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Summary of Selected Presentations

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THE PLACE OF IMMUNOMODULATION IN RECURRENT RESPIRATORY TRACT INFECTIONS, AN OVERLOOKED PANDEMIC

A narrative summary of selected presentations given at the second Encuentro Latinoamericano de Infecciones Respiratorias Recurrentes (ELAIR), an educational summit held in Buenos Aires, Argentina, 4th–5th July 2015

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ABSTRACT

This educational summit, supported by an independent grant from OM/Vifor Pharma, brought together physicians specialising in pulmonary medicine, otolaryngology, surgery, immunology, and paediatrics. Delegates from the USA, Europe, and Latin America met and discussed the current unmet needs of patients suffering respiratory tract infections (RTIs). The meeting included plenary lectures, workshops, and interactive sessions, allowing delegates and presenters to debate the most pressing local and international issues in the field.

UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN AND ADULTS

Upper respiratory tract infections (URTIs) affect the whole population, but are more frequent in children under 5 years of age. In Argentina, acute RTIs are the primary reason for visiting healthcare services, and respiratory diseases are the primary cause of consultation and hospitalisation in all age groups. A high proportion (60%) of children under 1 year of age, and half of those who are less than 5 years of age, have at least one episode of RTI in a given year.[1] Lower respiratory tract infections (LRTIs) are predicted to be the fourth leading cause of death worldwide by 2020.[2]

The higher frequency of URTI in children derives from: immune system immaturity; physiological characteristics; the effects of growth on anatomy; rapid inflammatory responses; functional immaturity of the Eustachian tube; and close contact with other children either directly, for example at school, or indirectly through those attending school (e.g. siblings).

Viruses and bacteria are the major pathogens responsible for RTIs in humans. Performing a differential diagnosis between viral and bacterial infection is challenging due to their interrelation. Bacterial infections often develop from viral infections, and the time course of this transition is generally poorly understood. Viral infection predisposes to bacterial infection due to a number

of factors, including damage to the respiratory mucosal surface leading to an increase in the number of bacterial receptors, which promotes the possibility of bacteria adhering to the mucosal membrane. Viral infection also alters mucociliary transport, leads to mucus thickening, and affects the process of phagocytosis, all of which promote viral–bacterial co-infections that may result in a vicious cycle of recurrent infections.

The major bacterial agents responsible for RTIs have remained the same for the past 20–30 years and include: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, beta-haemolytic Group A *Streptococcus*, anaerobes, and *Pseudomonas*. In an ideal world, the first step towards curing a RTI would be the identification of the infectious agent, allowing a targeted evidence-based approach to treatment. This is not practical in many cases, however, which leads to the use of empirical treatment. Although a prudent strategy to protect against morbidity and mortality, empirical treatment may also lead to the inappropriate use of antibiotics for simple and self-limiting bacterial and viral infections. Indiscriminate antibiotic use promotes bacterial resistance and is a prevalent problem worldwide, and is rapidly worsening in Latin America in particular.

Resistance mechanisms can be divided into three broad classes. The first two are well known and act via inhibition or inactivation of antibiotics. A third mechanism that is becoming more important is evasion, for example, though the formation of biofilms.[3] Biofilms are an emergent problem that may contribute to serious issues with respect to infection control. There are currently no antibiotics that can penetrate the protective polysaccharide layer of these bacterial communities.[4]

CLINICAL PRESENTATION, BURDEN, AND EPIDEMIOLOGY OF RECURRENT AND CHRONIC RESPIRATORY TRACT INFECTIONS

Recurrent infection presents a major challenge particularly in the paediatric setting. There are a number of definitions of recurrence, the most common of which are ≥3 episodes in 6 months or ≥4 episodes in 1 year in adults, and ≥6 episodes in 1 year in children.[5]

An important epidemiological longitudinal study conducted in the Netherlands investigated the burden of recurrent upper respiratory tract infections (rURTIs) during childhood. It was found that nearly 70% of 693 children followed from birth had experienced rURTIs by the age of 21 years. Peak prevalence was from 2–4 years of age, with close to 45% of children experiencing rURTIs during this period. Approximately 80% of children were prescribed antibiotics due to rURTIs and almost one-third required more than two antibiotic prescriptions. Perhaps the starkest statistic was that almost half of the children in this study underwent surgery due to rURTIs between birth and the age of 21 years.[6]

The major rURTIs in paediatric patients are represented by tonsillopharyngitis, otitis media, and rhinosinusitis. Recurrent tonsillopharyngitis tends towards improvement with growth and is more common in children over 3 years of age. It is relatively easy to identify Group A *Streptococcus* as the causative agent of acute tonsillopharyngitis, allowing the use of targeted therapy that may improve outcomes. Rapid antigen detection tests and blood agar cultures are the most common bacteriological tests used to diagnose tonsillopharyngitis. However, diagnosis based on surface cultures may be insufficient due to bacterial internalisation, and cultures obtained from deeper tissues often differ in terms of the strains present.[7] Therapy failure is the main cause of recurrence in tonsillopharyngitis and therefore preventative therapy is extremely important. Preventative therapies including lyophilised bacterial products and vitamin C may be successful if there is no marked tonsil hypertrophy.

Recurrent acute otitis media (rAOM), such as recurrent tonsillopharyngitis, tends to resolve with growth. The condition is more common in children under 3 years of age due to their immunological immaturity and the increased likelihood of tubaric dysfunction. Diagnosis of rAOM may be challenging due to the relative difficulty in visualising the tympanic membrane. Similarly, from a bacteriological standpoint it is difficult to identify the causative agent of rAOM, and therefore empiric therapy is generally used to treat this condition.

Worldwide, 15% of children will suffer rAOM over a given 12-month period, with a similar proportion (13.33%) found in unpublished data from Argentina. There are a number of important risk factors for developing rAOM (pacifier use, short duration of breastfeeding, winter season, URTI, and adenoid hypertrophy), only some of which are avoidable. The relationship with other URTIs makes

preventative therapy, targeting infection in general, a theoretically useful option.

A recent European Position Paper classifies rhinosinusitis, the third major rURTI that affects children, in terms of symptom duration and severity. Acute/intermittent and chronic/persistent rhinosinusitis are separated by a symptom-resolution cut-off of 12 weeks. The cut-off between mild and moderate/severe is 4 on a visual analogue scale assessing severity of the main symptom or addition of symptoms. In the USA, an incidence of 2–3 episodes of viral rhinosinusitis per year is estimated for adults, with approximately double the incidence in children. Chronic rhinosinusitis (CRS) affects approximately 14% of the adult population in the USA.[8,9]

The classification of rhinosinusitis is similar in both adults and children, and both patient groups present with a similar pathophysiology in acute rhinosinusitis. Clinical diagnosis is used as standard for both adults and children, and plain sinus X-ray films do not help for diagnosis or follow-up. Rhinorrhoea is a common symptom in both patient groups, as is the aetiological switch from infection, which predominates during acute rhinosinusitis, to inflammation, which predominates in CRS. However, acute rhinosinusitis is more frequent in children and the condition rarely becomes chronic. Conversely, CRS is more often found in the adult population. Cough is an important symptom in children and there is a relationship between enlarged adenoids and rhinosinusitis in this population. Surgery is rarely indicated in children with rhinosinusitis, and surgery for CRS in adults is controversial due to diverse underlying aetiologies.

Symptoms and recurrence of respiratory infections have a major impact on quality of life. Recurrent infections are frequently associated with risk factors that may be amenable to preventative therapies, which modulate immune-system responses and reduce recurrence. Preventative therapies for recurrent rhinosinusitis include immunomodulators, adenoidectomy, endoscopic surgery, and allergy management. Bacterial lysate therapy, topical steroids, and nasal irrigation have the highest current evidence grades for the treatment of CRS in adults.[9]

IMMUNOMODULATORS FOR THE PREVENTION OF RECURRENT RESPIRATORY TRACT INFECTIONS

Prevention of rURTIs requires adequate diagnosis and identification of predisposing factors, which may be environmental (e.g. parental smoking), immunological (e.g. immunoglobulin deficiency), or related to comorbidities (e.g. allergic rhinitis). Prophylaxis against environmental factors may be undertaken through parental education measures. Antibiotic prophylaxis should be reserved for special situations such as in immunocompromised patients presenting with recurrent infections. Surgery including tonsillectomy, sinus surgery, ventilation tubes, or adenoidectomy may be an option for some patients, yet many physicians are unlikely to recommend a surgical procedure for rURTIs alone without the presence of other debilitating symptoms such as hearing loss or obstructive sleep apnoea.

Further effective prophylactic strategies that do not increase the rate of antibiotic resistance and have less impact on the patient than surgery are needed. Two such options are vaccination and the use of immunomodulatory agents. Despite initial promise, vaccines have proved less effective than initially hoped. For example, anti-influenza virus and anti-pneumoccocal vaccines have only shown a 6–7% benefit for all causes of AOM.[10] In contrast, the oral immunomodulator OM-85, which consists of lyophilised extracts of 21 strains of 8 species and sub-species of bacteria (*H. influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *K. ozaenae*, *Staphylococcus aureus*, *Streptococcus pyogenes* and *Streptococcus viridans*, and *M. catarrhalis*), has shown marked efficacy in the prevention of a number of rURTIs in paediatric and adult populations.

The integrated nature of the human immune system is central to the rationale behind the efficacy of orally administered immunomodulators in the prevention of RTIs. The gut-associated lymphoid tissue (GALT) contains the majority of the body's lymphocytes (85%), and similar to all mucosa-associated lymphoid tissue, including that of the respiratory mucosa, it contains both inductive and effector sites. Effector sites may be remote from the inductive sites where an immune response begins, and the efficacy of oral immune modulators in RTIs

relies on activity in Peyer's patches, the inductive sites of the GALT, leading to immune responses in the diffuse effector sites of the respiratory mucosa.

Dendritic cells (DCs) within Peyer's patches are central to an integrated immune response, and the most crucial cell type for host response against pathogens. DCs are key to both antibody recognition for adaptive immunity, and activation of the broader innate immune response via pathogen-associated molecular patterns (PAMPs). PAMP-associated activation of DCs drives both DC maturation and release of cytokines, leading to downstream activation of naïve T helper (Th) cells, B cells, and innate immune cells such as natural killer cells. Following activation, these cells migrate from Peyer's patches to the respiratory mucosa where they may directly fight infection through the production of secretory antibodies or cytotoxic activity, or support the mounting of an immune response through the production of inflammatory cytokines.

As the product of multiple bacterial strains, OM-85 contains numerous antigens and PAMPs. There is now a large body of evidence showing that orally administered OM-85 modulates the respiratory immune response, with recent findings suggesting that activation of DCs is key to its activity.[11-17] OM-85-induced activation of DCs has been demonstrated *in vitro*, leading to the release of cytokines that activate downstream immune effect or cells, including neutrophils and B cells.[17] Induction of polyclonal immunoglobulin production by OM-85 has been demonstrated, offering protection against future bacterial and viral infections.[15] In addition, OM-85-induced production of the antiviral cytokine INFα has been demonstrated.[17] Furthermore, OM-85 has been shown to alter the balance of Th1/Th2-promoting cytokines in favour of Th1, thus reducing the risk of chronic inflammation in allergic and autoimmune conditions.[18,19]

In summary, OM-85-induced immune system modulation has been demonstrated at both the innate and adaptive levels of the immune system. Activation of DCs through PAMPs and antigens contained within the formulation of OM-85 is likely to be the key driver of its immunomodulatory effects. Mechanisms for prophylaxis against pathogens beyond those contained in the bacterial lysate have been demonstrated, as have theoretical protective mechanisms against allergic and chronic inflammatory conditions such as asthma.

CLINICAL EFFICACY OF OM-85 PROPHYLAXIS AGAINST RESPIRATORY TRACT INFECTIONS IN CHILDREN AND IN ADULTS

Efficacy data for OM-85 prophylaxis are available for the three principal rURTIs affecting the paediatric population: tonsillopharyngitis, rAOM, and rhinosinusitis. In a recent study on recurrent tonsillitis, defined as more than 3 incidents in 12 months, children aged 1–15 years (N=131) received OM-85 for the first 10 days of 3 consecutive months.

