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REVIEW

Oral Bacterial Lysate OM-85: Advances in Pharmacology and Therapeutics

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Background: Bacterial lysates are known for having immunomodulatory properties and have been used mainly for the prevention and treatment of respiratory tract infections (RTIs). However, rigorous studies are needed to confirm the clinical efficacy of bacterial lysates with various bacterial antigen components, preparation methods, administration routes and course of treatment. OM-85, an oral standardized lysate prepared by alkaline lysis of 21 strains from 8 species of common respiratory tract pathogens, is indicated as immunotherapy for prevention of recurrent RTIs and acute infectious exacerbations of chronic bronchitis. OM-85 acts on multiple innate and adaptive immune targets and can restore type 1 helper T (Th1)/Th2 balance. Sporadic studies have shown advances in pharmacology and therapeutics of OM-85, and thus an update review is necessary.

Methods: Literature was retrieved by searching PubMed, Web of science, Embase, CNKI, and Full Text Database of Chinese Medical Journals.

Results: New roles of OM-85 were discovered in prevention and treatment of lung cancer, pulmonary tuberculosis, SARS-CoV-2 infection, allergic rhinitis, pulmonary fibrosis, atopic dermatitis, and nephrotic syndrome. Pharmacoeconomic values of OM-85 were demonstrated in prophylaxis and treatment of RTIs, chronic obstructive pulmonary disease, asthma, chronic bronchitis, rhinosinusitis and allergic rhinitis. Two consecutive courses of OM-85 (6 or 12 months apart) could prevent recurrent RTIs in children. Maternal OM-85 treatment could offer benefits for offspring. Product-specific response was observed. The efficacy of OM-85 may be associated with patient's characteristics (eg, severity of the disease, age, immune response pattern, malignancy risk stratification).

Conclusion: OM-85 can improve effectiveness of standard care for some primary diseases, and carry significant pharmacoeconomic implications. The benefits shown by OM-85 in vitro and in vivo, when extrapolated to humans, are exciting but also require caution. Individualized treatment may need to be considered. It is necessary to compare the efficacy and safety of various bacterial lysate preparations.

Keywords: airway inflammatory disease, allergic diseases, bacterial lysates, immunomodulator, OM-85, pharmacoeconomic evaluation

Introduction

Bacterial lysates (BLs) are mainly prepared from common microorganisms in human respiratory tract infections (RTIs) and several different brands are currently available in many countries. BLs are known for having immunomodulatory properties. They interact with dendritic cells in the mucous membranes of the upper respiratory tract and the gastro-intestinal tract through toll-like receptors, allowing dendritic cells to present acquired antigens and promote the development of innate immune responses by releasing chemokines, thereby stimulating the maturation of monocytes and natural killer cells and promoting the migration of polymorphocytic neutrophils. In addition, they affect the adaptive immune system by stimulating an increase in specific antibodies against bacterial antigens. The effects of BLs include not

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only anti-inflammatory effects, but also restoring type 1 helper T (Th1)/Th2 balance and ameliorating the clinical manifestations of allergic diseases.[1]

OM-85 (Broncho-Vaxom) is an oral immunomodulator containing extracts from eight bacterial pathogens (ie, *Haemophilus influenzae, Diplococcus pneumoniae, Klebsiella pneumoniae, Klebsiella odorosa, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus viridans*, and *Neisseria catarrhalis*).[2] According to prescribing information, the indications of OM-85 are immunotherapy for prevention of recurrent infections of the airways and acute infectious exacerbations of chronic bronchitis, as well as comedication in treatment of acute airway infections.[3]

For preventive treatment and/or consolidation therapy in adults, one capsule (7 mg lyophilizate BLs) is taken daily on an empty stomach for 10 consecutive days per month for 3 months. For treating acute episodes in adults, one capsule is taken daily on an empty stomach until symptoms disappear (but for at least 10 days). In cases where antibiotics are required, OM-85 should be preferably used at the beginning of treatment. For children aged from 6 months to 12 years, there are two formulations (ie, capsule, sachet), with the same treatment schedule as for adults, but at half the dose.[3]

There have been a few sporadic studies demonstrating new pharmacological actions of OM-85 in cells, animal models, and patients, especially for off-label use. In addition, when OM-85 is prescribed for patients with approved indications, some new findings have also been revealed, involving pharmacoeconomic comparisons, optimal course of treatment, product-specific response, patient characteristics-dependent pharmacological and therapeutic effects. Therefore, we wrote an update narrative review of this aspect to bring the latest advances to clinicians and to promote research and practical exploration.

Methods

Search Strategy

Potentially relevant literature containing "OM-85" in the title or abstract within the last 10 years up to the end of October 2023 were retrieved by searching PubMed, Web of science core collection, MEDLINE, Embase, China National Knowledge Infrastructure (CNKI) and Full Text Database of Chinese Medical Journals.

