British Journal of Medicine & Medical Research
4(1): 368-381, 2014

SCIENCEDOMAIN *international*
www.sciencedomain.org

The Effect of the Oral Bacterial Extract OM-85 BV on Asthma Control- a Prospective Study

Antonios Christopoulos[1*], Lilia Pandeli [2] and Panagiotis Demopoulos[3]

[1]School of Health and Wellfear Professions, Department of Nursing Patras, Greece.
[2]Asthma" Outpatient Clinics Patras, Greece.
[3]University Hospital of Patras, Greece.

Authors' contributions

Author AC was the principal investigator and was responsible for the conception and design of the study and the analysis and interpretation of the data. Authors LP and PD contributed to the acquisition of study data and the follow up of the patients. All authors had access to the study data, contributed equally to the development of the submitted article, revising it critically for important intellectual content, and had the responsibility for the final approval before submission for publication.

Research Article

Received 7th April 2013
Accepted 6th September 2013
Published 28th September 2013

ABSTRACT

Aims: To identify the effect of the oral bacterial extract OM-85 on essential parameters of asthma control.
Study Design: This was a double blind, prospective study, consistent of a 4 week run-in and a 24 week double blind period.
Place and Duration of Study: An outpatient clinic, in collaboration with "St Andrew's'' General State Hospital in Patras/Greece, between October 2010 and April 2011.
Methods: Patients (aged 15-57, N=130) with persistent allergic asthma, were assessed and divided accordingly, in three strata: *Stratum I* (not controlled asthma, NCA), *stratum 2* (partly controlled asthma, PCA) and *stratum 3* (controlled asthma, CA). At the end of the run-in period were randomized to receive additionally to their standard treatment (appropriate doses inhaled budesonide and formoterol), 7mg oral OM-85 BV or matching placebo. Primary end-point was the proportion of patients with controlled asthma in every group. Change from baseline budesonide, mean FEV1, PEF, daytime asthma symptoms score, night awakenings, rescue b2-agonist use and serum interferon-γ (INF-γ) levels were also recorded and included in the final analysis.

**Corresponding author: Email: antonchrist2004@yahoo.gr;*

Results: At the end of the 24 week follow up, stratum I patients, treated additionally with OM-85 BV, presented significantly higher proportion of subjects with controlled (28.09% versus 18.7%, P<0.001), and partly controlled asthma (57% versus 43.7%, (P= 0.04). Almost all patients demonstrated significant increases (P<0.001) from baseline in FEV1.The percentage change from baseline FEV1 was 21.8% for OM-85 BV versus 12.1% for the placebo group. Same tendencies were recorded in every stratum and concerned al secondary end points, despite a lower dose of budesonide.
Conclusions: Patients treated additionally with OM-85 BV achieved better asthma control despite a lower dose of budesonide.

Keywords: Asthma control; OM-85; Broncho Vaxom; bacterial lysate.

1. INTRODUCTION

Asthma is a serious global health problem. The rising trends in asthma and the high healthcare costs mandate the development of therapies that may influence its natural history [1].

OM-85 BV is an extract of immune-stimulating fractions from eight pathogens, frequently responsible for bronchopulmonary, ear, nose and throat infections (*Haemophilus influenzae*, Diplococcus pneumoniae, *Klebsiella pneumoniae* and ozaenae, *Staphylococcus aureus*, *Streptococcus pyogenes* and viridans and *Moraxella catarrhalis*). Each bacterium is cultivated separately, killed, fractionated, and further purified and lyophilized to provide the final product.

The oral administration of this bacterial lysate is common in our every day practice, although it is not commercially available in US pharmacies at this time, as It offers a significant protection against respiratory tract infections (ARTIs) [2-7].

In the current study was evaluated the additive effect of oral OM-85 BV, to the combination of inhaled glucocorticosteroids (ICS) plus long-acting b2-agonist (LABA), upon the level of asthma control in young adolescents and adult patients.

Our hypothesis was that OM-85 BV would provide additional benefit, as measured by the proportion of patients who would achieve asthma control in the lowest step and dose of treatment necessary.