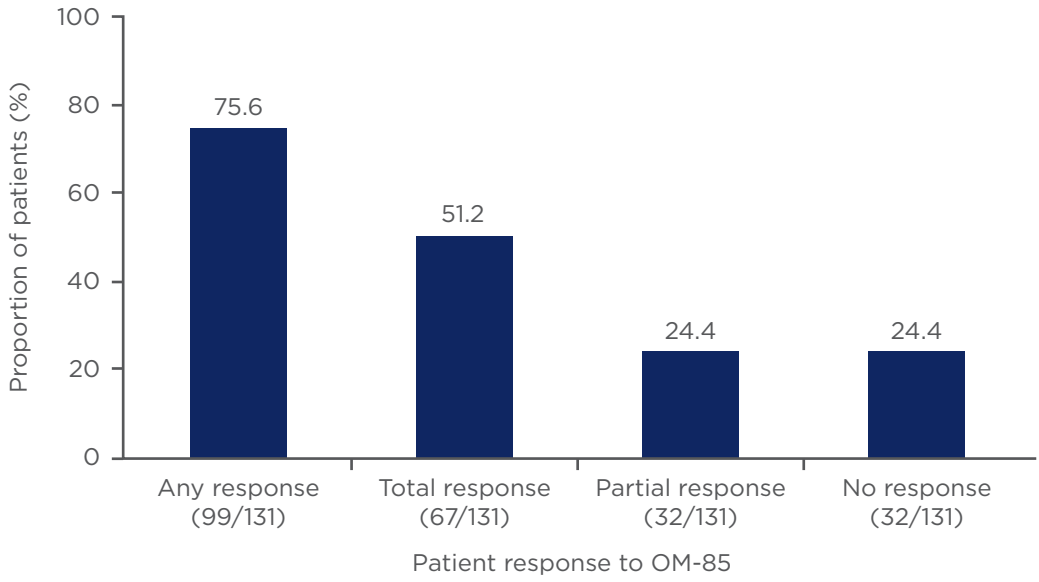

Figure 1: Reduction in tonsillectomy in total (decrease in episodes >50%) and partial (decrease in episodes <50%) responders to OM-85 treatment.[20]

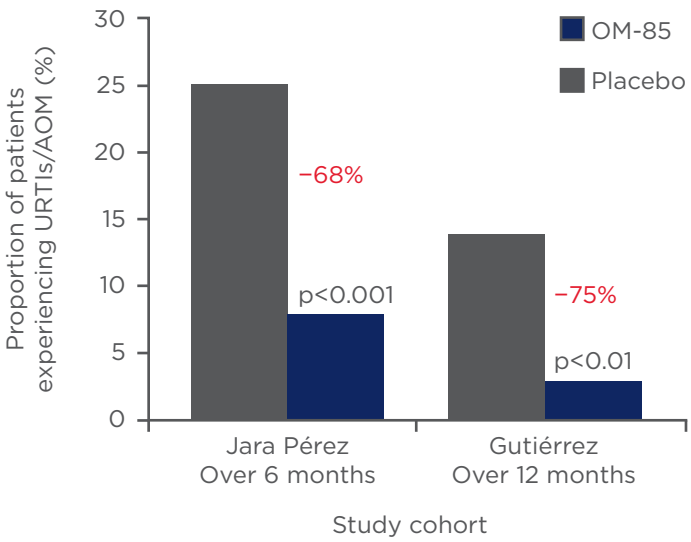

Figure 2: Efficacy of OM-85 in preventing URTIs/AOM over 6 and 12 months in children.[21,22]
URTI: upper respiratory tract infection; AOM: acute otitis media.

Three-quarters (76%) of the treated children experienced a reduction in the frequency of recurrent tonsillitis over the 6-month study. In addition to reduced incidence, treatment resulted in 68% of children in the 3-month responder group losing their indication for tonsillectomy during follow-up (median: 9 months) (Figure 1).[20] This represents a marked clinical benefit in terms of reduced surgical interventions, particularly given the high prevalence of surgery due to rUTIs (approximately 50%) in patients followed up to the age of 21 years.[6]

Two double-blind, randomised studies have investigated the efficacy of OM-85 in preventing rURTIs/rAOM over 6 and 12 months in children aged 1–13 years (N=200 and 54, respectively). The participants had a history of recurrent infections, and in the 6-month trial were at high risk due to communal living within an orphanage. Significant reductions in the incidence of rURTIs were found in both trials, with a 68% reduction over 6 months ($p<0.001$) and 75% reduction over 12 months ($p<0.01$) (Figure 2). In addition, significant reductions in the number of antibiotic courses prescribed were demonstrated in both trials.[21,22]

In a 6-month study, there were marked and statistically significant reductions in both incidence (−65%, $p<0.05$) and duration (−73%, $p<0.01$) of recurrent acute episodes in children with CRS treated with OM-85 compared with placebo. Furthermore, duration of antibiotic treatment was significantly reduced ($p<0.025$). The authors concluded that OM-85 is a curative and preventative treatment for paediatric CRS. Interestingly, the authors also showed a steady decrease in IgA during treatment, which was significantly different from placebo at Month 5 ($p<0.01$) and Month 6 ($p<0.05$).[23]

In all of the above studies, OM-85 was well tolerated with mild adverse events. A large study (N=792) further investigated OM-85's safety in children from 6 months to 12 years of age. Only 6.3% of patients suffered adverse effects, all of which were very mild gastrointestinal symptoms with no need for treatment interruption.[24] These data have been confirmed in a systematic review of eight randomised trials (N=851) of rRTIs in paediatric populations. OM-85 therapy resulted in 25% fewer recurrences compared with placebo, and the reduction was greater in high-risk patients. A similar proportion of mild adverse events were experienced by those receiving OM-85 or placebo (approximately 18%), serious events were rare (1%), and no causal relationship was determined between any adverse event and OM-85.[25]

In the adult population, OM-85's efficacy has been investigated in a study on chronic purulent sinusitis (N=284). Treatment resulted in significant decreases in headache ($p<0.001$), purulent nasal discharge ($p<0.001$), coughing ($p<0.001$), and expectoration ($p<0.001$). There were also clinically and statistically significant improvements in exacerbations (−45%) and blocked sinuses (−65%) compared with placebo (Figure 3). The tolerability profile was similar in both groups.[26]

These data led to the first inclusion of an immunomodulator in international guidelines for rhinosinusitis (evidence level Ib, recommendation B).[27] In the updated guidelines, OM-85's recommendation grade has been increased to A, although further work to establish relevance within the treatment regimen is necessary.[9] Bacterial lysates are also recommended for prophylaxis against recurrent rhinosinusitis and CRS in Brazil.[28]

COST-EFFECTIVENESS OF OM-85

A cost-effectiveness study investigating OM-85 prophylaxis in children at risk of recurrent rhinopharyngitis was carried out in France. The study used an expert-validated, decision analysis model and estimated direct costs of €49.39 for an acute episode of rhinopharyngitis.

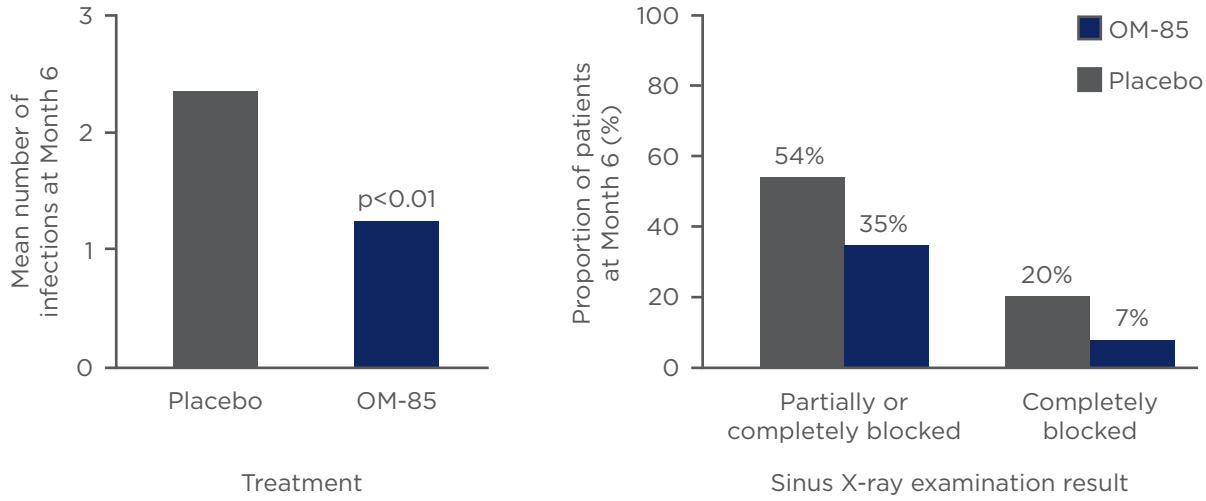

Figure 3: Effect of OM-85 versus placebo in adult patients with chronic purulent sinusitis.[26]

OM-85 prophylaxis prevented 1.52 infections/month, saving €67.83 in direct costs for a child with recurrent episodes. Direct cost savings of between €6.28 and €303.64 were achieved for each individual receiving prophylaxis. The authors concluded that OM-85 prophylaxis is economically profitable if more than 0.15 infections are prevented, and if direct costs of care for an acute infection are greater than €4.78.[29]

In a recent study carried out in China, the cost-effectiveness of OM-85 was assessed in a mixed population of adult patients with CRS or chronic bronchitis. Treatment with OM-85 reduced the cost of CRS exacerbations by 40% compared with treatment with placebo.[30] These data are in agreement with a number of other studies carried out in both adults and children with various pathological conditions, including chronic obstructive pulmonary disease, chronic bronchitis, and URTI, which demonstrate cost savings with OM-85 over both 6 and 12-month study periods.[31-33]

A CASE STUDY OF OM-85 FOR CRS IN ADULTS

A 36-year-old male patient from Buenos Aires, Argentina, presented with recurrent tonsillitis and recurrent nasal sinus congestion. Despite multiple therapies and good resolution of each acute episode, there had been no improvement in recurrence. The patient had persistent episodes of rhinosinusitis and tonsillitis over many years, with up to five episodes/year. In the last 3 years, recurrences had been more frequent and polysymptomatic with increased symptom severity, including bouts of intense headache and persistence of purulent, foul-smelling anterior and posterior rhinorrhoea.

There was lifelong evidence of resistance in the airway, including mouth-breathing, cyclic nasal ventilatory insufficiency, and recurrent congestion. During childhood, a tonsillectomy was prescribed but not carried out. A nasosinusal endoscopic surgery plus septoplasty was performed in 2011. In 2013, he required hospitalisation for intravenous therapy with a left peritonsillar abscess. In summary, this was a patient with symptomatic pathology evolution since the early years of life, evolving throughout and recently worsening.

Following endoscopic examination and imaging (computed tomography and magnetic resonance imaging), and laboratory tests (erythrocyte sedimentation rate, C-reactive protein, IgG/A/M/E, secretory IgA, thyroid function tests, vitamin D, antinuclear antibody test, skin prick test), the patient was diagnosed with an IgA deficiency (IgA <15 mg/dL; secretory IgA <5 mg/dL) with no evidence of atopy. The patient received OM-85 therapy (10 days/month for 3 consecutive months), and showed significant improvement of nasal ventilatory function and posterior rhinorrhoea, no more headaches, and no new episodes of tonsillitis.

CONCLUSION

RTIs are a significant burden in terms of quality of life due to symptoms and recurrence in both children and adults. In addition, repeated infections and related complications are a burden on

the healthcare system. The immunomodulator OM-85 demonstrates efficacy in reducing recurrent infections and is cost-effective in both children and adults.

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RESPIRATORY TRACT INFECTIONS IN PAEDIATRIC PATIENTS: PREVENTION OF RECURRENCE AND BEYOND

A narrative summary of selected presentations given at the second Encuentro Latinoamericano de Infecciones Respiratorias Recurrentes (ELAIR), an educational summit held in Buenos Aires, Argentina, 4th–5th July 2015

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ABSTRACT

This educational summit, supported by an independent grant from OM/Vifor Pharma, brought together physicians specialising in pulmonary medicine, otolaryngology, surgery, immunology, and paediatrics. Delegates from the USA, Europe, and Latin America met and discussed the current unmet needs of patients suffering respiratory tract infections. The meeting included plenary lectures, workshops, and interactive sessions, allowing delegates and presenters to debate the most pressing local and international issues in the field.

INTRODUCTION

Respiratory tract infections (RTIs) are a major burden in the paediatric population. RTIs are more frequent in children <5 years of age and affect 50% of patients in a given year. In children <1 year of age, 60% will experience an RTI each year.[1] Lower respiratory tract infections (LRTIs) are also common in children, as are their associated complications, including bronchiolitis/bronchitis, pneumonia, and recurrent wheeze/asthma. In addition, less common but serious conditions such as bronchiectasis and post-infectious bronchiolitis obliterans may result from LRTIs in the paediatric population.