Selection Criteria

Two reviewers (ZLL and WYH) independently searched the literature and screened relevant studies. If they disagreed with including or excluding a document, the third reviewer (QZ) was consulted. Sixty-eight articles were retrieved from PubMed, 77 from Web of Science Core Collection and MEDLINE, 98 from Embase, 129 from CNKI, and 9 from Full Text Database of Chinese Medical Journals. Two hundred and twenty-eight papers were further evaluated after exclusion of duplicate literature. After reviewing the abstracts, 181 documents were excluded due to reasons [eg, the contents were not closely related to OM-85 role (n=38), or language was not English or Chinese (n=3), articles which focused on treatment of respiratory diseases related to the indications described in the package insert of OM-85 [eg, acute bronchitis, chronic bronchitis, asthma, chronic obstructive pulmonary disease (COPD), emphysema, viral respiratory infections, post-influenza bacterial super-infection, recurrent respiratory infections, chronic rhinosinusitis] and did not reveal particularly new findings (n=140)]. Full-text articles were further assessed for eligibility. Fourteen documents were excluded, including conference abstracts due to text unavailability, review-type documents (ie, meta-analysis, systematic reviews and Cochrane reviews) that were not the most latest. Thirty-three papers were finally chosen according to the inclusion/exclusion criteria (Figure 1). Valuable information was summarized and discussed.

Results and Discussion

Table 1 is the summary of diseases that OM-85 is applied to combat. Among these, seven diseases have been reported to be prevented or treated by off-label use of OM-85.

Off-Label Respiratory Diseases

Lung Cancer

In vivo Study

Sun et al investigated the immunomodulatory effects of OM-85 on early-stage lung adenocarcinoma and its possible mechanisms.[4] Genetically engineered mouse KT model (KrasLSL-G12D Tgfbr2loxp/loxp) and mouse K model

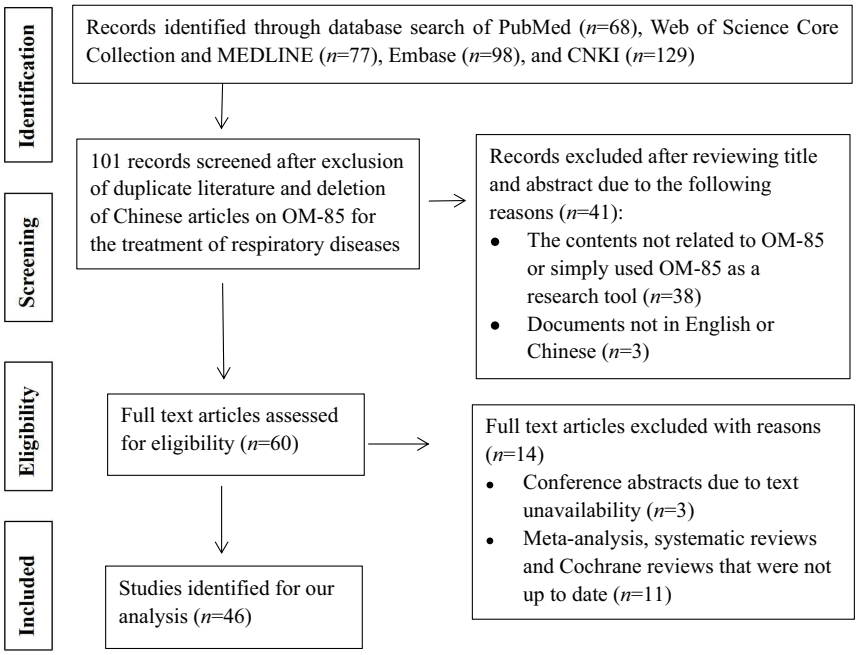

Figure 1 Flow chart showing selection of literature.

(KrasLSL-G12D) were established, representing human early-stage lung adenocarcinoma and human benign lung nodules, respectively. In the OM-85 intervention group, the levels of tumor growth, immune cells and factors were similar to those in the benign nodule control group, and the number of activated immune cells was higher than that in the early lung adenocarcinoma control group. It suggests that OM-85 may inhibit the progression of early lung adenocarcinoma by regulating the number and activity of T cells, natural killer cells, and macrophages.

Clinical Studies

After first-line carboplatin-pemetrexed chemotherapy for advanced lung adenocarcinoma, OM-85 maintenance immunotherapy (7 mg/day, 10 days/month) combined with 13-*cis* retinoic acid (0.5 mg/kg, 5 days/week, 3 weeks/month) until

Table 1 Summary of Diseases That OM-85 is Applied to Combat

Types of Diseases	Detailed Information
Respiratory diseases related to the indications described in OM-85 package insert	Acute bronchitis Asthma Chronic bronchitis Chronic obstructive pulmonary disease Chronic rhinosinusitis Emphysema Post-influenza bacterial super-infection Recurrent respiratory infections Viral respiratory infections
Off-label respiratory diseases	Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection Allergic rhinitis Lung cancer Pulmonary Fibrosis Pulmonary tuberculosis
Off-label non-respiratory diseases	Atopic dermatitis Nephrotic syndrome

progression induced a significant increase in lymphocyte account, with favorable effects on progression-free survival and overall survival. At a median follow-up of 22 months, 41 patients (75%) had a clinical benefit.[5]