2. METHODOLOGY

2.1 Study Design

This was a randomized, double blind, parallel group, prospective study conducted in outpatient clinics in Greece in accordance with the Declaration of Helsinki and Good Clinical Practice. Patients gave written informed consent. The study consistent of two treatment periods: a 4 week run-in and a 24 week double blind (October 2010- April 2011).

2.2 Patients

Patients were aged 15-57 years and had a history of persistent asthma for a year or longer, associated with allergy in aeroallergens. The diagnosis of asthma was verified by physical examination, imaging (x-ray and occasionally computed tomography), lung function measurements and skin prick tests for inhaled allergens. All patients had at least one positive skin prick test (Parietaria Mix n=45, Olea Europea n=52, Mix Grasses n=70 and Alternaria n=17) and were in regular treatment with combinations of ICS plus LABA, for at least 8 weeks before entering the study.

Enrolled patients had a Forced Expiratory Volume in one second (FEV1) 60% to 80% of predicted normal, at least 12% reversible to inhaled salbutamol and 15% to 30% diurnal change of Peak Expiratory Flow (PEF).

Exclusion criteria included a smoking history of ≥10 pack-years and systemic use of corticosteroids. Patients with a respiratory tract infection affecting asthma and those who received oral or parental corticosteroids during the 4 week run-in period, chromones, leukotriene receptor antagonists or inhaled anticholinergics during the last 2 weeks, and theophylline or antihistamines during the last week of the run in period were not eligible for randomization. As variations in the exposure to domestic mite allergens have a significant impact on asthma related symptoms, patients with history and/or positive skin prick tests for indoor allergens were not included to the study. The baseline characteristics of the patients are shown in Table 1.

Table 1. Baseline characteristics of randomized patients. Data are means(SD), P value is for the two treatment groups

Characteristic	**OM-85 BV**	**Placebo**	***P***
	(n=70)	**(n=60)**	**for mean baseline values)**
Range age (years)	14-57	14-54	0.49
Sex, n (%)			
Male	25 (35%)	22 (36%)	
Female	45 (65%)	38 (64%)	
Mean (SD) Body mass index	28.0 (4.6)	26.9 (4.7)	0.43
Ex-smokers (%)	25%	28%	
Mean (SD) use puffs/day salbutamol	1.7 (0.67)	1.6 (0.84)	0.38
Budesonidedose level, * n (%) 200-400 mcg/day	24 (35%)	22 (36%)	0.85
Mean(SD) morning PEFR	3.15 (0.43)	3.11 (0.43)	0.41
Mean (SD) PEFR diurnal change (%)	18.1 (3.07)	18.2 (3.07)	0.46
Mean(SD)asthma symptom score	3.8 (4.2)	4.1 (4.2)	0.45
Mean (SD) nocturnal awakenings (nights/4 weeks)	2.8 (0.78)	3.0 (0.78)	0.28

2.3 Run-in Period

Entering the study, we assessed the severity and level of asthma control of the patients in the current treatment. Following, eligible patients received non-blinded the appropriate maintenance treatment (inhaled budesonide 200-800 μg/day plus formoterol 18mcg/day, administered twice daily) according to GINA/NIH guidelines [8]. The selection of the budesonide dosage was determined by the patients' level of asthma control and the treatment already commenced. Patients were inhaled budesonide and formoterol from a Turbuhaler (Pulmicort 200μg and Oxez 9μg respectively, AstraZeneca Liquid Production, Sweden). During the last 2 weeks of this period, single blind placebo OM-85 BV was added.

2.4 Double-blind Period

In the end of the run-in period patients were reassessed to establish their adherence to the current regimen and level of asthma control. Following, eligible patients were divided accordingly, in three strata: *Stratum I* (uncontrolled, NCA), *stratum 2* (partly controlled asthma, PCA) and *stratum 3* (controlled asthma, CA).

In NCA patients the dose of budesonide was stepped up to 4 times the dose used (up to 1600 μg/day). In PCA patients the dose of budesonide was increased by 50%, while in CA patients budesonide dosage was stepped down by 50%.