Bronchiolitis and bronchitis, essentially inflammation of the bronchioles or bronchial tube portions of the LRT, are common in childhood and have many causal agents. Human rhinovirus (hRV) is associated with 73% of respiratory infections during the first year of life in otherwise healthy children.[2] Despite being frequently considered as primarily upper respiratory tract pathogens, hRV serotypes are now recognised as important pathogens in many cases of bronchiolitis.[3] Furthermore, hRV may be associated with a wide range of symptom severity and is also the most common cause of mild-to-moderate wheezing symptoms in high-risk infants, as well as being a significant pathogen in severe infections.[4] Respiratory syncytial virus (RSV) is the second most common upper respiratory tract pathogen detected during the first year of life (11%) in otherwise healthy children.[2] The prevalence of

RSV increases in parallel with the RTI symptom severity.[4] RSV is a significant contributor to severe infections in infants at high risk of developing wheezing and asthma, is the most common pathogen in LRTI in premature babies (particularly in cases of severe infection), and is the most common cause of bronchiolitis in general.[3-5]

Pneumonia is a frequent disease in early life and is defined as inflammation of the lung alveoli caused by infectious disease. A prospective study in the USA revealed community-acquired pneumonia requiring hospitalisation to be relatively common, affecting around 45% of children aged <2 years and 25% of children aged 2–4 years, with the incidence decreasing steadily with age. Most cases were viral, with RSV most commonly detected followed by hRV. The incidence of bacterial infections did, however, increase with age.[6]

Wheezing is a common symptom of LRTIs such as bronchiolitis and pneumonia. Almost half (47%) of all children in Latin America experience one bout of wheezing during the first year of life, with 21% suffering from recurrent wheezing (≥3 bouts).[7] There are three main wheezing aetiologies during childhood: transient wheezing, virus-associated wheezing, and atopic wheezing.[8,9] Early transient wheezing may affect any child and usually resolves spontaneously or becomes less frequent after 3 years of age. The main risk factors for transient wheezing are premature birth and parental smoking, and the condition does not appear to increase the risk of developing asthma. Virus-associated wheezing is episodic, with symptoms concomitant to RTI but otherwise absent. Patients display bronchial hyperreactivity, with wheezing following viral bronchitis and no history of atopy. Children with virus-associated wheezing respond well to bronchodilators. Atopic wheezing is characterised by intermittent symptoms related to sensitisation by, and exposure to, aerial allergens. Patients display high IgE levels, with positive skin sensitivity and pulmonary function tests also commonly seen.

A recent report by the Argentinean Pediatrics Society suggests that wheezing incidents occurred in almost half of children during the first 6 years of life, with 20% experiencing early transient wheezing, 14% persistent wheezing, and 15% late-onset wheezing.[10] Wheezing bouts during childhood may be associated with the development of asthma, a serious condition with 250,000 exacerbation-related deaths per year worldwide.[11] Many of these deaths are avoidable and caused by misdiagnosis, treatment errors, or patients failing to seek medical attention, with the majority occurring in patients with advanced disease.

RISK FACTORS FOR PAEDIATRIC INFECTION AND ASTHMA

Anatomical, immunological, and societal factors all contribute to the higher frequency of RTI in children. Anatomical risk factors include differences in growth as well as tubaric dysfunction, while functional immaturity of the immune system is the major immunological risk factor in the paediatric population (described in more detail below). The majority of children in Latin American countries, such as Brazil (80%), and around the world now attend day-care centres, which alters the pattern of early-life infections. Rates of 6–7 infections per year are common in children, particularly if they go to day-care centres or have siblings who attend school, and the tools available to physicians are relatively limited.

Viral LRTIs and sensitisation to allergens are important risk factors for developing asthma. There is a strong body of evidence for hRV-associated asthma risk, and data also suggest an RSV-associated risk. Children with dual viral/allergen exposure exhibit the greatest risk of developing asthma, suggesting a synergistic relationship. In children <3 years of age, 95% of asthma exacerbations are associated with viral infections; in school-age children, 85% of exacerbations are associated with viruses, and in adults the figure is 80%. In this regard, asthma can be understood as an allergic disease driven by exaggerated responses to viral infections.

FUNCTIONAL IMMATURITY IN THE IMMUNE SYSTEM AND INCREASED RISK OF INFECTION AND ALLERGY

Functional immaturity of the immune system is a major driver of infection and allergy in children. *In utero*, the fetal immune system is in a quiescent state favouring the Th2 cytokine interleukin (IL)-4, with the Th1 response limited in order to protect the placenta from the toxic effects of interferon gamma (INFγ). Th2 continues to predominate during the early neonatal period via mechanisms such as temporary hypermethylation of the INFγ promoter in Th cells. Conversely, IL-17, which acts to protect the early neonatal immune system and

placenta, reaches a peak in the neonatal period before declining with age. Th2 maturation is evident from the fourth month of life, while Th1 function and INFγ production are delayed until 18 months. INFγ concentrations then gradually increase with age until reaching adult levels, although lower INFγ levels are common in patients with a history of atopy and recurrent respiratory tract infections (rRTIs). The Th1/Th2 imbalance during the neonatal period may predispose neonates to infection and allergic disease.[12]

A number of factors other than Th1/Th2 imbalance contribute to immune system immaturity continuing beyond the neonatal period into the early years of life. The activation of $CD14^+$ monocytes involved in innate immunity varies with age, with different cytokines (IL-12, IL-6, IL-10, IL-18, IL-3, and tumour necrosis factor alpha [TNFα]) produced in response to stimulation by both INFγ and bacterial lipopolysaccharide. Furthermore, dendritic cell (DC) numbers are inversely proportional to the frequency of RTIs during the first year of life, suggesting that fewer cells increase susceptibility to infection. In addition to circulating DCs, mucosa-associated DCs and the T cells that regulate their activity also show a deficiency in early life.[12]

In summary, susceptibility to infections is at a maximum during early life, with the risk of atopy running in parallel. Immune system deficiencies are widespread and affect all aspects of immune function. The Th1/Th2 imbalance, attenuated monocyte function, and deficiencies in circulating and mucosal DC populations all contribute to immune system immaturity. In addition, there is a decrease in the regulatory T cells that control the activation of mucosal DCs.

IMMUNOMODULATOR PROPHYLAXIS IN THE PAEDIATRIC POPULATION

The increased risk of infection during childhood predisposes children to complications, including allergic conditions such as asthma. In addition, functional immaturity of the immune system, which is in itself a risk factor for increased infection, directly predisposes children to allergic disease. These interrelated factors make immunomodulation an attractive therapeutic option in children due to both infection prophylaxis and immunomodulatory effects, which may rebalance the immune system away from chronic conditions such as asthma or allergy.

OM-85 is a bacterial lysate therapy composed of immunomodulatory fractions from 21 of the most common strains of respiratory pathogen. Despite solely being composed of bacterial extracts, OM-85 has been shown to increase the concentration of the anti-viral cytokine INFα via the activation of DCs. In addition, increases in IL-6 and B-cell activating factor offer a further mechanism through which OM-85 may prevent a broad spectrum of viral and bacterial infections via the production of polyclonal antibodies.[13] Indeed, OM-85 was shown to reduce mortality in mice infected with both *Salmonella typhimurium*, a bacterial strain not used in the OM-85 manufacturing process, and the H1N1 strain of viral influenza, in a recent *in vivo* study.[14] Furthermore, *in vivo* efficacy against viral/bacterial co-infection (H1N1 followed by *Streptococcus pneumoniae* or *Klebsiella pneumoniae*) was shown in mice, with associated increases in $CD8^+$ cytotoxic T cell activity and activation of B cells. The production of polyclonal antibodies was also confirmed, including the production of influenza-specific IgA and RSV specific IgG in the airways of naïve mice,[15] confirming a mechanism via which OM-85 may protect infants from these key drivers of infection-related respiratory complications. These data illustrate mechanistic pathways through which OM-85 may reduce both viral and bacterial infections in the paediatric population.

The data described above offer a rationale for prophylaxis against a broad range of infection types and the consequent possibility of reducing resultant complications such as asthma. In addition, the immunomodulatory effects of OM-85 may directly address aspects of immune system immaturity that predispose to allergy. OM-85 increases IgG2b, a Th1-related immunoglobulin isotype, in neonatal rats and upregulates INFγ while downregulating Th2-specific IL-4 in a mouse model of asthma.[16,17] OM-85-induced reductions in Th2-related IgE, IgG1, and IL-4 have also been demonstrated in a mouse model of allergic rhinitis.[18] All these changes are indicative of a potential to rebalance the Th2 bias found in the neonatal immune system and in allergic conditions. Similar changes have been confirmed in humans, where OM-85 increased INFγ (Th1) and reduced IL-4 (Th2) in addition to increasing the anti-inflammatory and pro-Th1 cytokine IL-10.[19]

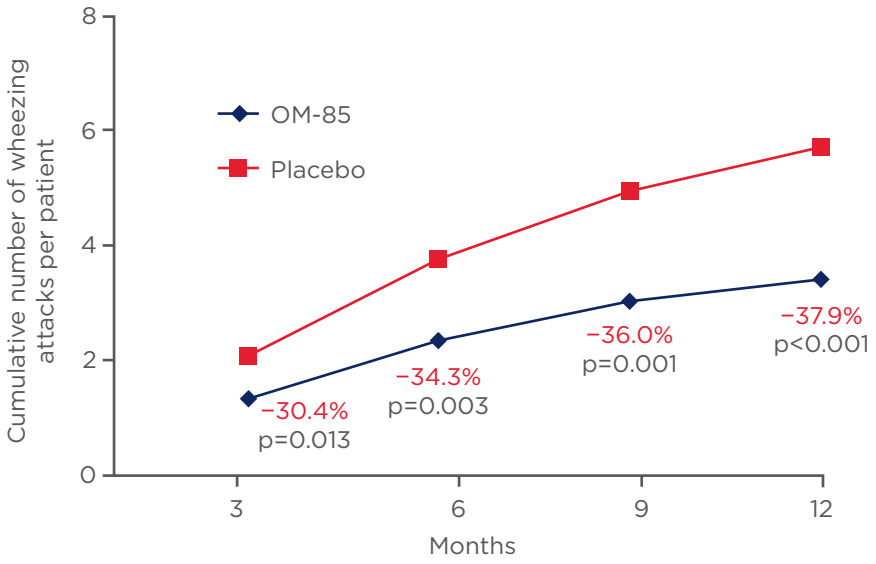

Figure 1: Cumulative number of wheezing attacks in children treated with OM-85 versus placebo.[26]

OM-85 IMMUNOMODULATION FOR PAEDIATRIC RESPIRATORY TRACT INFECTIONS

Acute otitis media (AOM), tonsillopharyngitis, and rhinosinusitis are three of the most common forms of RTI affecting children. OM-85 has demonstrated efficacy in reducing recurrent upper respiratory tract infection (rURTI) and recurrent AOM in children in both 6 and 12-month randomised trials. Prophylaxis with OM-85 resulted in significant reductions in infections over both the 6-month (68%, p<0.001) and 12-month (75%, p<0.01) time periods, and reduced antibiotic use in both trials.[20,21] In a 6-month randomised trial in children with recurrent tonsillitis, the majority of participants (76%) treated with OM-85 experienced a reduction in the frequency of recurrence. In addition, there was a dramatic reduction (68%) in the need for surgery in the 3-month responder group during the follow-up period.[22] In a 6-month randomised trial conducted in children with chronic rhinosinusitis, both the incidence and the duration of recurrences were reduced (−65% [p<0.05] and −73% [p<0.01], respectively) in conjunction with a significant reduction in antibiotic use.

Meta-analyses and systematic reviews offer the highest quality evidence available for physicians considering the efficacy of therapeutic interventions. A recent systematic review assessed OM-85 in paediatric rRTIs as a whole. Pooled data from 8 well-designed and well-conducted studies including 851 participants were analysed; mean age was 6.3 and 6.4 years for OM-85 and placebo-treated patients, respectively. There were 25.2% fewer RTIs in the OM-85-treated group compared with the placebo group, and the effect was greater in patients who were at increased risk of recurrent infection.[23] Similar results were found in a systematic review of four meta-analyses, which found that bacterial lysate therapy reduced recurrences of RTIs and the need for antibiotics while producing no significant adverse effects.[24] Finally, in a recent Cochrane Review on the efficacy of immunomodulators for the prevention of acute RTI in children with a history of rRTI, pooled data (N=852) revealed a highly significant 35% reduction (95% confidence interval: −49.46 to −22.35) in the prevalence of acute RTI.[25]

OM-85 IMMUNOMODULATION FOR PAEDIATRIC WHEEZING AND ASTHMA

Razi and colleagues[26] assessed the efficacy of OM-85 in a randomised, placebo-controlled study in preschool children aged 1–6 years with recurrent wheezing. Although participants were not on asthma medication at the start of the study, they all began taking it during the study, suggesting that the data may be extrapolated to patients with asthma and persistent wheezing. OM-85 treatment reduced wheezing attacks by 2.18 per patient/year and by 38% overall (p<0.001) (Figure 1). OM-85 also achieved a reduction in the incidence of RTIs by 31% (p<0.001). A reduction in the duration of

wheezing was also noted, as were decreases in airway inflammation and structural alterations.