A population-based retrospective study (ChiCTR2200064396) identified beneficial changes in lung nodules during follow-up after oral OM-85 treatment in patients with high-risk lung nodules identified by CT screenings. For high-risk pulmonary nodules found 1 year ago and followed up for more than 3 months, OM-85 treatment significantly slowed the trend of nodular enlargement compared with blank controls (1.42% vs 6.94%, P=0.023).[6]

Therapeutic Implications

The clinical manifestation of early lung cancer is lung nodules. In the low-dose CT screening programs, more than 20% of participants were found to have one or more lung nodules that needed further examination at the first scan. In the Pan-Canadian Early Detection of Lung Cancer Study (PanCan), the incidence of cancer among persons with nodules was 5.5%.[7] It is interesting to observe the preliminary efficacy of OM-85 in lung cancer prevention and adjuvant treatment, although such findings need to be confirmed by randomized controlled trials. No other BLs preparations have been reported for the prevention or adjuvant therapy of lung cancer. Considering the overwhelming cost of lung cancer, it is necessary for clinicians to further explore whether the addition of OM-85 brings therapeutic and economic benefits.

Pulmonary Tuberculosis

Clinical Study

Cai investigated the effect of short course chemotherapy combined with OM-85 on the prognosis of new smear positive pulmonary tuberculosis. The control group was treated with 2HRZE/4HR chemotherapy regimen [ie, isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol (E) for 2 months, HR treatment for 4 months], and the experimental group was treated with OM-85 (7 mg once daily for 10 consecutive days each month) on the basis of the control group. After 2, 4 and 6 months of treatment, the experimental group had significantly higher sputum negative conversion rates (90.0% vs 72.5%, 95.0% vs 80.0%, 97.5% vs 85%, respectively, all P<0.05) than the control group. Six months after treatment, the experimental group had significantly higher pulmonary lesions absorption (97.5% vs 82.5%, P<0.05) and immune function (IgA, IgG, IgM, CD3+, CD4+, CD4+/CD8+) (All P<0.05) compared to the control group, with no increase in the incidence of adverse drug reactions during the whole observation period.[8]

Therapeutic Implications

The progression of the disease following *Mycobacterium Tuberculosis* infection is closely associated with the host's immune response. The vast majority of patients with tuberculosis have reduced immune function. Immunotherapies can regulate the immune system in patients with latent tuberculosis infection or active disease, resulting in better control of *Mycobacterium Tuberculosis*(MTB) replication.[9] The current evidence for the benefit of OM-85 in patients with tuberculosis is encouraging.[8] The mechanism by which protective effects of OM-85 work against MTB may be enhanced cellular and humoral immune responses that control MTB infection and play an important role in its clearance.

In addition, multidrug-resistant tuberculosis (MDR-TB) is increasingly prevalent, and it is estimated that no more than 69% of patients with MDR-TB are cured.[10] It is interesting to conduct clinical studies to test whether the addition of OM-85 could improve the efficacy of MDR-TB chemotherapy and curb the spread of MDR-TB.

In this clinical study, the consecutive two course (ie, 6 months) of OM-85 treatment was utilized and clear dynamic clinical efficacy was observed. The optimal course of medication is worth further investigation.

Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

In vitro Studies

Fang et al studied the effect of OM-85 treatment for 5 days on the expression of spike protein-binding proteins in human bronchial epithelial cells. OM-85 significantly decreased the expression of angiotensin converting enzyme 2 (ACE2), dipeptidyl peptidase-4 and cellular heparan sulfate, while significantly upregulated the expression of disintegrin and metalloproteinase 17. Additionally, OM-85 significantly increased the levels of soluble ACE2, hyaluronic acid, and hyaluronan synthase 1. It was observed that SARS-CoV-2 spike protein pseudo-typed lentivirus infection was reduced in

OM-85 pretreated cells, and all effects of OM-85 were concentration- and time-dependent. The results show that OM-85 can reduce the binding of SARS-CoV-2 spike protein to epithelial cells by modifying host cell membrane proteins and specific glycosaminoglycans.[11]

OM-85 could not only significantly downregulate ACE2 and transmembrane protease serine 2 (TMPRSS2) transcription and surface ACE2 protein expression in epithelial cell lines and primary bronchial epithelial cells, but also strongly inhibit SARS-CoV-2 spike protein subunit S1 binding, SARS-CoV-2 spike protein-pseudotyped lentivirus invasion, and SARS-CoV-2 infection of epithelial cells.[12]

Ex vivo and Clinical Studies

Cassão et al examined the therapeutic effects of OM-85 and recombinant human beta interferon (rhINF-β) after SARS-CoV-2 infection. Nasopharyngeal cells from Coronavirus disease of 2019 (COVID-19) patients were collected and treated with OM-85 or rhINF-β ex vivo, and gene expression was analyzed 24 h later. OM-85 decreased the expression of SARS-CoV-2 N1 gene and increased the expression of RIG-I (DDX58) in these cells; however, no ACE2 expression was detected in these samples.[13]

