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Esberitox® N as Supportive Therapy when Providing Standard Antibiotic Treatment in Subjects with a Severe Bacterial Infection (Acute Exacerbation of Chronic Bronchitis)

A Multicentric, Prospective, Double-Blind, Placebo-Controlled Study

Wilfried Hauke[a] Gert Köhler[b] Hans-Heinrich Henneicke-von Zepelin[b] Johannes Freudenstein[b]

[a]EPA-Europharma Auftragsforschung, Kronberg, and [b]Schaper & Brümmer, Salzgitter, Germany

Key Words

Chronic obstructive pulmonary disease · Acute exacerbation · Immunomodulation · Antibiotic treatment · Echinacea · Thuja-Babtisia-Phytomedicine · Herbal treatment · Echinacea purpureae · Echinacea pallida · Bacterial infection

Abstract

53 patients with planned antibiotic therapy for the treatment of acute exacerbation of chronic bronchitis as an example of a severe bacterial infection requiring antibiotics were included in a prospective, multicentre, double-blind, placebo-controlled study. The chronic bronchitis was staged by forced expiratory volume of the 1st second (FEV_1) measured in the infection-free interval prior to the current episode and had to be between 35 and 75% for the predicted value. Patients were randomly assigned to receive newer macrolide antibiotics plus either Esberitox® N or placebo. Antibiotic therapy was administered according to generally accepted guidelines and Esberitox N or placebo was given for 28 days. The baseline-adjusted means for FEV_1 (%) on day 10 were 68.7 points for the Esberitox N group and 59.2 points for the placebo group ($p = 0.0303$). For FEV_1 the difference between the two treatment groups was 267 ml ($p = 0.0499$). The time to half maximal improvement was 5.7 days in the Esberitox N group compared to 12.8 days in the placebo group. The treatment was well tolerated; no serious adverse events were documented. In conclusion, comedication of antibiotics with Esberitox N in subjects with acute exacerbation of chronic bronchitis seems to be of benefit for the patient. Apparently, therapy with Esberitox N leads to a faster recovery from this severe bacterial infection, possibly via preventing an impairment of the host's immune system which might otherwise occur as a consequence of aggressive antimicrobial therapeutics.

Investigators: H.-P. Mayer-Anhalt, Marburg (20 patients), H.-P. Wendl, Annweiler (20 patients), W. Ihl-Beste, Ober-Mörlen (6 patients), P. Schöpe, Mörfelden-Walldorf (4 patients), K. Weyland, Ingelheim (2 patients), and C. Kunz, Frankfurt am Main (1 patient).

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Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

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Dr. Gert Köhler
Schaper & Brümmer GmbH & Co. KG
Bahnhofstrasse 35
D–38259 Salzgitter (Germany)
Tel. +49 5341 307 510, Fax +49 5341 307 524, E-Mail gert.koehler@schaper-bruemmer.de

Introduction

Chronic bronchitis is a common problem affecting a large proportion of the adult population [1] It is clinically defined as an excessive cough and abnormal production of sputum on most days for at least 3 months during at least 2 consecutive years (WHO definition). Particularly in advanced stages it is often complicated by acute infectious exacerbation leading to chronic obstructive pulmonary disease (COPD) [2, 3]. COPD is a progressive disease characterized by reduced expiratory air flow which is relatively stable over several months of observation [4]. An acute exacerbation of COPD is usually defined as an episodic respiratory decompensation without an objectively documented cause. Among severe bacterial infections, the infectious exacerbation of chronic obstructive pulmonary disease is of major importance as it tends to relapse frequently, reduces the patients' quality of life significantly, and bears the risk of aggravating the patients' general state of health [2, 5, 6]. Primarily it is characterized by an increasing cough combined with increasing purulence in sputum. Therapeutic guidelines recommend the treatment with antibiotics, although the role of bacterial infection in exacerbations is still controversial [7–11]. Additionally, the efficacy of the antibiotic therapy either for a short-term or a long-term benefit remains unclear. A causal relationship can be inferred by the appearance of an acute antibody response in serum to these bacteria and by an increase in inflammatory mediators in purulent sputum [12]. In a further study patients were stratified according to their symptoms in order to predict a response to antimicrobic therapy. The results from this study showed that patients having at least two bronchitis symptoms benefit from antibiotic therapy leading to improved clinical outcome, fewer therapeutic failures and a more rapid rate of lung function recovery compared to placebo. This stratification is used as Winnipeg criteria in numerous treatment studies for bronchitis [13].