Multiple linear regression analyses revealed the main difference between the two groups was a reduction in the number of acute RTIs. Cases of nasopharyngitis were reduced by an extent (38%) similar to the reduction in wheezing events and overall RTIs. OM-85 was well tolerated and the authors concluded that treatment achieved a clinically significant reduction in recurrent virus-induced wheezing in preschool children and may be a useful complementary therapy alongside current treatments for wheezing.[26]

A recent study investigated the effect of OM-85 on human beta-defensin-1 (hβD-1) and IgG levels in children with asthma and rRTI. hβD-1 is found in lung bronchi mucus and acts as an antimicrobial agent as part of the innate immune system. The study was a double-blind, placebo-controlled trial in children with asthma and rRTI (N=62). There was a significant clinical benefit in terms of the frequency of infections at both 6 and 12 months ($p<0.05$) and levels of hβD-1, IgA, and IgG were significantly increased ($p<0.05$).[27] As previously noted, OM-85 has been shown to modulate the cytokine profile in children with asthma.[19] In this same study, children treated with OM-85 in conjunction with an inhaled steroid versus steroid therapy alone showed a reduced incidence of asthma attacks and RTIs, as well as a reduction in antibiotic use.[19] The above data suggest that OM-85 has efficacy both in children at risk of developing asthma and in those already living with the condition.

OM-85 IMMUNOMODULATION IN PAEDIATRIC PATIENTS WITH IMMUNODEFICIENCIES

Data from the registry of the Latin American Group for Primary Immunodeficiency Diseases for the year 2007 showed that more than half of the immunodeficiencies in the region were predominantly antibody-related (Figure 2), similar to the pattern seen worldwide. More than half (55%) of these antibody deficiencies were of the heavy-chain class or isotype, which includes IgG subclass and IgA deficiencies.[28]

IgG subclass deficiencies are defined as a selective and persistent reduction in ≥1 IgG subclass, with normal total IgG concentration and normal B cell counts.[29] Patients are frequently asymptomatic, with a minority showing poor antibody response to specific antigens and recurrent viral and bacterial infections.[30] The efficacy and safety of OM-85 in children aged 3–6 years with IgG subclass deficiency and rURTI was tested in a prospective, randomised, placebo-controlled trial. Despite conflicting data from other human and animal studies, there was no significant change in the IgG subclass levels following therapy, possibly due to drug dose or species differences.[27,31-34] From a clinical perspective, however, OM-85-treated patients showed an almost 50% reduction in the number of acute RTIs compared with placebo-treated patients (2.8 versus 5.2; $p<0.001$). Adverse events were mild and similar in number in both groups.[34]

IgA deficiency with the risk of autoimmunity is the most common primary immune deficiency.

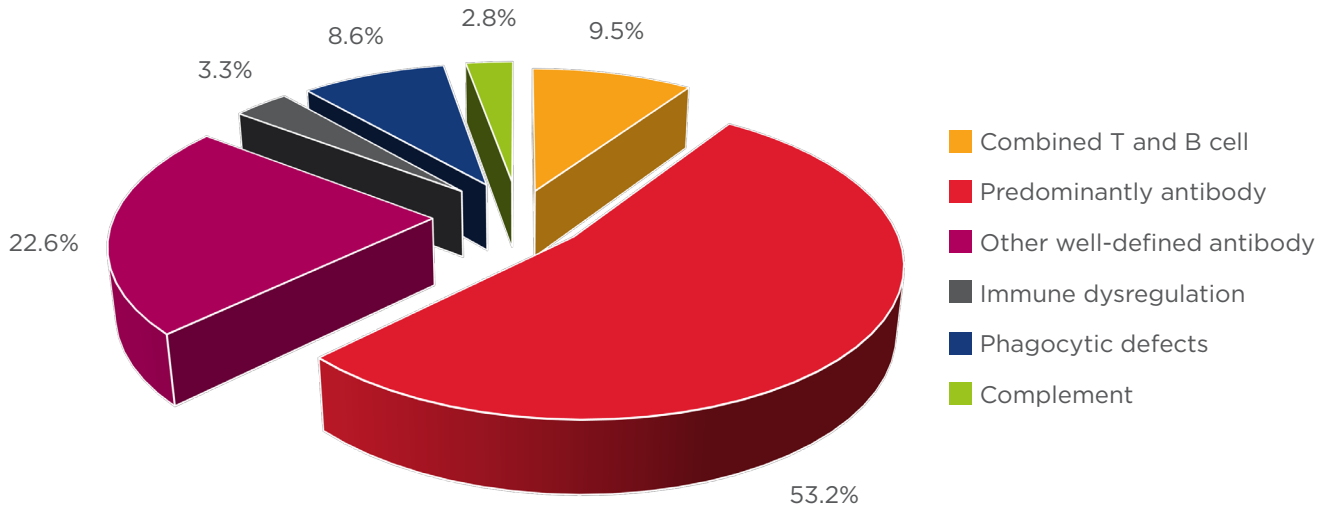

Figure 2: Primary immunodeficiency diseases in Latin America.[28]

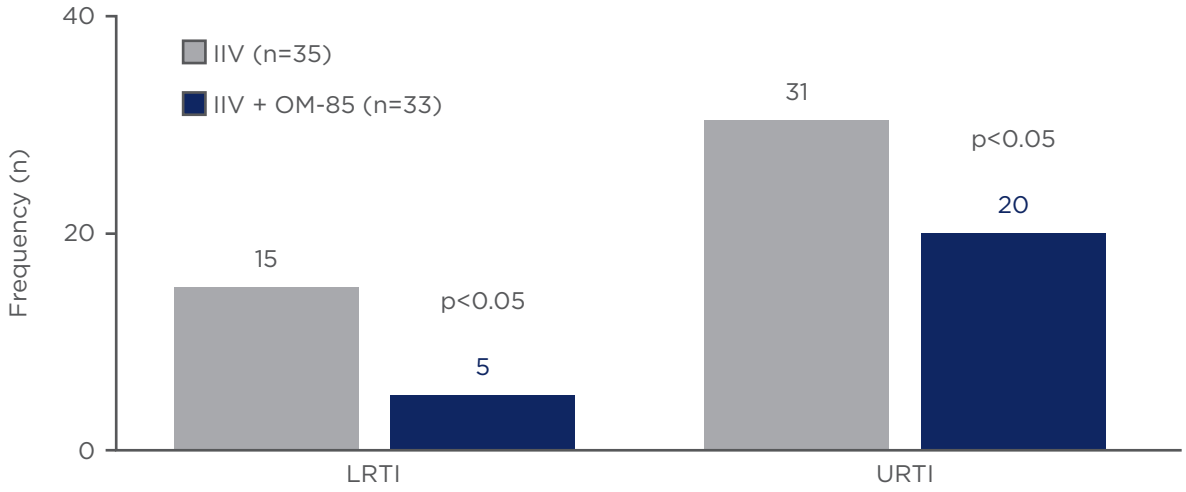

Figure 3: Number of patients suffering a lower respiratory tract infection (LRTI) or upper respiratory tract infection (URTI) following treatment with OM-85 + inactivated influenza vaccine (IIV) versus IIV alone.[36]

Two-thirds of patients are asymptomatic, but IgA deficiency increases the risk of rRTI. Allergic diseases such as rhinitis, asthma, and conjunctivitis, as well as autoimmune conditions such as purpura, arthritis, systemic lupus erythematosus, and vitiligo may also be manifest in these patients.[30] Given the ability of OM-85 to modulate immune responses, and the risk of cross-reactivity with host antigens through molecular mimicry with antigens in the bacterial lysate, the possibility of adverse events in patients at risk of autoimmunity must be considered. Karaca et al.[35] assessed these risks in a placebo-controlled trial of 64 children (aged 4–17 years) with IgA deficiency and rRTI. Over the lengthy follow-up (mean: 4 years) there were no signs of clinical autoimmunity and no differences in the number of infections (mean: 6.2/year). Both groups showed signs of serological autoimmunity, but there were no between-group differences. Overall, the data suggest that patients with an IgA deficiency have a predisposition to develop autoimmunity, but OM-85 did not increase this risk.

COMBINED IMMUNOMODULATION WITH OM-85 AND AN INFLUENZA VACCINE IN THE PAEDIATRIC POPULATION

There are 3–5 million severe cases of influenza causing 250,000–500,000 deaths per year worldwide. High-risk groups include individuals under the age of 5 years or over 50 years, and those with cardiopulmonary disease. Physicians recommend vaccination of at-risk groups in autumn. Three forms of influenza vaccine are currently available: inactivated vaccines are safer but less immunogenic; attenuated vaccines are more immunogenic but are associated with more adverse reactions; while recombinant vaccines combine both safety and immunogenicity but are not currently widely available.

The use of OM-85 as a complementary prophylactic was recently assessed in a prospective, randomised, single-blind study (N=68) comparing an inactivated influenza vaccine (IIV) alone and in combination with OM-85 for the reduction of rRTIs in children aged 2–5 years. Participants had ≥6 practitioner-attended episodes in 1 year and had received an IIV previously. There was a marked reduction in the incidence of both URTIs (−35%) and LRTIs (−67%) in patients treated with combination therapy versus IIV alone (Figure 3). In addition, children who received OM-85 and IIV had a lower mean number of antibiotic courses (−72%) and lower school absenteeism (−52%). IIV-induced humoral immunity was not affected by OM-85 and the combination therapy was well tolerated.[36]

COST-EFFECTIVENESS OF OM-85 IN CHILDREN

A study was carried out to assess the cost-effectiveness of OM-85 in children at risk of rURTIs using data from four randomised clinical trials. Cost savings per family based on one prevention cycle were €107.42 (41%) over 6 months, and €196.05 (31%) over 1 year with two prevention cycles. Societal savings were €231.26 (45%) over 6 months and €422.02 (34%) over 1 year, and savings

to the healthcare system were €48.52/patient over 6 months. The data showed that one cycle of therapy with OM-85 prevented a mean of 1.60 episodes/child. The authors concluded that OM-85 was a cost-effective option for the treatment of rURTIs in children.[37]

A REAL-WORLD CASE STUDY OF PAEDIATRIC RECURRENT RESPIRATORY INFECTION

A 12-month-old male infant presented with a history of three episodes of LRTI with concurrent wheeze and family history of mild asthma. Born prematurely at 29 weeks, weighing 1,220 g, the patient required mechanical ventilation for 10 days and supplemental oxygen for 35 days. He was discharged in September and returned to the hospital with severe bronchiolitis in December. The patient suffered two further wheezing episodes in March and April and was diagnosed with respiratory RSV infection.

Treatment options included: RSV monoclonal antibody (palivizumab); inhaled steroids; montelukast; environmental prophylaxis such as good hand hygiene, limiting contact with other children and adults with RTIs, avoidance of tobacco smoke, breastfeeding, and removal from day care; and OM-85 prophylaxis. Data suggest that palivizumab reduces the number of wheezing incidents during the first year of life in preterm infants.[38] Experts suggest that inhaled steroids should not be used in children <2 years of age due to the scant evidence of efficacy and risk of interference with lung development. In comparison, OM-85 is a well-tolerated option in the paediatric population and has shown efficacy in reducing rRTI in high-risk populations. Combined treatment using palivizumab and OM-85 may be a viable therapeutic option for the patient.

CONCLUSION

Children are at high risk of RTIs and associated complications due to changes in child care and anatomical changes associated with growth. In addition, the functionally immature immune system predisposes children to both RTIs and allergic conditions. The immunomodulatory properties of the immunomodulator OM-85 act to both reduce the risk of infection and rebalance the functional Th2 bias that predisposes children to allergy. OM-85 has shown efficacy in reducing recurrent infection in the overall paediatric population and in special paediatric populations without increasing the risk of autoimmunity in high-risk patient groups.

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THE KEY ROLE OF PREVENTATIVE STRATEGIES IN CHRONIC LUNG DISEASES: CHRONIC BRONCHITIS AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

A narrative summary of selected presentations given at the second Encuentro Latinoamericano de Infecciones Respiratorias Recurrentes (ELAIR), an educational summit held in Buenos Aires, Argentina, 4th–5th July 2015

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ABSTRACT

This educational summit, supported by an independent grant from OM/Vifor Pharma, brought together physicians specialising in pulmonary medicine, otolaryngology, surgery, immunology, and paediatrics. Delegates from the USA, Europe, and Latin America met and discussed the current unmet needs of patients suffering respiratory tract infections (RTIs). The meeting included plenary lectures, workshops, and interactive sessions, allowing delegates and presenters to debate the most pressing local and international issues in the field.