A recent observation study showed that none of the patients in group A (8 patients treated with OM-85 from December 2020 to June 2021) were affected by COVID-19 during the observation period, while in the control group (16 patients not treated with OM-85 after gender and age matching), two patients were infected with SARS-CoV-2 despite receiving three doses of the vaccine.[14]

Therapeutic Implications

Immune boosters are being studied in an attempt to reduce the frequency of SARS-CoV-2 infection. No other preparations of BLs have been reported for the prevention of SARS-CoV-2 infection. Based on current evidence, OM-85 may be a novel additive for COVID-19 therapy. The mechanism of OM-85 against SARS-CoV-2 mainly involves downregulating the expression of SARS-CoV-2 receptor ACE2.[11–13] Well-designed clinical studies are needed to confirm the efficacy of OM-85 on COVID-19 prevention.

Allergic Rhinitis

Animal Study

Han et al studied the immunomodulatory effect of OM-85 on allergic rhinitis in mice and established a mouse nasal mucosal allergic inflammation model induced by ovalbumin. Pretreatment with OM-85 for 3 months prior to sensitization (long-term) protected mice from most allergy-specific symptoms. Specifically, OM-85 inhibited nasal symptoms, nasal eosinophilic infiltration, inflammatory infiltration and Th2 response by reducing cytokines [interleukin (IL)-4, IL-5, or IL-13] in nasal lavage fluids, reducing IgE and IgG1 levels, and increasing interferon (IFN)-γ. Furthermore, treatment with OM-85 for 1 month (short-term) neither decreased nasal symptoms nor increased IFN-γ, although Th2 cytokine and IgE levels were reduced.[15]

Clinical Studies

Meng et al observed that OM-85 could alleviate persistent allergic rhinitis in patients by improving Th1/Th2 cytokine balance of nasal mucosa. After 3-cycles of standard OM-85 treatment, patients achieved the following benefits compared with placebo group (ie, significantly decreased medication score, total nasal symptom score, individual nasal symptom scores, levels of IL-4 and IL-13 in nasal lavage, and eosinophils in nasal smear, along with markedly increased level of INF-γ and sustained favorable changes for at least four to eight weeks post OM-85 treatment).[16] A multicenter, prospective, randomized, double-blind, placebo-controlled study also confirmed that the clinical course of allergic rhinitis caused by grass pollen in children can be improved by treatment of polyvalent mechanical BLs (PMBL) sublingual tablet (Ismigen, Lallemand Pharma AG, Massagno, Switzerland) containing 7 mg of BLs from 7 kinds of bacteria which are the same ones that make up OM-85.[17]

Therapeutic Implications

Allergic rhinitis is one of the most common allergic inflammatory diseases worldwide. Evidence has shown immunomodulatory effects of OM-85 in mouse models and patients with allergic rhinitis. Thus, OM-85 may be a low-cost candidate for the prevention of allergic rhinitis.

Pulmonary Fibrosis

In vivo Study

Zhu et al observed that aerosolized pretreatment with OM-85 could protect against bleomycin-induced pulmonary fibrosis in mice, which was demonstrated by a greater reduction of Ashcroft's fibrotic score and hydroxyproline levels in the lungs, a decreased IL-4 expression in the bronchoalveolar lavage fluid (BALF), and a greater ratio of IFN-γ/IL-4 ($P < 0.01$). Compared to the controls (phosphate-buffered saline), aerosolized OM-85 did not cause any noticeable structural abnormalities in the lung tissues, whereas intratracheal infusion of bleomycin caused significant pulmonary fibrosis.[18]

Therapeutic Implications

Idiopathic pulmonary fibrosis is a unique form of chronic, progressive, fibrosing interstitial pneumonia of unknown etiology. The development of pulmonary fibrosis may be related to the deficiency of pulmonary innate immunity. This preliminary study may provide a therapeutic modality for alleviation of symptoms in patients with pulmonary fibrosis because the adherence to treatment of representative agent nintedanib or pirfenidone is limited by poor toleration.

Non-Respiratory Diseases

Atopic Dermatitis

Clinical Studies

A randomized double-blind placebo-controlled trial tested the efficacy and safety of oral OM-85 for established atopic dermatitis in children aged 6 months to 7 years. Patients received conventional treatment, including emollients and topical corticosteroids, as well as 3.5 mg of OM-85 or placebo daily for 9 months, followed by a 3-month follow-up period without treatment. In patients receiving OM-85 adjuvant therapy, new flares were significantly reduced and delayed. The first new flare occurred on average 18 days later in the OM-85 group compared to placebo. Taking into account potential confounding factors (eg, family history of atopy and corticosteroids use), the hazard ratio for recurrence of new events was 0.82. In addition, OM-85 was well tolerated and no significant side effects were reported.[19]

Therapeutic Implications

Atopic dermatitis is a common chronic, immune-mediated inflammatory skin disease characterized by a predominant type 2 immune response and it can have serious negative physical and psychological effects on patients. Multiple cytokines (eg, IL-4 and IL-13) are considered pivotal to the pathogenesis and key therapeutic targets of atopic dermatitis.[20] The promising results of Bodemer et al' study suggest a possible wider use of OM-85 in the treatment of established atopic dermatitis.[19] BLs can restore Th1/Th2 balance, decrease Th2-related cytokines (IL-4, IL-13) levels, and increase Th1-related cytokines (IFN-γ) levels. The re-establishment of the balance of the immune response may reduce the incidence of atopic reactions and the risk of inflammation.[1] Further work is also needed to compare potential differences between different BLs products. Also, considering the emerging role of Janus kinase (JAK) inhibitors for the treatment of atopic dermatitis,[21] it is interesting to investigate the feasibility of combination use of OM-85 and JAK inhibitors.