Following patients in each stratum were randomized according to a central computer generated schedule, (in the statistical service of the medical school of Patras), to receive either 7mg of OM-85 BV (Bronho-Vaxom; OM PHARMA;Geneva; Switzerland)) once daily orally, fasting in the morning, or matching placebo. The investigators were not involved and were blinded to the randomization.

Treatment assignments (1:1) were stratified in every stratum according 3 budesonide dose levels (200-400, 400-800 and 800-1600 mcg/day). In the absence of exacerbations and/or adverse events, patients were reassessed every 12 weeks and the dose of budesonide was titrated each time, as prescribed above.

During the study, use of theophylline, leukotriene modifiers and extra formoterol was not permitted. Nedocromyl nasal spray and eye drops were permitted, in order to treat allergic rhinitis and conjunctivitis respectively.

2.5 Evaluations

The primary end point was the proportion of patients with NCA, PCA and CA in every stratum, in each treatment group, at the end of the active treatment period. Percentage change from baseline in budesonide dosage, mean FEV1 before using a b2 agonist, mean PEF, diurnal variability of PEF, daytime asthma symptoms score, number of night awakenings and total daily as-needed b2 agonist use were recorded. Serum interferon- γ (INF- γ) levels were also detected.

Spirometry was performed at screening, at randomization, and in every reassessment. The largest FEV1 from a set of three acceptable maneuvers was recorded as the true value. Spirometric measurements were recorded with a standard spirometer (KoKo spirometer, PDS instrumentation, Louisville, USA), which was calibrated every day. The enclosed

software ensured uniform adherence to European Respiratory Society standards of acceptability and reproducibility [9].

All patients were given a peak flow meter (Mini Wright model, Micro Medical Rochester UK) and a practice diary card for recording daily day time asthma symptom score, asthma related nocturnal awakenings, salbutamol use, morning and evening PEF. Measurements of PEF were performed twice daily, immediately upon awakening and 12 hours later, 15 to 30 minutes following formoterol inhalation. The diurnal PEF variability was estimated as the difference between the pre-bronchodilator morning value and the post bronchodilator value from the previous evening, expressed as a percentage of the mean daily PEF value.

Day time asthma symptoms were recorded on a scale of 0-5, where 0 = no symptoms, 1= symptoms for one short period, 2 = symptoms for two or more short periods, 3 = symptoms for most of the day that did not affect normal daily activities and 5 = symptoms so severe that normal daily activities could not be performed. Night-time asthma symptoms were scored as 0 (no symptoms) or 1 (symptoms caused an awakening or early waking). In addition, patients recorded the number of as-needed salbutamol puffs per day.

Blood samples for measurements of INF-γ serum levels were collected at entering and the end of the active treatment period. INF-γ was measured using an ELISA kit (R&D Systems Inc. USA) with a detection limit 5 units/ml. Blood samples for ELISA assay were collected in Thrombotect tubes which contained EDTA, 2-chloroadenosine and procaine. The samples were immediately placed on ice and within 1 hour were centrifuged at 400 x g for 30 min at 4ºC. The plasma was then centrifuged at 20,000 x g for 20 min at 4ºC and the platelet depleted plasma frozen at -80 ºC until testing.

A week with controlled asthma (CA) was defined as a week with twice or less daytime symptoms, no nocturnal symptoms/awakenings, no exacerbations, twice or less need for reliever medication, and a normal morning PEF. A partly controlled asthma (PCA) week, was defined as a week with more than twice daytime symptoms, any nocturnal symptoms, more than twice/week need for reliever medication, no exacerbations and a morning PEF < 80% of the predicted or personal best value every day. Patients not achieving at least a partly controlled status for at least 10 of the 12 weeks between assessments were considered as not controlled (NCA).

Exacerbations were defined as days when any of the following occurred: an asthma attack or, on 2 consecutive days, nocturnal awakening, increase from baseline of more than 50% in symptoms score, use of at least 4 puffs/day of b2 agonist, decrease from baseline of more than 30% or more than 100 l/min in PEF, or daily variability of more than 20% in PEF.