INTRODUCTION

The definition of chronic obstructive pulmonary disease (COPD) has shifted with the increased understanding of contributory factors and disease evolution. Previously classified as an irreversible airway obstruction, COPD is now understood to be partially reversible with treatment, as recognised in the most recent GOLD definition: a common preventable and treatable disease, characterised by *persistent airflow limitation*. COPD is usually a progressive condition characterised by chronic inflammation. The chronic inflammation is driven by a vicious cycle of epithelial injury, comorbid infections, exacerbations, and impaired lung defences, which contribute to the severity of the condition. Diagnostic features include dyspnoea, chronic cough, and sputum production as well as a history of exposure to risk factors such as smoking. COPD is diagnosed by spirometry showing persistent airflow limitation (post-bronchodilator FEV_1/FVC <0.70).[1]

BURDEN OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND CHRONIC BRONCHITIS

Approximately 15 million Americans have been diagnosed with COPD, and data suggest that up to 63% of people with COPD may currently be undiagnosed.[2,3] Diagnosis may not occur until the disease progresses due to a lack of serious symptoms, poor recognition of clinical symptoms in the early phase, insufficient use of spirometry, or patient reticence in seeking medical assistance.[4]

The epidemiology of COPD may be changing, with younger patients, who are currently

underdiagnosed, likely to constitute a greater proportion of the patient population in the future. Indeed, the patient population has already altered, with COPD mortality in women eclipsing that in men in the USA at the turn of the 21st century. COPD is the third leading cause of death in the USA and is predicted to be the third leading cause worldwide by 2020, with lower RTIs in fourth position.[5-7] COPD-related morbidity is a major economic and societal burden: 41% of patients have visited their doctor due to symptoms within the last year and 13% have had hospital or emergency department visits. In addition, shortness of breath is reported to affect quality of life (QoL) in 58% of patients.[1,2] In the USA, direct and indirect costs, 75% of which are due to exacerbations, amount to approximately $30 billion and $20 billion per annum, respectively.[2,4]

Chronic bronchitis (CB) is a common COPD comorbidity. Excessive mucus accumulation is a key diagnostic feature of CB; indeed, pulmonary specialists now talk in terms of excess mucus in COPD rather than CB. Mechanisms contributing to excessive mucus accumulation can be grouped into those that contribute to increased production (inflammatory cells, oxidative stress, and viral or bacterial infection) and those that contribute to decreased elimination (poor ciliary clearance, airway occlusion, reduced peak expiratory flow, and respiratory muscle weakness). The prevalence of CB in adults ranges from 3–22%. In the subpopulation of patients with COPD, prevalence of CB is 27–35%. Smoking remains the major risk factor, with biomass exposure, air pollution, and gastro-oesophageal reflux disease also contributing to the risk of developing the condition.[8] Historically, CB has been viewed as a relatively benign condition. However, assessment of the disease burden reveals a different clinical reality. In those without COPD, CB is associated with an accelerated decline in lung function (1.7–22.8 mL/year), particularly in women, and an increased risk of developing COPD (1.85 to 2.88-fold increase), particularly in older patients. In patients with COPD, CB is associated with poor health status, increased exacerbations, and hospitalisations (2 to 4-fold increase), and increased respiratory and all-cause mortality.[9-13]

EXACERBATIONS, INFECTIONS, AND CHRONIC INFLAMMATION

Exacerbations are a diffuse phenomenon broadly defined as "an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication".[1] Other conditions such as pneumonia and congestive heart failure should be excluded before diagnosing an exacerbation.[14-16]

Exacerbations contribute to increased risk of death, accelerated decline in lung function, and reduced QoL.[17-19] In addition, exacerbations directly result in frequent visits to physicians' offices (13 million/year in the USA) and emergency rooms, leading to numerous hospitalisations and absenteeism.[20] Exacerbations also account for a substantial percentage of COPD treatment costs.[21] The importance of exacerbations in COPD progression is highlighted by their current prominence as a drug target.

The majority of exacerbations are related to infections (70–80%) from either bacterial (50–60%), viral (30–50%), or atypical (2–5%) organisms. Non-infectious causes account for 10% of exacerbations and 30% have an unknown aetiology.[22-27] With the increased use of sensitive techniques such as polymerase chain reaction (PCR), it is likely that many exacerbations of unknown aetiology will be reclassified as infectious. Microbes known to have a significant relationship with acute exacerbations include *Haemophilus influenzae* (20–30%), *Streptococcus pneumoniae* (10–15%), and *Moraxella catarrhalis* (10–15%). In more severe disease, *Pseudomonas aeruginosa* (5–10%) is an important driver of exacerbations. Recent work suggests that, despite previous assumptions, *H. haemolyticus* and *H. parainfluenzae* do not have a role in exacerbations. The role of *Enterobacteriaceae* spp. and *Staphylococcus aureus* is currently unclear, although they are known to be important in pneumonia.[28]

The mechanism of bacterial exacerbations in COPD is complex. Previous theories were based around a change in bacterial load overwhelming the immune system. However, evidence suggests that exacerbations are in fact driven by the acquisition of new strains of bacteria from the environment. Inflammatory defence mechanisms then cause the increased symptoms that characterise an exacerbation. The next stage is the development of strain-specific adaptive immunity, which eliminates the infecting strain but does not protect against subsequent acquisition of new bacterial strains, leaving the door open to subsequent infection and acute exacerbation events.[16,28-33]

The related 'Goldilocks hypothesis' postulates that dysregulation in the adaptive immune response to exacerbations is key to driving progression. Dysregulation may result in either too little a response, failing to clear the infection resulting in prolonged symptoms, or too great a response, resulting in prolonged or excessive inflammation.[34]

Acute infections and subsequent exacerbations are not isolated disease processes in COPD, rather acute infection acts as a comorbidity in COPD. Key to this concept is an understanding that comorbid conditions, rather than merely existing simultaneously, have a synergistic relationship with one another. Acute infection as a comorbid condition increases inflammation and obstruction, while chronic inflammation increases susceptibility to infection and the severity of the subsequent consequences.[35] Hence, acute exacerbations and chronic processes in COPD act as two intersecting cycles, at the centre of which is impaired lung defence (Figure 1). Much of this impaired defence is due to dysfunction in the innate immune system, making this a central target for therapies that can improve both the chronic and acute processes driving progressive loss of function in COPD.[36]

COLONISATION VERSUS CHRONIC INFECTION

In addition to acute bacterial infection driving exacerbations and the acute cycle in COPD, bacteria also play a key role in the chronic inflammatory cycle of COPD (Figure 1). New molecular techniques, principally 16S rRNA amplification, have led to the identification of a complex microbial ecosystem colonising the lungs of healthy individuals (the lung microbiome). The lungs of COPD patients exhibit decreased diversity, with significant heterogeneity in species at different lung locations.[37] Following the culturing of bacteria from a sputum sample, a differential diagnosis between bacterial colonisation and an acute infection was traditionally made on the basis of the presence or absence of symptoms. However, the true difference between colonisation and infection is the absence of both an immune response and damage to the host by colonising bacteria.[38]

Several lines of evidence suggest that some bacteria present in stable COPD may represent infection rather than colonisation. Firstly, using bronchoalveolar lavage and traditional culture techniques, a greater proportion of ex-smokers with COPD (35%) had $\geq 10^2$/mL potentially pathogenic microorganisms (PPMs) than ex-smokers without COPD (0%) and healthy non-smokers (6.7%) (p=0.003). Those COPD patients with PPMs showed increased indices of airway inflammation, including higher numbers of neutrophils, increased levels of interleukin (IL)-8, and an increased level of MMP-9, a metalloproteinase involved in extracellular matrix degradation. These data suggest that both an immune response and cell damage are occurring, which is indicative of infection. Furthermore, similar but larger increases in neutrophils, IL-8, and MMPs are found during exacerbations.[32] Another line of evidence for infection over colonisation is immune system reorganisation. This includes the formation of germinal centres and lymphoid follicles, which are increased in number and dimension in severe COPD. This is likely to occur as a response to infection, although autoimmunity may also have a role.[39]

Further data supporting the key role of bacteria in COPD comes from studies conducted in mice. Exposure to tobacco smoke alone resulted in an emphysema-like phenotype, while exposure in combination with *H. influenzae* resulted in a COPD-like phenotype with lymphoid follicles, mucus hypersecretion, and airway changes.[40,41] In addition, bronchiectasis, bronchial, and bronchiolar dilation related to infection appears to be common in patients with moderate-to-severe COPD (58%), and patients with bronchiectasis have more severe COPD, higher concentrations of PPMs, and a greater likelihood of being hospitalised.[42,43] These data suggest that bronchiectasis may be a diagnostic feature of patients with COPD strongly driven by chronic infection.

A recently published prospective cohort study (N=41) collected symptoms daily using the Breathlessness, Cough, and Sputum Scale (BCSS) for 4 years and plotted symptom scores against colonisation, determined by biweekly culturing and PCR.[44,45] As expected, exacerbations were associated with higher BCSS scores; however, colonisation was also associated with a significantly higher BCSS score compared with no colonisation. The difference was 0.7, indicative of a moderate and clinically significant effect. In the same study, inflammation measured by sputum IL-8 followed the same pattern, peaking during exacerbations with elevated levels during colonisation.[45] These data further illustrate that chronic infection in COPD patients increases both vulnerability to exacerbations and also daily symptoms.

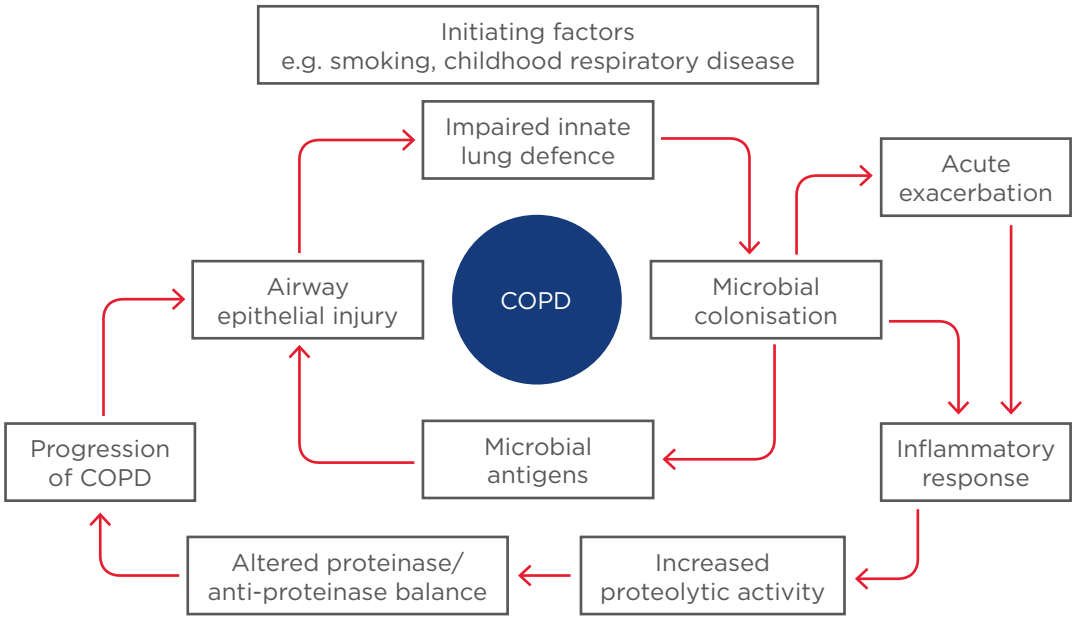

Figure 1: Vicious cycle of infection and inflammation in COPD.[36]
COPD: chronic obstructive pulmonary disease.

To summarise, evidence of immune system activation, increased inflammatory cytokines, and increased symptoms associated with the presence of an increased number of bacteria in stable COPD suggests that these bacteria represent an infection rather than a colonisation in a subset of COPD patients. The presence of chronic infection and associated inflammation is likely to drive the progression of COPD as previously indicated (Figure 1).

HIGH-RISK PATIENT PHENOTYPES AND UNMET NEED

There is currently significant unmet need in exacerbation management. Standard management of exacerbations involves treatment with bronchodilators and steroids, as well as antibiotics in cases of increased sputum volume and purulence. In a study of prednisone added to antibiotics, the relapse rate was 26% within 1 month in the steroid-treated group.[46] Similarly, in a study from the Netherlands in patients treated with doxycycline and corticosteroids, the treatment failure rate at 1 month was approximately 50%, with a quarter of patients going on to relapse.[47] Even in a specialised tertiary care population in which close to 80% of patients were treated with long-acting bronchodilators and inhaled steroids, approximately 47% of GOLD 4 patients had ≥2 exacerbations/year, with 33% of GOLD 3 and 22% of GOLD 2 patients also having frequent exacerbations.[48]

The frequent-exacerbator phenotype (≥2 exacerbations/year) has been suggested as a patient group that should be targeted for prophylaxis. In addition, patients who have experienced ≥1 hospitalisation due to exacerbation (7%, 18%, and 33% of GOLD 2, 3, and 4 patients, respectively) may also represent a viable COPD phenotype for prophylaxis. However, given the high costs of even a single hospitalisation, earlier preventative therapy may be desirable.[48]

Prevention strategies can be split into those that are infection-specific and those that are not. Non-specific strategies include: smoking cessation (prophylactic after 10 years); anti-inflammatory drugs, including inhaled steroids and phosphodiesterase 4 inhibitors; bronchodilators; mucolytics/anti-oxidants; specific anti-inflammatory drugs, which are in development but yet to show efficacy (anti-IL-1 receptor and Nrf2 agonists); and pulmonary rehabilitation, which has shown efficacy in reducing exacerbations. Infection-specific strategies include: vaccines; oral bacterial lysates; and prophylactic antibiotics.

