of OM-85 was characterized by a favorable cost/benefit ratio (73). The study estimated a saving of approximately $85 regarding the cost of each IR episode when using OM-85 as compared to standard care. The cost reduction considered both direct and indirect costs, as well as the reduced use of antibiotics and days of work lost by parents to care for the ill child (73).

Cardinale and colleagues underlined the OM-85 effectiveness in modulating the *in vivo* immune response against different pathogens, including influenza and respiratory syncytial virus; OM-85 also reduced the wheezing rate and attack duration in wheezing-prone children (74).

An expert consensus from the World Association of Infectious Diseases and Immunological Disorders summarized the characteristics of OM-85, underlining its limitation consisting in the absence of biomarkers predicting the best responder profile in the context of the precision medicine (75). The expert consensus stated that OM-85 should be recommended for preventing respiratory recurrence in RRI-prone children ($\geq$ 6 months old). A very recent meta-analysis evaluated 14 studies including 1,859 children, 890 treated with OM-85 (76). The results showed that OM-85 use was significantly related to lower frequency of respiratory tract infections ($p< .001$), lower total duration of respiratory tract infections ($p< .001$), lower incidence of respiratory tract infections (OR 0.40; p .006), lower number of antibiotic courses ($p= .03$), and lower antibiotic use (OR 0.38; $p< .001$). Moreover, OM-85 use was not significantly related to adverse event rate (OR 1.02; $p= 0.94$) or to wheezing attack frequency ($p= 0.14$). The authors concluded that OM-85 is recommended for children with high risk of RRI.

Evidence in adulthood

Several experimental and observational studies evaluated the role of OM-85 in reducing the care burden, clinical severity, and costs of respiratory diseases in adult patients. In particular, the study model was mainly represented by COPD and/or chronic bronchitis, evaluated by randomized, double-blind, placebo-controlled trials.

A historic study involved 354 elderly institutionalized patients with chronic bronchitis who had had more than four episodes of lower RI in the six months prior to enrollment (77). The patients were followed-up for six months, including three months of treatment with OM-85 (7 mg/day) or placebo, for ten days per month for three consecutive months, followed by a 3-month follow-up. This study demonstrated a significant ($p<0.05$) reduction in the number of lower respiratory tract infections in patients treated with OM-85 (112 events in 147 patients) as compared to the placebo group (156 events in 143 patients). The OM-85 treatment affected acute bronchitis episodes but not pneumonia. Furthermore, the number of antibiotic prescriptions was also 28% lower in the OM-85 group than the placebo group ($p <0.05$), as shown in Fig. 6.

Another randomized, double-blind, placebo-controlled, 6-month study enrolled 381 long-term heavy smokers or former smokers with severe COPD (78). The purpose of the study was to evaluate the efficacy of OM-85 in preventing COPD exacerbations. Patients received OM-85 (7mg/day) or placebo for 30 days the first month, followed by ten days per month from the 3rd to the 5th month). The frequency of exacerbations was similar between the two groups (44.5% *vs* 43.7%, respectively), but the number of hospitalization days for respiratory disease was 55% lower in the OM-85 group (287 days) as compared to the placebo group (642 days), as shown in Fig. 7. In addition, the number of hospitalizations was also decreased by the OM-85 prophylaxis, but not by placebo (44 *vs* 57 hospitalizations, respectively). Finally, the mean days of hospitalization for respiratory problems were significantly lower in the OM-85 group (1.5 days) than in the placebo group (3.4 days).

The effectiveness of OM-85 was more evident in smokers, as documented by a multicentric, randomized, double-blind, placebo-controlled study that involved 273 patients with a recent history of chronic bronchitis or mild COPD (79). The patients were randomized to receive treatment with OM-85 (7 mg/day) or placebo for 30 consecutive days in the first month and ten days per month from the 3rd to the 5th month. At the end of the treatment, the frequency

of respiratory infections was 29% lower in subjects treated with OM-85 than in the placebo group (0.61 *vs* 0.86, respectively; p = 0.03). This outcome was even more relevant in the subpopulation of smokers and former smokers: the mean cumulative frequency of exacerbations was approximately 40% lower in the OM-85 group than the placebo group (0.62 exacerbations with OM-85 and 1.04 with placebo; p <0.01). Another multicentric, randomized, double-blind, placebo-controlled study, lasting five and a half months, enrolled 428 patients with chronic bronchitis or COPD (80). The patients took OM-85 (7 mg/day) or placebo for ten days/month for three consecutive months. The percentage of smokers or former smokers was very high (approximately 60%). The study evaluated the proportion of patients with exacerbations. The OM-85 group had a more significant reduction than the placebo group (-10%) after the end of treatment at 12 weeks (23.4% for OM-85 *vs* 33.3% for the placebo; p = 0.03). This trend in favor of OM-85 was maintained in the follow-up period (32.8% in the OM-85 group *vs* 38.0% in the placebo group; p = 0.277).