Nephrotic Syndrome

Clinical Studies

Ge et al observed that OM-85 could improve the immune function of children with relapsing primary nephrotic syndrome on corticosteroid and/or immunosuppressant therapy, and could effectively prevent the frequent recurrence of primary nephrotic syndrome induced by RTIs. The control group (n=22) was treated with prednisone and/or immunosuppressive therapy, while the treatment group (n=28) was treated with OM-85 (3.5mg once a day for 10 consecutive days per month for 6 consecutive months) on the basis of the control group. Compared with the control group, the treatment group

suffered fewer times of respiratory infections and the resulting nephrotic relapse, shorter duration before urine albumin turns negative ($P<0.05$), higher overall remission rate (89.3% vs 77.3%, $P<0.05$), and better changes in serum immunoglobulins (Ig A, Ig G, Ig E) and T cell subsets (CD4+, CD8+, CD4+/ CD8+) after the treatment ($P<0.05$).[22]

Wang investigated whether OM-85 could improve immune function in children with steroid-dependent nephrotic syndrome. The control group were treated with prednisone. Based on the control group, the observation group was treated with OM-85 (3.5 mg once daily for consecutive ten days per month for 6 consecutive months). After treatment, the observation group had significantly higher total remission rate (91.3% vs 73.9%, $P=0.028$) and values of four indicators (IgA, IgG, CD4+, CD4+/CD8+), while it had significantly lower number of renal recurrence and RTIs, as well as levels of IgE and CD8+ compared to the control group. Meanwhile, the two groups did not exhibit statistically significant difference in hormone dose and the incidence of adverse reactions.[23]

Therapeutic Implications

Nephrotic syndrome refers to a group of clinical syndromes caused by a variety of causes, with increased glomerular basement membrane permeability, manifested as massive proteinuria, hypoproteinemia, hyperedema and hyperlipidemia. Children with nephrotic syndrome may have many complications, and infection is the most common and serious complication, which can lead to the recurrence of nephrotic syndrome. Adding OM-85 to steroid and/or immunosuppressive therapy can effectively improve immune function in children, and this finding provides clinicians with a new treatment strategy.

Pharmacoeconomic Implications of OM-85

Latin America

Pharmacoeconomic evaluations have been carried out regarding OM-85 against RTIs, COPD, asthma, chronic bronchitis, rhinosinusitis and allergic rhinitis. Buendía et al studied the cost-utility of supplementing OM-85 to decrease the likelihood of recurrent RTIs in pediatric patients in Colombia. The expected annual costs for OM-85 and placebo-treated patients were $843 and $1167, respectively, while per capita quality-adjusted life-years (QALYs) were 0.91 and 0.89, respectively. OM-85 seems cost-effective in reducing the recurrence rate of RTIs in children.[24] Berber et al demonstrated the cost-effectiveness of OM-85 in preventing acute RTIs in children in day care centers or preschoolers in Mexico. Based on the incidence of acute RTIs and the average direct cost of acute RTIs plus the cost of having a parent absent to care for a sick child, the average cost-effectiveness of using OM-85 compared with not using OM-85 was −86.89 US dollars. The main reasons for cost reduction were reduced parental absenteeism and lower consumption of medications, especially antibiotics.[25] In Argentina, the cost-effectiveness of OM-85 prophylactic treatment for patients with allergic rhinitis, asthma and COPD was demonstrated, with cost savings of 15–60% compared to the same patients who received only standard care in the previous year.[26]

Europe

In Italy, two pharmacoeconomic studies were conducted. A cost consequence analysis showed that the prophylactic use of OM-85 in children susceptible to recurrent upper RTIs resulted in savings of 40.30 euro/patient from a National Health Service (NHS) perspective and 182.99 euro/patient from a community perspective.[27] Troiano et al found that a negative cost-effectiveness ratio favored OM-85 in treating patients with COPD, saving significant amounts of money for the NHS and potentially reducing antibiotic resistance.[28]

China

In China, the health economic impact of OM-85 in preventing acute exacerbations of chronic bronchitis and sinusitis has been demonstrated. From a Chinese payer's perspective, OM-85 is a cost-effective treatment compared to placebo (standard care), as it can prevent an additional full episode exacerbation, adding only 653 yuan (chronic bronchitis) and 1,182.84 yuan (rhinosinusitis) to the cost. However, each acute exacerbation will cost 4510.10 yuan (chronic bronchitis) and 1807.21 yuan (rhinosinusitis).[29,30]