INFECTION-SPECIFIC PROPHYLACTIC STRATEGIES FOR COPD AND CHRONIC BRONCHITIS: A FOCUS ON VACCINES AND IMMUNOMODULATORS

Different stages of the immune response appear to be important at different stages of COPD. The innate immune response is important in the very early stages of COPD (formerly GOLD 0 and GOLD 1) and continues to play a role throughout the pathological process. Remodelling of the lung immune tissue begins in GOLD 2, with the adaptive immune response becoming important in the later stages (GOLD 3 and 4).[39] Both immune dysregulation and infections are key drivers of exacerbations in COPD, making treatment with both immunomodulators and vaccines useful prophylactic strategies. The efficacy of influenza vaccines in reducing serious COPD-related illness is noted in the most recent GOLD guidelines, and the pneumococcal polysaccharide vaccine is now recommended for COPD patients ≥65 years of age and for COPD patients <65 years of age with FEV_1 <40% of predicted.[1]

OM-85 is currently the most studied immunomodulator for the prevention of COPD exacerbations and recurrent respiratory infections. OM-85 is a lysate of 21 strains of respiratory bacteria, encompassing the main strains involved in respiratory infections. As noted above, dysfunction in the innate immune system has a major role in the impaired lung defence at the heart of the vicious cycle of COPD. OM-85 has been shown to stimulate monocyte and macrophage activity, promote dendritic cell (DC) maturation and activity, and stimulate the activity of neutrophils and natural killer cells.[49-54]

OM-85 has been shown to elicit a mild and dose-dependent activation of DCs from healthy donors and those with COPD *in vitro*, with the highest doses resulting in a similar response to that caused by lipopolysaccharide. The activation of DCs by OM-85 produces a pre-alert phenotype, essentially creating a primed immune system with barriers raised against infection.[54,55] Moreover, OM-85 has been shown to increase the release of the protective cytokine IL-10 from the DCs of both healthy donors and COPD patients (Figure 2).

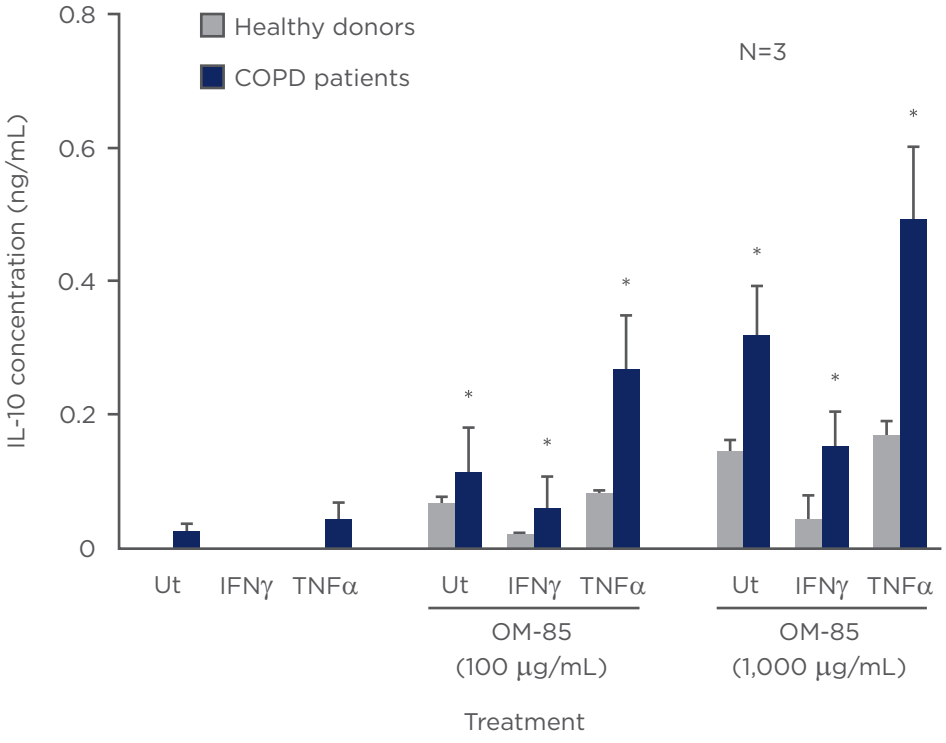

Figure 2: Release of IL-10 from peripheral blood mononuclear cells in COPD patients and healthy donors following treatment with OM-85.[54]

*p<0.05, COPD patients versus similarly treated healthy donors.

COPD: chronic obstructive pulmonary disease; IFNγ: interferon gamma; IL-10: interleukin 10; TNFα: tumour necrosis factor alpha; Ut: untreated.

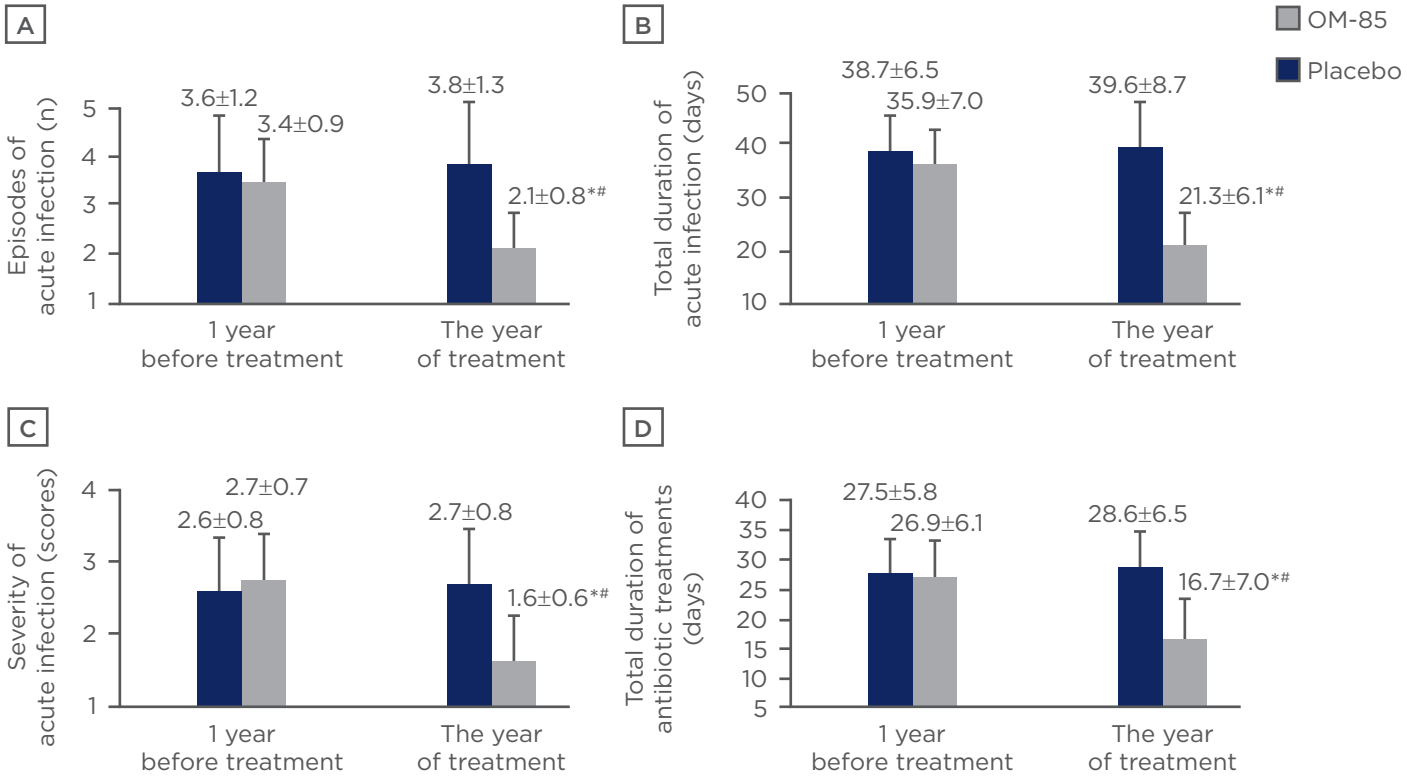

Figure 3: Number (A), duration (B), and severity (C) of acute infections, and total days of antibiotic treatment (D) in OM-85-treated and placebo-treated patients.[64]

*p<0.01 versus placebo; #p<0.01 versus before treatment.

This figure is based on a study first published in *Chin Med J.* 2004;117(6):828-34.

IL-10 release was more pronounced under inflammatory experimental conditions (addition of interferon gamma [IFNγ] and tumour necrosis factor alpha [TNFα]), and COPD patients showed a more pronounced OM-85-induced release of IL-10 than healthy donors under all conditions. Therefore, OM-85 may reduce inflammation-related tissue damage in patients with COPD.[54]

The adaptive immune system drives exacerbations and has a major role in advanced stages of COPD, and OM-85 has been shown to modulate adaptive immunity. Treatment with OM-85 preferentially increases serum IgA and increases levels of serum IgG and IgM. Secretory IgA, which is the main immunoglobulin involved in the adaptive response to respiratory infection, is also stimulated by OM-85. Furthermore, OM-85 boosts T and B cell activity: key cellular constituents of the adaptive immune response.[52,53,56-61]

Multiple studies have demonstrated the therapeutic potential of OM-85 in patients with COPD and CB.[62-66] In a 6-month placebo-controlled study in patients with CB or COPD, OM-85 was prescribed for 30 days, followed by three 10-day courses during Months 3, 4, and 5. Acute exacerbations were reduced by 29% at the end of treatment (p<0.05).[65] A 12-month placebo-controlled study in CB and COPD used a different (standard) dosing frequency of 10 days for each of the first 3 months. The number, severity, and duration of exacerbations and the duration of antibiotic use in patients receiving OM-85 was significantly reduced (p<0.01) over the study period compared with the previous year and compared with untreated patients. Cough, sputum, and dyspnoea scores were all significantly lower in patients treated with OM-85 versus placebo (Figure 3).[64]

High-risk patients are an important target population for prophylaxis and OM-85 has been shown to reduce hospitalisation in patients with severe COPD (p<0.05), who are prone to frequent exacerbations.[48,63] In the elderly population with CB, a vulnerable and understudied group, OM-85 reduced the number of RTIs by 28% and exacerbations by 40%.[62]

In a recent double-blind, placebo-controlled trial (N=428), patients with COPD received standard OM-85 treatment. The primary endpoint of a

reduced proportion of patients with ≥2 acute exacerbations during the 3-month treatment period was met in both the full analysis population and the per-protocol population (23.4% versus 33.3%, p<0.05 and 17.0% versus 31.2%, p<0.05; respectively). The prevalence of recurrent exacerbations was numerically lower in those treated with OM-85 versus placebo (32.8% versus 38.0%; p=0.277), but the difference was significantly in favour of OM-85 only in the per-protocol population (26.3% versus 36.1%; p=0.038). Tolerability was good, with similar rates of adverse events in both groups.[66]

The clinical findings from placebo-controlled trials provide evidence that OM-85 has a preventative effect as an adjuvant medication in the management of COPD and/or CB, thereby reducing the number, duration, and severity of recurrent exacerbations and also the use of antibiotics in this patient population.

COST-EFFECTIVENESS

From the perspective of healthcare providers, cost-effectiveness is a key factor in evaluating which drugs should be prescribed. In 2001, Collet and colleagues[67] carried out a pharmacoeconomic analysis of their 1997 double-blind, placebo-controlled trial. In total, 381 patients with moderate-to-severe COPD participated in the trial. Direct costs included treatment, visits, tests and diagnostic procedures, and hospitalisation. Indirect costs included absenteeism and care costs. OM-85 achieved a 44% (p=0.02) reduction in mean cost of respiratory-related hospitalisation per patient, a 42% (p=0.02) reduction in all-cause hospitalisation per patient, and there was a trend towards a reduction in indirect costs. In a similar Italian study on the cost-effectiveness of OM-85 for the treatment of CB, the cost of treating exacerbations was reduced by 36% in patients treated with OM-85 compared with those who were not.[68]

CONCLUSION

In summary, most COPD exacerbations are the consequence of infectious events, which in turn are the consequence of immune dysregulation. The above data from both clinical and basic studies indicate that these defences can be positively modulated using treatments such as OM-85. This immune modulation leads to the prevention of COPD exacerbations, reducing both symptoms and the number and severity of exacerbations, thus reducing costs and potentially modifying the natural course of the disease.

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RESPIRATORY IMMUNITY AND THE RATIONALE FOR IMMUNOMODULATION IN THE PREVENTION OF RESPIRATORY TRACT INFECTIONS

A narrative summary of selected presentations given at the second Encuentro Latinoamericano de Infecciones Respiratorias Recurrentes (ELAIR), an educational summit held in Buenos Aires, Argentina, 4th–5th July 2015

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ABSTRACT

This educational summit, supported by an independent grant from OM/Vifor Pharma, brought together physicians specialising in pulmonary medicine, otolaryngology, surgery, immunology, and paediatrics. Delegates from the USA, Europe, and Latin America met and discussed the current unmet needs of patients suffering respiratory tract infections (RTIs). The meeting included plenary lectures, workshops, and interactive sessions, allowing delegates and presenters to debate the most pressing local and international issues in the field.