2.6 Rescue Protocol for Exacerbations

All patients had a written action plan based on symptoms and peak flow measurements that outlined how to manage asthma attacks. Mild episodes were treated with salbutamol inhalations. In case of incomplete or poor response, the patients contacted the clinician immediately. After assessment of the severity of the episode, appropriate treatment was undertaken at home or in a hospital-based emergency department. If that be the case, patients were withdrawn from the study. Any patients with symptoms that persisted 14 days after stepping up to the highest budesonide dose (1600 mcg/day), contacted the investigator. The investigator implemented alternative treatment as necessary but the patient was excluded from the study.

2.7 Statistical Methods

All analyses were performed for the intention-to-treat patient population that included all patients who had both a baseline and at least three post-treatment assessments. The results were expressed as mean ±SD values averaged each time for the number of patients that remained in the study. At the end of the study, the number of the patients with NCA, PCA and CA (expressed as % values) in every stratum in OM-85 BV treatment group, were compared with the respective numbers from the placebo group. For those efficacy outcomes with a baseline value, the mean % changes from baseline were calculated. Least square means (LS) standard error (SE) changes from baseline were also computed. All hypothesis testing was done using two-sided alternative hypotheses, and p-values <5% were considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Patient disposition and baseline characteristics

Of 145 patients assessed at the entry point of the study, 130 were randomly assigned to receive double blind treatment, 70 were assigned to OM-85 BV and 60 to placebo (Table 1). Of these 112 (86%) completed the 24 week follow up as planned for the study. Reasons for not randomizing patients and for discontinuation are shown in Table 1. For randomized patients, mean baseline characteristics were comparable for the two treatment groups, mean budesonide dosage in each stratum included (Table 2, 3).

Discontinuation was not similarly distributed between OM-85 BV (8.7%) and placebo (16.6%) groups (Table 1). Fourteen patients (10.7%) were withdrawn following a severe asthma exacerbation. In ten of the cases a respiratory tract infection was identified as the trigger, 2 in OM-85 BV (2.8%) and 8 in placebo group (13.3%).

Table 2. Flow chart of study patients

Registered patients: 145		
Randomized patients after run in period: 130		
	Bronho-Vaxom	**Placebo**
Received:	70	60
Complete follow up as planned:	63	49
Discontinued before the planed 90 day follow up:	7	11
- asthma exacerbation:	6	10
- following ARTI	2	8
- non compliance:	1	1
Included in the main analysis:	63	49

Of the 15 who were not randomized, 2 deviated from the protocol, 8 experienced an adverse clinical event, 3 were not cooperative and 2 were lost to follow up.

Table 3. Participants entering the double blind, active treatment period in three strata based on the control of their asthma, and the mean (SD) budesonide dose commenced in every stratum at intake

OM-85 BV treatment group:	N	Mean (SD) mcg/day budesonide	*P* value
Stratum I (NCA)	25	846 (497)	0.95
Stratum II (PCA)	32	800 (346)	0.74
Stratum III (CA)	13	828 (531)	0.98
Placebo treatment group:			
Stratum I (NCA)	21	854 (498)	
Stratum II (PCA)	27	770 (349)	
Stratum III (CA)	12	833 (577)	

P value is for differences in budesonide dosage between the treatment groups, CA is for controlled asthma, PCA is for partly controlled asthma and NCA is for uncontrolled asthma

3.2 Efficacy End Points

Patients in each stratum with CA, PCA and NCA, budesonide dosage and percentage change from baseline, are presented in Table 3.

At the end of the 24 week follow up, *stratum I* patients (NCA), treated additionally with OM-85 BV, presented a significantly higher proportion of subjects with controlled asthma (28.09% versus 18.7%, P<0.001), and partly controlled asthma (57% versus 43.7%, P =0.04), despite a lower dose of budesonide dosage.

The same tendencies were recorded in *stratum* II and *stratum* III patients treated additionally with OM-85 BV. Higher proportions of subjects controlled their asthma and tolerated better the tapering of budesonide (Table 4).