Exploration of the Optimal Course of Treatment

The Durability of Response

A double-blind, placebo-control, randomized clinical trial evaluated the preventive effect of OM-85 on acute exacerbations in patients with COPD or chronic bronchitis in China. Patients were treated with OM-85 or placebo for 10 days per month over 3 consecutive months, with a 10-week follow-up. OM-85 significantly reduced the proportion of patients with acute exacerbations after 12 weeks of treatment and this benefit seemed to be maintained up to 22 weeks.[31] Throughout the 22-week study period, the proportion of patients with recurrent acute exacerbations was lower in the OM-85 group than in the placebo group (26.3% vs 36.1%, $P<0.05$).

Six Months Apart

Gutiérrez-Tarango et al compared the safety and efficacy of OM-85 and placebo in the prevention of acute RTIs in susceptible children with two consecutive courses (6 months apart). Patients were followed up for 12 months, including the dosing period. OM-85 had a preventive effect on acute RTIs in the susceptible children for 12 months with a statistically significant decrease in the antibiotic requirements and the number of days suffering acute RTIs.[32]

Twelve Months Apart

Esposito et al further investigated the efficacy of OM-85 (3.5 mg once a day for 10 days for 3 months of each year) administered in children with recurrent RTIs for two consecutive years (12 months apart). In the first and second year, there were significantly fewer patients without any new episodes of RTIs in children treated with OM-85 than in children not treated with OM-85, and the number of RTIs, wheezing episodes, doctor visits, and antibiotic courses was also lower than in children not treated with OM-85. The data suggest that a second yearly course of OM-85 administration may help maintain the protective effect, which is especially important for young children with RTIs, where immune-boosting measures may be helpful because their immune capacity is not yet mature.[33]

Therapeutic Implications

The course of treatment is not described in prescribing information for OM-85. Results from the above three clinical studies indicate that OM-85 dosing 6 months apart is feasible to prevent recurrent RTIs in children. For other types of patients, further investigations are warranted.

Maternal OM-85 Treatment and Its Benefits for Offspring

In vivo Studies

Maternal oral treatment during pregnancy with OM-85 could transplacentally accelerate functional immunocompetence of the fetal innate myeloid compartment, thus significantly reducing the susceptibility of offspring to allergic airway inflammation at wean.[34] Furthermore, Mincham et al found that the enhanced viability of XBP1-ERN1-dependent conventional dendritic cell in the airway mucosal tissue microenvironment may be a key element of OM-85-mediated transplacental innate immune training that leads to postnatal resistance to airway inflammatory diseases.[35]

The protective effects of maternal OM-85 treatment against fatal neonatal respiratory virus infection were confirmed in BALB/c mice. The main mechanisms were accelerated development of innate immune mechanisms, including quickened postnatal development of the myeloid compartment, and up-regulated expression of TLR4/7 and IL-1β/NLRP3 inflammasome complex in the neonatal lungs.[36]

Therapeutic Implications

Prescribing information for OM-85 specifies that the product should be administered cautiously during pregnancy. If the findings in the mouse model can be extrapolated to humans, it means that OM-85 administration is permissible during pregnancy. It is beneficial not only for pregnant women with related diseases, but also for their offspring. It is worthwhile to conduct clinical studies on the protective effects of BLs products on postpartum infants after administration in pregnant women.

The Combined Use of OM-85 and Influenza Vaccine

Clinical Study

Esposito et al investigated the impact of OM-85 on the immunogenicity, safety and tolerability of inactivated influenza vaccine in children with recurrent RTIs. This randomized controlled trial is the only published study of the combined administration of OM-85 BV and influenza vaccination. The children receiving OM-85 (3.5 mg once daily for 10 days during three consecutive months) were vaccinated 15± 2 days after the end of the 10-day course. The addition of OM-85 did not interfere with the humoral and cell-mediated immune response of children to influenza vaccine (eg, seroconversion or seroprotection rates, geometric mean titres, dendritic cells or the frequency of influenza-specific memory B cells in the peripheral blood); however, OM-85 appeared to significantly reduce the recurrence of RTIs and respiratory morbidity ($P<0.05$).[37] OM-85 seemed to be well tolerated in combination with influenza vaccine.

Therapeutic Implications

The immunogenicity and efficacy of inactivated influenza vaccines are not completely satisfactory in children. A systematic review and meta-analysis of randomized controlled trials showed that concomitant prebiotics or probiotics supplementation with influenza vaccination may hold great promise for improving vaccine efficacy.[38] As postbiotics, OM-85 does not reduce the immunogenicity of influenza vaccines, nor does it increase adverse reactions, but it reduces respiratory related mortality. Thus, it is feasible to combine using OM-85 and inactivated influenza vaccine in children with recurrent RTI requiring influenza vaccination.

Product-Specific Response

Few comparative studies have been conducted on different oral BLs products, but some have been examined. Table 2 lists product-specific response of various BLs.