INTRODUCTION

The immune system may be thought of as a battleship providing both defensive armour and offensive firepower against infections. These elements do not always fully protect against pathogens, however, and it is the physician's role to understand the root cause of these failures in order to facilitate both the prevention and cure of infection. The immune response can be divided into innate immunity, which is non-specific and has no memory, and acquired immunity, which is specific and retains a memory to fight future infections. These two aspects can be further divided into systemic and mucosal immunity, the latter of which is the major barrier against respiratory infection.

The mucosal membranes of the human body represent a large surface area. The intestinal mucosa constitutes the largest subdivision of the mucosal membranes, followed by the respiratory mucosa and the urogenital mucosa. Of the three mucosal membranes, the respiratory mucosa has the most regular direct contact with the exterior environment, via the act of breathing, and is therefore a key front in the battle against infection.

ORGANISATION OF THE RESPIRATORY MUCOSA

The innate immune system contributes a first and second line of defence in the respiratory mucosa. The first line is composed of the mucous covering the epithelial cells, which both traps foreign particles and contains antimicrobial molecules (defensins), and the epithelial cells themselves, which are linked to one another by tight junctions and which act as a further mechanical barrier to foreign particles/molecules. Trapped particles are removed by mucociliary clearance, the most primitive and general respiratory defence

mechanism. The second line of innate defence is represented by phagocytic neutrophils and macrophages, the cytotoxic natural killer (NK) cells, and the antigen-presenting dendritic cells (DCs). Antigen-presenting DCs migrate through the epithelial layer and act as a bridge between the innate system and the downstream effectors of the third line of defence, adaptive immunity.

The seat of the adaptive immune response is the mucosa-associated lymphoid tissue (MALT), represented by inductive sites where antigen sampling and recognition occurs, and diffuse effector sites found throughout all mucosal tissue.[1] The effector cells of the adaptive immune system are the T and B cells. T cells can be further subdivided into, amongst others, the large subclass of $CD4^+$ T helper cells (Th) and the $CD8^+$ cytotoxic T cells (Tc). Th cells, including Th1, Th2, and Th17 subclasses, support other immune cells through the release of cytokines that stimulate and promote cell proliferation and survival. Cytokines produced by Th cells include Th1-related interferon gamma (IFNγ), which supports the inflammatory immune response and activates macrophages, and Th2-related interleukin (IL)-4, which stimulates activated B cells and promotes naïve Th cell (Th0) maturation. Tc cells act similarly to NK cells in destroying virus-infected, tumoural, and other damaged cells. A third class of regulatory/suppressor T cells (Treg) can express both CD4 and CD8, and are key to homeostasis in the immune system.

B cells generate various classes of antibody: IgG, IgA, and IgM. IgA, specifically secretory IgA (sIgA), is the most important immunoglobulin for mucosal immunity. IgA makes up approximately 70% of immunoglobulins in the respiratory mucosa, with the remainder being IgG. sIgA forms in plasma cells, a differentiated form of B cell, with IgA monomers being linked by joining chain (J chain) molecules. Following this, the linked IgA molecules are absorbed by epithelial cells and secreted, along with the secretory component acquired during absorption/secretion, into the respiratory lumen. sIgA is active at all levels of the respiratory system from the nostril to the alveoli, and acts through an immune exclusion mechanism: binding bacteria in the lumen and excluding them from entering the deeper layers of the respiratory system.[2]

INTEGRATED MUCOSAL IMMUNITY

The MALT contains both inductive sites where the initial adaptive immune response begins through antigen sensing, represented by Waldeyer's ring at the oropharyngeal level in the respiratory system and by Peyer's patches in the gut-associated lymphoid tissue (GALT), and numerous effector sites that execute the immune response. A key aspect of the integrated immune response is that inductive and effector sites may be remote from one another. In fact, they may be located in distinct subsections of the immune system, enabling activation of inductive sites within the GALT to confer increased resistance to infection in the respiratory mucosa.

The vast majority (80–85%) of the body's 10^{12} lymphocytes are found within the GALT, which contains 10^{11} lymphocytes in total. Each Peyer's patch constitutes a follicle-associated epithelium containing M cells, a sub-epithelial area or dome containing DCs, a lymphoid follicle containing B cells, and finally an extra-follicular area containing T cells.[3] Antigens that enter the gut are captured by the M cells, which are closely associated with sub-epithelial lymphocytes and DCs. These absorbed antigens are subsequently released by the M cells and taken up by DCs that proceed to stimulate cellular constituents of the adaptive immune system.

In addition to antigens, particular structural elements of pathogens known as pathogen-associated molecular patterns (PAMPs) are important in alerting the immune system. The peptidoglycan constituent of the cell wall of gram-positive bacteria and the lipopolysaccharide (LPS) constituent of the external membrane of gram-negative bacteria represent important PAMPs for these two groups of pathogens. Host recognition of PAMPs is mediated by a number of receptor classes, including the Toll-like receptors (TLRs).[4]

TLRs are present on many cell types, including macrophages and DCs. Binding of different TLRs results in the activation of various intracellular transcription pathways. One major consequence of TLR activation is the production of cytokines via two alternative pathways mediated by either the transcription factor NF-κβ or by mitogen-activated protein (MAP) kinases that bind the transcription factor AP1. Cytokines are the major effector molecules in the immune system and are potent, low-molecular-weight proteins that act upon many

cell types with differing effects depending on both the cytokine type and its concentration. The cytokines produced via TLR activation can be subdivided into classes including chemokines, cellular chemo-attractants, and adhesion molecules that mediate cell adhesion to the endothelium.[5] TLR-induced activation of DCs lies at the crux of the immune response and leads to activation of both the innate and adaptive components.[6] As well as directly activating innate immune cells through cytokine release and adaptive immunoglobulin-producing B cells through antigen presentation, DC cells are capable of activating Th0. These activated CD4+ Th cells then release further cytokines that stimulate and potentiate the innate immune response, as well as support immunoglobulin-producing B cells.

The final element in the integrated GALT-respiratory immune response is the process of immune cell homing, which allows the DC-mediated immune response in the inductive Peyer's patches to result in immune activity at the effector sites of the respiratory mucosa. Following activation of Th cells, innate immune cells, and B cells within Peyer's patches, the cells migrate via the thoracic duct and bloodstream to the respiratory mucosa in response to inflammation and immune challenge. Once in the effector site of the respiratory mucosa, the CD4+ T cells further stimulate the innate immune response through cytokine release and induce B cell differentiation into plasma cells. Mature plasma cells then produce IgA dimers that are released into the respiratory mucus following binding with the secretory component. Therefore, PAMP-induced TLR activation of DCs in the GALT results in both innate and adaptive immune response in the respiratory system (Figure 1).

ORAL IMMUNOMODULATORS AND RESPIRATORY IMMUNITY

Relapse and recurrence driven by immune dysfunction are common in RTIs. Immunomodulators may enhance both regulation and expression of an integrated response from the immune system that protects against RTI. Bacterial immunomodulators come in different forms, including bacterial lysates and ribosomal extracts. In all cases these are formed from dead microorganisms with novirulence but retained immunogenicity. The lyophilised and standardised bacterial lysate OM-85, formed from 21 strains of 8 bacterial species and sub-species (5 genera), is the most studied of the bacterial immunomodulators.

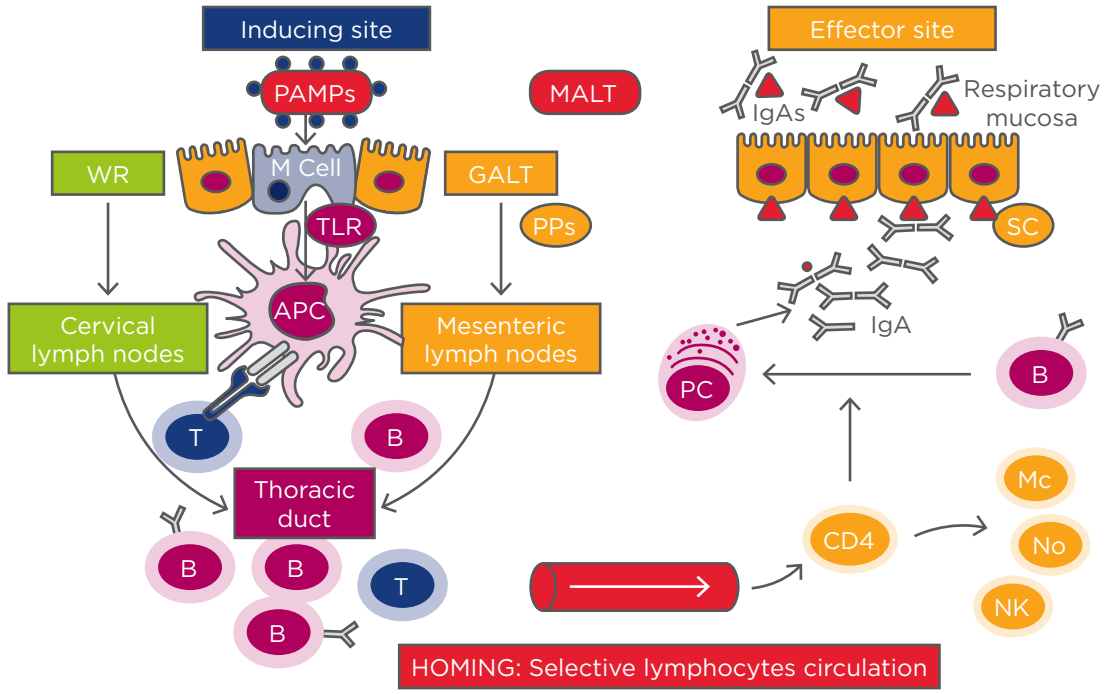

Figure 1: Immune responses in the mucosa-associated lymphoid tissue.
APC: antigen-presenting cell; GALT: gut-associated lymphoid tissue; MALT: mucosa-associated lymphoid tissue; Mc: monocyte; NK: natural killer; No: neutrophil; PAMP: pathogen-associated molecular pattern; PC: plasma cell; PPs: Peyer's patches; SC: secretory component; WR: Waldeyer's ring.

OM-85 and Innate Immunity

OM-85 has a number of effects on the innate immune system derived from modulation of human DCs. DC activation occurs in a modulated manner and is of a lower intensity, with slower kinetics, than that produced by LPS. Stimulation of DCs by OM-85 *in vitro* results in the release of chemokines (CCL2 and CCL3) that act on monocytes and NK cells; pro-phagocytic chemokines CXCL1, CXCL6, and CXCL8; and the chemotactic factors CCL20 and CCL22. OM-85-derived DC maturation leads to production of cytokines, chemokines, and adhesion molecules. The resulting putative increase in non-specific phagocytosis at the mucosal level may promote non-specific respiratory immunity. OM-85 also promotes the production of interferon alpha by DCs, which is the most important cytokine for defence against viral infections. These data suggest that, despite its bacterial constituents, OM-85 stimulates a basal antiviral state in the human immune system. The central message from these data is that OM-85 modulates DC activity, creating a mild activation that promotes downstream immune activity resulting in a pre-alert state protecting against future bacterial and viral infections.[7]

A recent *in vivo* study confirmed the ability of OM-85 to stimulate antiviral innate immunity and to protect against primary viral infections and secondary bacterial infections, in this case by *Streptococcus pneumoniae* or *Klebsiella pneumoniae*, which often follow a primary viral infection. Mice received OM-85 or placebo daily for 10 days before infection with the H1N1 influenza virus, with a bacterial agent being introduced 1 week after viral infection. Markers of DC activation and maturation were increased following OM-85 treatment. OM-85 enhanced the innate immune response, resulting in more rapid control of the infection and a reduced viral H1N1 load in the lungs. The innate response was also faster in OM-85-treated mice as shown by the lower number of neutrophils ($p<0.05$) in the lungs 5 days post-H1N1 infection, which is indicative of a quicker resolution of the immune response. These OM-85-induced improvements in immune responses against influenza virus protected against the effects of secondary bacterial infections, including bacteraemia, weight loss, and temperature increase.[8]

Cells from patients with chronic bronchitis (n=28) treated with OM-85 were compared with those from healthy controls. Bronchoalveolar lavage cell counts revealed an increase in the CD4/CD8 (helper/suppressor) cell ratio in favour of CD4 in patients with chronic bronchitis following treatment ($p=0.04$). In addition, both macrophage activity ($p=0.03$) and concentration of IFNγ ($p=0.03$), a promoter of NK cell activity, were increased following OM-85 therapy.[9] *In vitro* data from human peripheral blood mononuclear cells demonstrates that OM-85 also stimulates NK cell activity, as well as increasing the concentration of the related cytokine IL-2.[10] In human lung fibroblasts, OM-85 also induces increased expression of IL-8, the major chemotactic factor for neutrophils, in a concentration-dependent manner.[11] Three studies from the early 1990s, summarised in a 1994 review by Jacques Mauël, demonstrated increases in adhesion molecules, polymorphonuclear leukocytes, and phagocytosis.[12] In addition, a recent Chinese study on children with concomitant asthma and recurrent RTI demonstrated an increase in the neutrophil, macrophage, and epithelial cell-derived antimicrobial human beta-defensin 1 (hβD-1) following treatment with OM-85.[13]

In summary, OM-85 acts on the primary sentinel cells of the innate immune system, DCs. Numerous downstream immune processes indicative of DC activation and immune system activity have been demonstrated. OM-85 promotes $CD4^+$ T cells, leading to an increase in the innate immunity-related cytokines IFNγ and IL-2, which promote activity of lymphocytes, including NK cells. OM-85-associated increases in adhesion molecules and IL-8 further promote innate immune cell activity, in particular that of neutrophils. In turn, these cells promote increased phagocytosis and production of the antimicrobial hβD-1. Therefore, OM-85 promotes innate immune responses via multiple pathways.