Table 4. Participants at the end of the double blind treatment period, by asthma control, mean (SD) and mean % change from baseline in budesonide dose

OM-85 BV group:	CA	PCA	NCA	m.(SD) BD	m. change BD	LS (SE)	*P* value
		N (%)		mcg/day	%		
Stratum I	6 (28,09)	12 (57)	3 (14.2)	1000 (600)	18	0.18 (0.02)	< 0.001
Stratum II	16 (53.3)	14 (46.7)		606 (240)	-24	-0.42 (0.04)	0.01
Stratum III	12 (100)			446 (350)	-46	-0.29 (0.02)	< 0.001
Placebo group:							
Stratum I	3 (18.7)	7 (43.7)	6 (36)	1152 (565)	34	0.37 (0.02)	0.04
Stratum II	6 (30.3)	14 (46.7)		628 (252)	-18	-0.51 (0.04)	0.1
Stratum III	12 (100)			600 (273)	-27	-0.54 (0.02)	< 0.001

P value is for differences in proportion of patients with CA and p value is for difference in mean % change in budesonide dose between treatment groups, BD is for budesonide, CA is for controlled asthma, PCA is for partly controlled asthma and NCA is for uncontrolled asthma*

Almost all patients demonstrated significant increases (P<0.001) from baseline in FEV1 (Fig. 1). The Least square mean (SE) change from baseline was 1.05 (0.17) in patients treated with concomitant OM-8 BV versus 0.87 (0.17) in the placebo group (effect difference 0.18, 95% CI 0.12 to 0.54, *P*= 0.03). Averaged for the 24 weeks of treatment, the percentage change from baseline FEV1 was 21.8% for OM-85 BV versus 12.1% for the placebo group (Fig. 1). These results were independent from the budesonide dose level (*P*= 0.69).