OM-85 versus Pulmonarom

Roth et al assessed the in vitro protective effects of two slightly different oral BLs (OM-85 and Pulmonarom) on rhinovirus- (RV-) infected human bronchial epithelial cells.[39] Compared with Pulmonarom, OM-85 was more effective in reducing RV-16-infection and ICAM expression, inducing the release of β-defensin and IFN-β, and improving host cell survival. In mouse bone marrow-derived dendritic cells (BMDCs), OM-85, but not Pulmonarom, could upregate type I IFN-β, a key element of host defense against viral infection. The composition of OM-85 differs from Pulmonarom. Both products contain lysates from *Diplococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Neisseria catarrhalis, Staphylococcus aureus, and Streptococcus pyogenes*. However, OM-85 also contains lysates from two additional bacteria (*Streptococcus viridans* and *Klebsiella ozaenae*), while Pulmonarom contains lysates from three additional bacteria (*Streptococcus agalactiae, Streptococcus dysgalactiae*, and *Streptococcus anginosus*). The product-specific response may be possibly triggered by different pathogen-associated molecular patterns (PAMPs) contained in BLs.

Table 2 Product-Specific Response of Various Bacterial Lysates

Comparisons	Detailed Information
OM-85 versus Pulmonarom	In BECs, OM-85 was more effective in reducing rhinovirus-16 infection and improving host cell survival. Also, OM-85, but not Pulmonarom, could upregate type I interferon-beta in BMDCs.[39]
OM-85 versus Lantigen B	ACE2 expression in oropharyngeal cells appeared to decline earlier in the presence of Lantigen B rather than OM-85.[40]
Alkaline BLs versus mechanical BLs	Both BLs generated a similar pro inflammatory response in the lung and conferred same level of protection against pneumococcal pneumonia. However, compared to alkaline BLs, mechanical BLs induced stronger pro-inflammatory activity in human alveolar cells.[41]

Abbreviations: ACE2, angiotensin-converting enzyme2; BECs, human bronchial epithelial cells; BLs, bacterial lysates; BMDCs, mouse bone marrow-derived dendritic cells.

Lantigen B versus OM-85

Lantigen B is a suspension of bacterial antigens obtained from *Streptococcus pneumoniae* type 3, *Streptococcus pyogenes* Group A, *Branhamella catarrhalis, Staphylococcus aureus, Haemophilus influenzae* type b and *Klebsiella pneumoniae*. At clinical dose, Lantigen B could regulate the expression of major SARS-CoV-2 receptor in oropharyngeal cells, and significantly reduce viral yield. Although the role of Lantigen B versus OM-85 in modulating SARS-CoV-2 cellular receptor ACE2 was not directly compared, the two products seem to exhibit some differences.[40] The results derived from OM-85 study were obtained using high concentrations of bacterial lysate (from 0.24 to 1.92 mg/mL),[11] a dose that seems to be difficult to achieve in the body, given that a single OM-85 capsule contains 7 mg of the active ingredient. In addition, ACE2 expression decreased after 24 h in the presence of Lantigen B, whereas the effect of OM-85 was observed after a longer period of time under the experimental conditions (eg, ACE2 expression by lung Calu-3 cells was significantly inhibited only after 72 and 96 h, and only when fresh OM-85 was replaced after 48 h of culture).[11,40]

Alkaline BLs versus Mechanical BLs

Two polyvalent lysates, formulated with bacterial species (*Staphylococcus aureus, Klebsiella pneumoniae* and *Haemophilus influenzae*), were prepared with the same composition but different method of bacterial cell disruption. The two lysates induced MyD88-dependent NF-kB activation to a similar extent, and both protected against a lethal challenge with *S. pneumoniae*. The only differences observed were that the mechanical lysate induced higher levels of pro-inflammatory mediators in human alveolar cells. Both lysates rapidly increased the transient gene expression of several proinflammatory chemokines (*Ccl20, Cxcl8, Cxcl1*) and cytokines (*Il6, TNF-α*) and antimicrobial peptides (*Lcn2, S100a9*). However, in most cases, the mRNA levels induced by PMBL were significantly higher compared to polyvalent alkaline BL (PABL).[41] OM-85 and Lantigen B are examples obtained by chemical lysis, while Ismigen and Ribomunyl-D 53 consist of unaltered antigenic particles obtained by mechanical cell disruption. However, there are currently no direct clinical studies comparing the biological effects of polyvalent BLs, either obtained through mechanical or chemical procedures.