OM-85 and Adaptive Immunity

The cytokines IL-6, IL-10, IL-11, and B cell activating factor (BAFF) are involved in B cell maturation and activation. OM-85 has been shown to activate DCs, leading to the production of IL-6, BAFF, and IL-10.[7] OM-85 also induces increased expression of IL-6 and IL-11 in human lung fibroblasts *in vitro*.[11,12,14] Puigdollers and colleagues[15] demonstrated increased sIgA in the saliva of healthy volunteers following oral administration of OM-85, and increases in serum (IgM and IgG) and intestinal (IgA and IgG) immunoglobulins were demonstrated in immunosuppressed mice.[16] Three further studies have demonstrated increased bronchial sIgA9 and serum IgA and IgG in response to OM-85.[13,17]

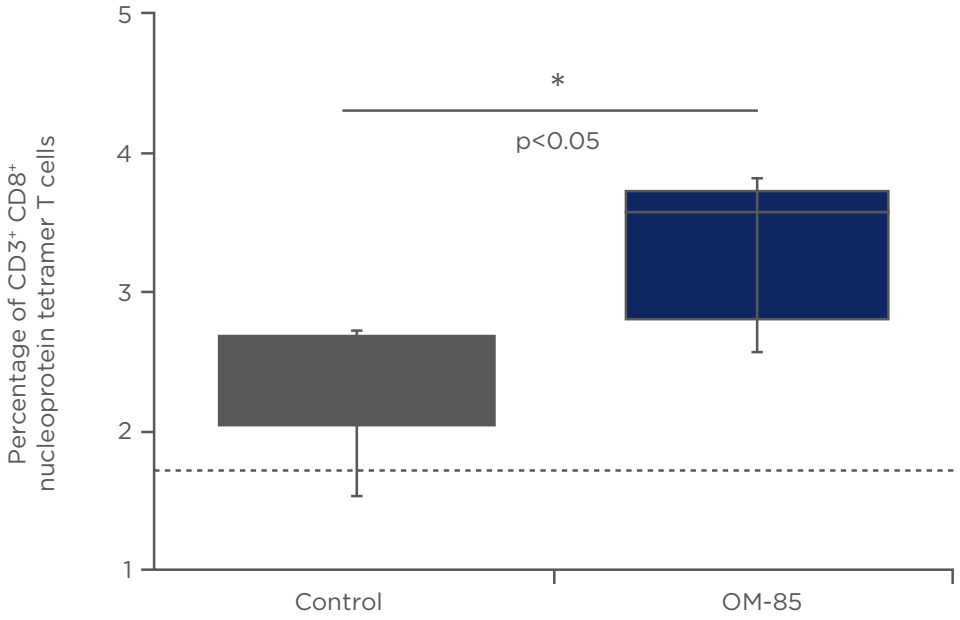

Figure 2: Cytotoxic T cell response in mice treated with OM-85 versus placebo.[8]

OM-85 administration has shown a protective effect in mouse models of both systemic bacterial and respiratory H1N1 viral infection. All mice infected with *Salmonella typhimurium* or H1N1 and treated with OM-85 survived, compared with 58% and 70%, respectively, of those treated with placebo. In addition, the appearance of clinical signs was delayed and their intensity and duration were reduced. Treatment-induced marked increases in serum levels of antibodies recognising all 21 strains of pathogen used in OM-85's manufacturing process. The authors suggest that activity of anti-*Klebsiella* immunoglobulins against the related species *S. typhimurium* may allow an adaptive response against this infection.[18]

The adaptive cellular immune response by cytotoxic $CD8^+$ T cells was significantly increased in mice who received OM-85 or placebo daily for 10 days before infection with the H1N1 influenza virus followed by introduction of *S. pneumoniae* or *K. pneumoniae* after 1 week ($p<0.05$; Figure 2). In non-infected mice, OM-85 caused an increase in influenza-specific IgA in both serum and bronchoalveolar lavage. Polyclonal IgG in the serum, and a trend towards increased polyclonal IgA and IgG in the airways, were also found in OM-85-treated mice, which is indicative of B cell activation leading to the release of antibodies active against multiple infectious agents.[8]

In summary, OM-85-induced increases in both cytokines (IL-6 and IL-11) and immunoglobulins have been demonstrated in the gut (IgA and IgG), in serum (IgA and IgG), and in secretory form (sIgA) within the respiratory system. A putative pathway leading to production of sIgA within the respiratory system derives from the previously mentioned activation of $CD4^+$ Th cells leading to release of cytokines (IL-6 and IL-11), which in turn induces B cell maturation into plasma cells. Plasma cells then go on to release sIgA dimers that are released into the respiratory mucosa through epithelial cells. In addition, the increase in $CD8^+$ cells and polyclonal IgG and IgA production offer a mechanism for protection against subsequent infections.

OM-85 and Allergy

When discussing any immunomodulatory therapy, such as OM-85, it is important to investigate any possible relationship with immune dysfunction that may affect allergy. Individual Th cell phenotypes have different cytokine profiles. Th1 cells produce IFNγ, which acts against intracellular pathogens, whereas the Th2 phenotype produces IL-4, IL-5, IL-6, and IL-13, which are related to allergy. In addition to the role of Th2 cells in allergy, recent data indicate that Type 2 innate lymphoid cells also have a key role in allergy.[19] The Treg phenotype produces transforming growth factor beta (TGFβ), IL-10, and IL-35, which act to regulate the immune response. Regulation is essential in order to control the balance between other Th cell phenotypes and avoid chronic inflammatory activity.

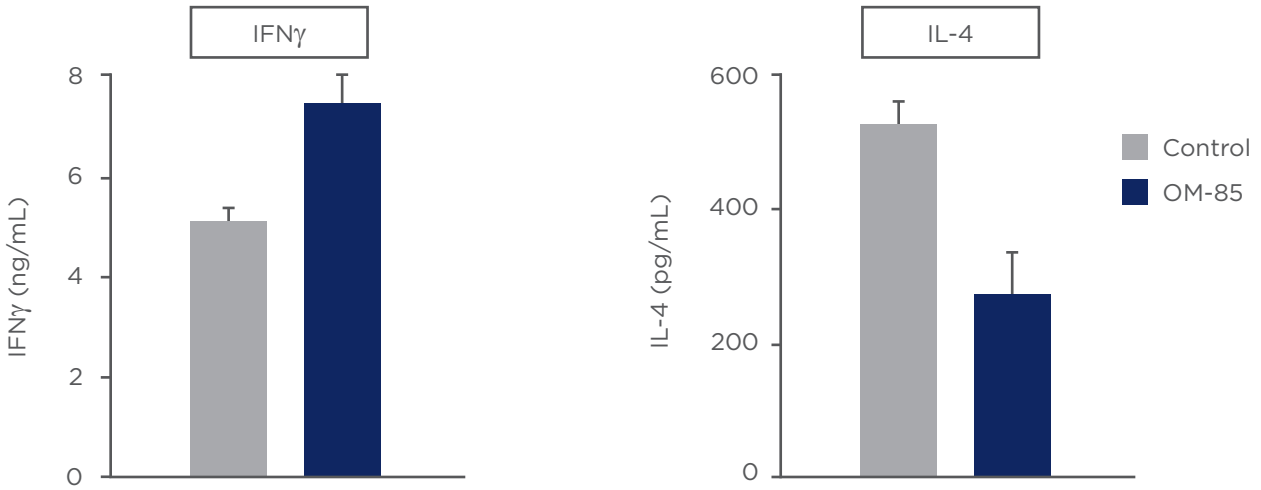

Figure 3: OM-85 favours Th1 activity (IFNγ) over Th2 activity (IL-4) in a mouse model of asthma.[27]
IFNγ: interferon gamma; IL-4: interleukin 4.

The balance between Th1 and Th2 cell activity is maintained by two forms of Treg cells, Th3 and Tr1. Th3 cells produce the cytokine TGFβ that acts to suppress Th1 activity, while Tr1 cells produce IL-10 that suppresses Th2 cell activity. In addition, the Th1 cytokine IFNγ suppresses Th2 activity, while the Th2 cytokine IL-4 suppresses Th1 activity. An imbalance of activity favouring Th2, and consequent suppression of Th1 activity by IL-4, predisposes toward allergy. Such a Th2 imbalance is important to protect the fetus during gestation but continues into childhood, predisposing towards allergic conditions and infection.

DCs also have a role in allergy as DC activation is key to the maturation of Th cells. The functional characteristics of DCs are adaptive and often change in response to inflammation or infection.[6] Recent data suggest that dysfunction in the response to allergens and viral pathogens by the DC network of the respiratory mucosa is a primary cause of both disease initiation and progress in asthma.[20] As mentioned above, OM-85 activates human DCs, providing a possible pathway via which dysfunction in allergic conditions such as asthma may be modulated.[7]

More direct evidence of a positive immunomodulatory role in allergy comes from the BALB/c mouse model of asthma. OM-85 suppresses airway inflammation via an IL-10 dependent pathway and increases Treg recruitment at the level of the trachea. In addition, transfer of purified $CD4^+$ cells from treated mice reduces inflammation in sensitised mice.[21] These data are supported by similar results from a different mouse model of asthma, which demonstrated attenuated airway inflammation, reduced Th2 cytokines, and increased Treg expansion and Th1 promoting/Th2 suppressing cytokines.[22] Similarly, OM-85 induced IL-10 release from the DCs of both healthy donors and patients with the inflammatory condition chronic obstructive pulmonary disease (COPD) *in vivo*. The increase in IL-10 levels was more pronounced in cells from COPD patients and in the presence of pro-inflammatory cytokines.[7]

There is a prevalence of Th2 signalling in infants that makes allergic conditions more prevalent. Treatment of neonatal rats with OM-85 resulted in the balancing of this Th2 bias, as indicated by upregulation of the Th1-related immunoglobulin isotype IgG2b.[23] In a study using a mouse model of allergic rhinitis, OM-85 reduced Th2-related cytokines (IL-4, IL-5, and IL-13) and immunoglobulins (IgE and IgG1).[24]

In another study using an asthma model, BALB/c mice were orally immunised with OM-85 and subsequently sensitised with ovalbumin. Those mice pretreated with OM-85 showed a decrease in both total and ovalbumin-specific IgE indicative of a reduction in allergic response. OM-85 favours the Th1 immune response in mice by upregulating Th1-specific IFNγ and downregulating Th2-specific IL-4 in spleen cell supernatants (Figure 3).[25] Similarly, in a study in children aged 13–14 years with RTIs (N=20), OM-85 stimulated T cell activity and IFNγ production compared with placebo, thus upregulating the cell-mediated immune response and promoting anti-viral and anti-bacterial activity.[26] The IFNγ/IL-4 balance is

important in forms of asthma associated with allergic reactions, suggesting a possible protective mechanism. Finally, OM-85 reduced both the frequency of asthma attacks and RTIs, as well as the use of antibiotics, in a human study. These clinical improvements occurred in conjunction with pro-Th1/anti-Th2 changes in cytokine levels (increased IFNγ and IL-10, reduced IL-4), with these changes likely mediated through an increase in NK T cells.[27]

The above evidence from multiple sources suggests that OM-85 promotes pathways leading from DC activation to Th cell maturation favouring Th1 activity via increased IFNγ and decreased IL-4. An additional OM-85-induced Treg pathway exists leading to increased IL-10 and thus further promoting Th1 activity. Therefore, immune modulation with OM-85 promotes balance of the Th1/Th2 system in allergic conditions in which Th2 activity is elevated.

CONCLUSION

OM-85 activation of DC cells at induction sites within the GALT leads to migration of activated immune cells to the respiratory mucosa, activating both innate (pro-phagocytic and antiviral cytokines) and adaptive (immunoglobulins, B cell activation/maturation, and $CD8^+$ cells) immune processes through the release of cytokines. In addition, OM-85 plays a rebalancing role in allergic conditions that feature immune dysfunction by promoting Th1 activity (increased IFNγ and IL-10) and reducing the upregulation of Th2 activity (reduced IL-4).

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