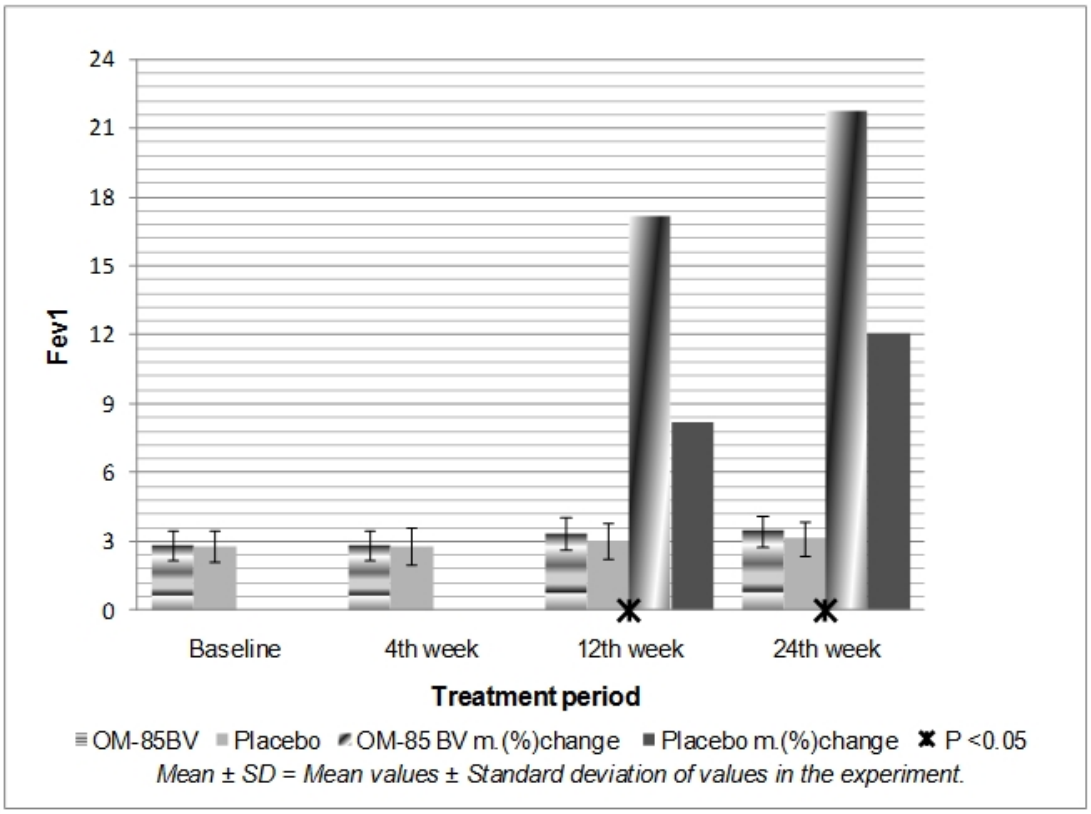

Fig. 1. Variations of FEV1 from baseline, during the 4-week run-in and the 24 week active treatment period in OM-85 BV and placebo groups of patients

The same tendency was recorded in all prespecified secondary efficacy end points (Table 5). Both treatment groups significantly increased from baseline morning PEF and decreased PEF variability, daytime asthma related symptom scores, number of nocturnal awakenings and the total daily use of reliever medication. The above improvements were also independent from the dose level of budesonide (*P*=0.05). For every particular efficacy outcome, the end point value recorded in the patients on concomitant OM-85 BV treatment was significantly improved.

Table 5. Secondary outcome parameters at the end of the 24 week follow up, mean values and mean percentage changes from baseline, in the two treatment groups.

OM-85 BV						
Outcome parameter	**m. (SD)value**	**95%CI**	**m. (%) change**	**LS (SE)**	**P value**	**P *value**
Morning PEF	3.82 (0.59)	3.62-4.03	21.3	1.23 (0.27)	<0.001	0.04
PEF diurnal change %	10.4 (1.77)	10.19-10.60	42.5	-0.23 (1.72)	<0.001	<0.001
Daily symptom score	0.5 (0.26)	0.19-0.60	86.8	-0.46 (0.05)	<0.001	0.003
Night awakenings/month	0.3 (0.48)	0.18-0.44	89.2	-0.10 (0.02)	<0.001	0.01
Puffs/day b agonist	0.3 (0.48)	0.17-0.72	82.3	-0.21 (0.48)	<0.001	0.04
Placebo						
Outcome parameter	m. (SD) value	95% CI	m. (%) change	LS (SE)	P value	
Morning PEF	3.38 (0.50)	3.19-3.58	8.8	1.06 (0.15)	<0.001	
PEF diurnal change %	13.6 (1.42)	13.40-13.79	25.2	-0.03 (0.02)	<0.001	
Daily symptom score	0.8 (0.65)	0.60-0.99	74.2	-0.23 (0.05)	<0.001	
Night awakenings/month	0.7 (0.56)	0.74-0.85	76.6	-0.3 (0.02)	<0.001	
Puffs/day b2 agonist	1.7 (0.48)	0.54-1.85	56.2	-0.03 (0.51)	0.005	

P is for differences from baseline, and P is for differences between treatment groups.*

OM-85 BV significantly increased the serum levels of the INF-γ (P <0.001). Entering the double blind period, there was detectable INF-γ (5-15 units/ml) in the serum of 9 patients randomized to receive OM-85 BV and 12 patients randomized to placebo (mean value 0.7 (0.5) units/ml and 1.3 (0.8) units/ml respectively). At the end of the 24 week follow up 38 patients treated with concomitant OM 85 BV had detectable serum INF-γ levels in comparison with 29 in the placebo group (mean values 3.6 (2.4) units/ml and 4.4 (2.8) units/ml). The Least square (SE) mean change from baseline was 1.2 (0.06) for the OM 85 BV and 0.7 (0.05) for the placebo group an effect difference 0.5, 95% CI 0.1 to 0.9, P= 0.02).

3.3 Discussion

Treating our patients with constant, individualized, low-medium doses of budesonide, in combination with formoterol, was achieved a good overall asthma control. However, it is known that some patients cannot obtain the targeted level of asthma control, even with the best therapy [10]. For patients with difficult-to-treat asthma, higher doses of ICS are often used after ensuring the diagnosis is correct, evaluating adherence and managing co-morbid conditions [8].