Individualized Therapy

Immunophenotypes

The inflammatory profile of children during severe asthma attacks is characterized by IRF7hi and IRF7lo immunophenotypes. The latter phenotype is accompanied with prolonged symptoms and shorter intervals between exacerbation episodes. de Jong et al elucidated the molecular basis for differences in IRF7-related response profiles after virus/allergen co-exposure in Piebald Virol Glaxo (PVG) and Brown Norway (BN) rats, which are, respectively, characterized by high versus low susceptibility to chronic, allergen-driven type 2-associated airways inflammation, and mirror the IRF7hi (PVG) and IRF7lo (BN) phenotypes.[42] The study showed that different IRF7-associated asthma risk immunophenotypes showed dichotomous responses to virus/allergen co-exposure, and respond differentially to OM-85 pretreatment. OM-85 had more profound effects in high-risk BN rats (eg, inducing immune-related gene expression changes in lung tissue at baseline and reducing excessive airway inflammatory responses to virus/allergen co-exposure), whereas OM-85 did not alter baseline gene expression, and had no effect on neutrophil or eosinophil influx over the time course of virus/aeroallergen co-exposure in low-risk PVG rats.

Age

A systematic review and meta-analysis showed that the effect of OM-85 as an add-on treatment for asthma was more pronounced in children than in adults [eg, greater improvement in forced expiratory volume in 1 second (FEV1%), significantly higher levels of sputum sIgA, a stronger intensity of reduction in peripheral eosinophil number, a greater decrease in IL-4 levels, and a higher increase in IFN-γ levels)].[43]

Severity of the Disease and Pattern of Immune Response

In a double-blind placebo-controlled trial, OM-85 did not reduce asthma exacerbations in the cohort of severe asthma patients; however, post hoc subgroup analysis showed potential clinical benefits for patients with type 2 inflammation [a specific immune response defined as blood eosinophils ≥150 cells/μL and/or forced expiratory nitrogen oxide (FeNO)

≥20 ppb].[44] The use of OM-85 was significantly associated with a delay in moderate COPD exacerbations (HR=0.68, *P*=0.02), rather than moderate-to-severe and severe exacerbations.[45]

Malignancy Risk Stratification

Ni et al observed that patients with high-risk pulmonary nodules who took OM-85 had a reduced probability of disease progression at a follow-up of more than 6 months and this trend was even more pronounced for patients with a very high baseline malignancy risk of pulmonary nodules (*P*=0.003) after the risk stratification assessment.[6]

Therapeutic Implications

If the results of de Jong et al's animal experiment are extrapolated to humans,[42] high-risk asthma patients with IRF7lo immunophenotype are more likely to benefit from OM-85 pretreatment. Current evidence show that the benefits of OM-85 in the treatment of asthma, COPD and pulmonary nodules may be associated with the patient's individual characteristics (eg, severity of the disease, age, immune response pattern, malignancy risk stratification). Therefore, attention should be paid to medication monitoring in clinical application of OM-85.

Perspectives and Further Research Opportunities

It is an interesting prospect for clinicians to focus on the new role of OM-85, an old drug released in the 1980s. There are many opportunities for further research in clinical practice. Firstly, it is necessary to identify the populations that would benefit most from OM-85 treatment. More detailed studies are needed to address the impact of immunophenotypes and population types. Secondly, longitudinal time-series analysis could be conducted to investigate whether the use of OM-85 combated antimicrobial resistance. Thirdly, it is of great interest to conduct high-quality randomized controlled clinical studies to verify the efficacy of OM-85 in the adjuvant treatment of diseases such as lung cancer, atopic dermatitis, COVID-19 infection, pulmonary tuberculosis and nephrotic syndrome. Fourthly, given the wide variety of oral BLs preparations available on the market, it is necessary to compare their differences in efficacy and safety.

Last but not least, there is a need for exploring the pharmacoeconomic value of OM-85 in the field of non-respiratory diseases from the perspective of different stakeholders. For example, a randomized, double-blind placebo-controlled clinical trial measured the cost-effectiveness of prophylactic treatment with BLs (Escherichia coli and Enterococcus faecalis) in newborns/small children with atopic dermatitis compared with placebo. Prophylactic use of the BLs in infants with single heredity for atopy for 26 weeks in the first year of life is cost-effective at the age of 3 and 6 years.[46] Therefore, it is also worth to study the pharmacoeconomic significance of OM-85 in the treatment of atopic dermatitis.

Conclusion

Understanding the latest research progress of OM-85 is helpful to broaden the vision of clinicians. The core pharmacological mechanism of OM-85 is acting on multiple innate and adaptive immune targets, and restoring type 1 helper T (Th1)/Th2 balance. OM-85 can be used for respiratory diseases associated with the indications described in the package insert; furthermore, seven diseases (ie, SARS-CoV-2 infection, allergic rhinitis, lung cancer, pulmonary fibrosis, pulmonary tuberculosis, atopic dermatitis, nephrotic syndrome) have been reported to be prevented or treated by off-label use of OM-85. The excellent safety of OM-85 guarantees the further study of its new effects. OM-85 can improve the effectiveness of standard care, and carry significant pharmacoeconomic implications in prophylaxis and treatment of RTIs, chronic obstructive pulmonary disease, asthma, chronic bronchitis, rhinosinusitis and allergic rhinitis. The benefits shown by OM-85 in vitro and in vivo, when extrapolated to humans, are exciting but also require caution. Individualized treatment of OM-85 may be required, taking into account the characteristics of the patients. Few comparative studies have been conducted on different oral BLs products, and thus it is necessary to investigate the possible product-specific response.

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