Some studies were also performed in clinical practice (the so-called real-life studies). A 12-month study involved 84 patients with chronic respiratory disease and RRIs; 29 had allergic rhinitis, 28 asthma, and 27 COPD (81). During the first nine months, the patients received standard therapy for COPD. Later, the standard therapy was associated with OM-85 add-on treatment (7 mg/day for ten consecutive days per month for three months), then, a 6-month follow-up ensued. The RI frequency decreased from 69 episodes to 38 (p<0.05), and exacerbations decreased by 36%. This study also demonstrated an increase in serum and secretory IgA levels. Another 130 patients with acquired immunodeficiency (HIV) and RRI were investigated in a single-center, observational, retrospective study lasting six years (82). The patients were stratified into various subgroups: patients with COPD and/or sinusitis (n = 42), recurrent sinusitis (n = 21), recurrent otitis media (n = 5), and smokers (n = 62). The number of respiratory infections, antibiotic use, and antibiotic cost before (2005-2006) and after (2008-2011) preventive treatment with OM-85 was compared longitudinally. The RI

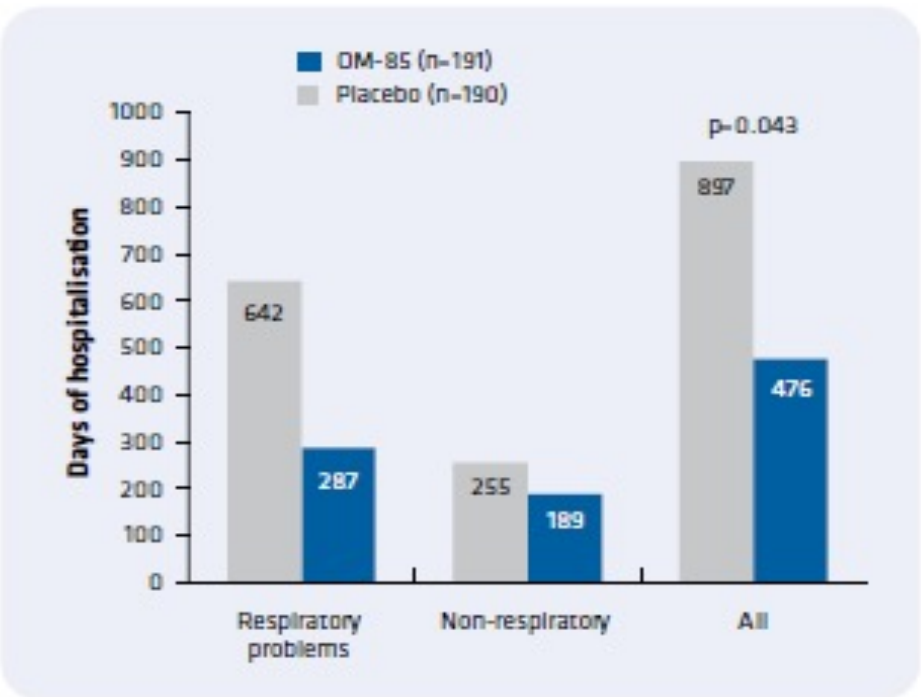

Fig. 7. *Impact of OM-85 on the reduction of hospitalizations in subjects with COPD (Adapted from Collet, ref. 78).*

frequency had decreased in all the subgroups. This finding was even more pronounced in COPD and/or sinusitis patients and smokers. There was also a reduction in the use of antibiotics.

Very recently, Gao and colleagues evaluated the preventive effect of a 3-month OM-85 treatment, compared to placebo, in patients with bronchiectasis (83). There was no significant difference between treatments concerning the number of exacerbations and the time to the first pulmonary exacerbation. However, the safety profile of OM-85 was good and the majority of adverse events was mild in both arms.

Safety of OM-85

OM-85 has been shown to have a particularly favorable safety profile, similar to that observed in patients treated with a placebo in both pediatric and adult studies. The Schaad's systematic review showed that OM-85 had a rate of adverse events similar to placebo (63). Specifically, minor adverse events were observed in 17.7% of patients treated with OM-85 compared with 18.2% of placebo patients. Serious adverse events were reported in 1% of subjects treated with OM-85 and 0.5% of patients taking placebo. The withdrawal rate from clinical trials for adverse events was 1.3% in the active treatment groups and 0.7% in the placebo groups. The most common minor adverse events were nausea, abdominal pain, and common cold. Nevertheless, it has to be noted that no causal relationship has been established between the adverse events observed and the use of OM-85 in the various studies considered (72).

OM-85 was also well tolerated by the various patient subpopulations, including patients with autoimmune nephrotic syndrome (84), HIV (81), COPD (78, 79), and chronic bronchitis (77-79). Furthermore, OM-85 was well tolerated even when administered in combination with a vaccine, as it did not interfere with seroconversion, seroprotection, and B memory cells (63).

CONCLUSIONS

The management of respiratory infections represents an ongoing challenge in clinical practice. Respiratory infections also represent a significant burden for the patients and society. Children and older people have a defective immune response, and aging is frequently associated with comorbidities. As a result, these age classes have a sustained susceptibility to respiratory infections and a reduced response to vaccinations. Therefore, the use of immunomodulating agents could be a valuable strategy to prevent RI and enhance the response to vaccines. This concept may be even more cogent in the era of the COVID-19 pandemic. In this regard, OM-85 may claim to have relevant evidence concerning the mechanism of action, clinical effectiveness, safety, and tolerability, documented by methodologically rigorous studies.

OM-85 can enhance the natural and acquired immune responses through a multifaceted mechanism of action. OM-85 can represent a preventive strategy in RI management, especially in frail subjects, such as children, including infants, older people, smokers, and subjects with immunodeficiency.

Robust evidence has shown that OM-85 can prevent recurrent respiratory infections, reduce the number of COPD exacerbations, and shorten disease duration at home or in the hospital. In addition, OM-85 can enhance the effectiveness of the flu vaccination without affecting vaccine tolerability. Finally, the preventive use of OM-85 can reduce the use of antibiotics, contributing to contrasting the antibiotic resistance and saving the high cost of chronic respiratory diseases. Further studies should identify the profile of the ideal candidate to OM-85, using specific biomarkers in the context of the precision and personalized medicine.

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