In the current study the number of patients that achieved asthma control at the end of the 24 week treatment period was significantly increased in the OM-85 BV group. The addition of the later resulted also in significant reductions in the dose of budesonide necessary to maintain control.

Both treatment groups improved significantly in all the studied parameters. The addition of OM-85 BV offered further benefit in this patient population. Patients on OM-85 BV demonstrated significantly higher FEV1, morning PEF, lower PEF variability, improved daily symptoms score, less night awakenings and lower supplemental salbutamol use. All the above were evident despite the large placebo effect, often recorded in clinical trials of asthma treatment, resulting probably from the frequently repeated disease assessments and the better adherence to treatment that occur in clinical trials [11].

3.1 Comparison with Other Studies

Improvements in asthma control following OM-85 BV administration has been reported in other studies. Czerniawska et al. reported a reduction in the as needed use of bronchodilators and an alleviation of the asthma related clinical symptoms in adults with recurrent acute bronchitis and bronchial asthma treated with OM-85 BV [5]. In another multicentre study, Begovic et al. administrated OM-85 BV as preventive treatment for childhood asthma. Improvements in patients' quality of life reduced use of antibiotics and fewer school absences were reported [6]. Shmelev EI et al. studied also the efficacy of OM-85 BV against bronchial asthma exacerbations [7]. Good results like reduction of disability duration, number of recurrences, cough intensity and discharged sputum were reported. It was interesting to notice that during the latter study an IgE decrease and a T4/T8 increase in bronchoalveolar lavage, were detected.

Numerous scientific studies, both in vitro and in vivo, have been carried out to determine the mechanisms by which OM-85 BV stimulates immune system. Manuel et al. established that OM-85 BV activates mouse peritoneal and bone marrow macrophages in vitro [12]. Further work performed by Fontages et al., showed that OM-85 BV stimulated the release of prostaglandin E2, IL1 and TNF-a from alveolar macrophages [13]. In a later study Keul et al.

exposed human lung fibroblasts to OM-85 BV and total RNA and Northern analysis performed for many cytokines. Transcription of IL 2, 3, 4, 5, 7, 10, GM-CSF and M-CSF was not recorded. In addition it was demonstrated that OM-85 BV specifically up regulated the production of IL-6, IL-8 and TNF-a, cytokines that are important mediators particularly of the Th1 immune responses [14].

Emmerich et al., examined the bronchoalveolar lavage fluid in adults, before and after treatment with OM-85 BV. It was clearly demonstrated that after treatment, IFN-γ levels and alveolar macrophage activity were increased significantly [3]. Findings verified later by Lusuardi et al. too [4].

It is demonstrated that high levels of INF-γ and the concomitant alveolar macrophages activation, detected after OM-85 BV treatment, diminishes Th2-cells responses inhibiting IL-4 production. This in turn, inhibits B lymphocyte activation and IgE production, thus improves asthma control [14-17].

Accepting the above observations one could speculate that the administration of OM-85 BV is capable of modulating immune responses in an altered trajectory away from the ‘’allergic’’ Th2 pattern more towards a ‘’protective’’ Th1 pattern. The increase in the INF-γ serum levels detected in the current study in the OM-85BV treated patients as credence to accept such a speculation which could explain the improvements in parameters of asthma control recorded, as well as the alleviation from the asthma related symptoms reported in both adults and children.

The aim of this study was not to determine the mechanisms by which OM-85 BV influences asthma’s natural history. Further studies are needed to verify whether the improvements in asthma control, recorded in this study after treatment with OM-85 BV were attributed to a swift in immune responses or were simply an extension of a lower incidence of respiratory tract infections. In the currents study, a protective effect of OM-85 BV against ARTIs was obviously demonstrated, resulting in significantly lower rate of ARTI associated asthma exacerbations in OM-85 BV as compared to placebo group of patients (8.5% vs 16.6% $P<0.001$, Table 2). However, as the improvements recorded concerned those patients who completed the follow up without exacerbations, any potential influence of ARTIs on asthma control was minimized.

4. CONCLUSION

For patients with persistent, atopy associated asthma, remaining symptomatic the addition of OM-85 BV to the combination of budesonide and formoterol, provided significant benefit. Improved asthma control was evident by the increased number of patients that remained asymptomatic despite the lower budesonide dosage, the increases in FEV1 and morning PEF before a b2 agonist use, the decreases in PEF variability, day time symptom score, number of night awakenings and puffs per day as needed salbutamol.

OM-85 BV deserves further studying in order to justify its use as an additional therapeutic option for patients suffering from asthma.

ACKNOWLEDGEMENTS

The authors thank all patients who took part and the staff of the participating clinical centers. The authors also thank Dr Ev. Ikonomopoulou (St. Andrews General State Hospital, Patraw/GR) for performing the immunoassays.

CONSENT

All authors declare that 'written informed consent was obtained from the patients for publication of this study.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Dr Antonios Christopoulos has received fees for speaking from USB, Novartis and MSD, and has participated as an investigator in clinical trials sponsored by Astra Zeneca, GSK, Novartis, Boehringer Ingelheim and Elpen.

REFERENCES

1. British Thoracic Society. Scottish Intercollegiate Guidelines Network (SIGN). British guidelines on the management of asthma. Thorax. 2003; 58(Suppl.1):1-94.
2. Manuel J. Stimulation of immune-protective mechanisms by OM-85 BV. Respiration. 1994;61:8-15
3. Emmerich B, Emslander HP, Panhmann K, et al. Local immunity and the effects of a bacterial extract, Bronho-Vaxom, on T lymphocytes, macrophages, gamma-interferon and secretory Immunoglobulin A in Bronchoalveolaren lavage fluid and other variables. Respiration. 1990;57:90-99.
4. Lusuardi M, Capelli A, Carli S, et al. Local airways immune modifications induced by oral bacterial extracts in chronic bronchitis. Chest. 1993;103:1783-1791.
5. Czerniawska-Mysik G, Adamek-Guzik T, Dyczek A, Kotlinowska T. Double blind clinical study with Bronho-Vaxom in the treatment of recurrent acute bronchitis and bronchial asthma. Int J Immunotherapy. 1992;8:153-159.
6. Begovic D, Maksimivic T, Popovic M, et al. Bronho-Vaxom therapy in childhood asthma. J Asthma. 2003;4(suppl):116.
7. Shmelev EI, Sokolova LV, Kosmiadi GA, et al. Use of Bronho-Vaxom in the treatment of patients with chronic obstructive bronchitis and bronchial asthma. Probl Tuberk. 1995;(3):37-41
8. American Thoracic Society. Standardisation of Spirometry, 1994 update. Am J Respir Care Med. 1995;152:1107-36.
9. Baterman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. Am J Respir Crit Care Med. 2004;170(8):836-44
10. Joyce DP, Jackevicius C, Chapman KR, et al. The placebo effect in asthma therapy trials: a meta-analysis. J Asthma. 2000;37:303-18.

11. Manuel J, Pham TV, Kreis B, Bauer J. Stimulation by a bacterial extract (Bronho-Vaxom) of the metabolic and functional activities of murine macrophages. Int J Immunopharmac. 1989;11:637-645.
12. Fontages R, Bottex C, Cristau B, Burchkart MF. Influence of a bacterial extract on antigen presentation and protection against experimental infections. Lung. 1990;168:716-719.
13. Keul R, Roth M, Papaconstantinou E, Nauck M, Perruchoud AP, Block LH. Induction of interleukin 6 and interleukin 8 expression by Bronho-Vaxom (OM-85 BV) via C-Fos/serum responsive element. Thorax. 1996;51:150-154.
14. Del Prete G. Human Th1 and Th2 lymphocytes: their role in the pathology of atopy. Allergy. 1992;47:450-455.
15. Barnes PJ. New directions in allergic diseases: mechanism-based anti-inflammatory therapies. J Allergy Clin Immunol. 2000;106(1Pt.1):5-16.
16. Romagnani S. Lymphokine production by human T cells in disease states. Annu Rev Immunol. 1994;12:227-57
17. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. (Review inc. Levels I and II).Updated 2007. Retrieved February 2008. Available: http://www.ginasthma.com

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=215&id=12&aid=2075