COPD is a common disease and patients are reported to have an average of one to four exacerbations per year. Severity and frequency of exacerbations correlate with the duration of chronic bronchitis. It is supposed that bacterial populations in patients with a long history of bronchitis and frequent episodes of bacterial infections in the past change from predominantly gram-positive to gram-negative germs which are generally more difficult to eradicate [14]. *Streptococcus pneumoniae, Haemophilus influenzae* as well as *Moraxella catarrhalis* are the most frequent isolated bacteria from sputum of patients suffering from acute exacerbation [15–18]. The antimicrobial treatment, however, gets more and more complicated because of an increase in individually acquired resistance due to frequent antibiotic therapy as well as increasing epidemiologic resistance [9, 14, 19]. A bacterial background cannot be made responsible in all patients since only in 50–60% of patients bacteria can be isolated. Viral pathogens either alone or combined with bacterial pathogens can also play an important role causing exacerbations.

These considerations led to the idea of combining antibiotic treatment with an allopathic phyto-immunomodulator (Esberitox® N), which is registered in Germany for several indications such as the supportive therapy of severe bacterial infections treated with antibiotics or treatment of the common cold and plays an important role in the treatment of patients in the general practice [20–22]. Esberitox N contains an extract of the herbal drugs, *Echinacea, Baptisia* and *Thuja* (cone flower, wild indigo and white cedar). These herbs are part of the traditional medicine used by native Americans for the treatment of several diseases affecting the immune system [23, 24].

The immune-stimulating properties of Esberitox N are mainly based on the activation of macrophages and other parts of the unspecific immune system [23, 24]. Furthermore, an increase of immunoglobulin synthesis can be noted. Hence, non-specific phyto-immunomodulation caused by Esberitox N is understood to have an antigen-independent influence on the immunoprotective systems of the organism [11] and the therapeutic benefit consists of a rapid onset of the improvement of symptoms [25, 26]. For this reason, it seemed obvious to use the immunoprotective properties of Esberitox N as a supportive therapy when providing standard antibiotic treatment in subjects with an acute exacerbation of chronic bronchitis.

So far several studies were conducted with Esberitox N, some of them in compliance with GCP [20, 23, 27; Scaglione, unpubl. data]. The most recent research focused on the efficacy of Esberitox N in the therapy of acute viral respiratory tract infection [22, 28]. Some papers on clinical studies are discussing the efficacy of the remedy as adjuvant drug in antibiotic therapy of bacterial infections [29, 30]. However, these studies need to be verified under GCP conditions. Therefore, it was decided to investigate whether the immunomodulating effect of Esberitox N is of benefit for subjects suffering from acute exacerbation of chronic bronchitis. We report the results of the pilot study followed by a new large-scale trial.

The antibiotic group of newer macrolides was chosen according to guidelines for the treatment of lower respiratory tract infections [9, 10, 31, 32].

Forced expiratory volume of the 1st second (FEV_1) is a well-accepted surrogate parameter of lung function and can be used to classify COPD [3, 14, 33]. Therefore and following the American Thoracic Society guidelines [34] it was chosen as primary objective. The benefit for the subject result in either stabilizing the decreased lung function or a prolongation of the infection-free interval between two episodes. Both results would increase the quality of life of the subjects and subsequently reduce health care costs [5].

Methods

Subjects

Eligible subjects were adult men and women (age < 75 years) with acute exacerbation of chronic bronchitis that had been clinically diagnosed before enrolment in the study. Only patients with FEV_1 stage I–II according to the ATS guidelines (value between 35 and 75% of the predicted value) measured in the infection-free period preceding the acute episode and showing clinical signs according to Winnipeg type I and II were enrolled. Patients taking antihistamines such as terfenadine or astemizole were excluded due to the risk of an interaction with macrolides. The criterion for administering the study drug was the clinically approved diagnosis of acute exacerbation of chronic bronchitis in patients who had at least two episodes per year. Patients were not allowed to receive additional immunomodulating treatments or systemic corticoids. The restricted use of inhalative corticoids was permitted.

The protocol was approved by the relevant ethics committees for each participating centre. The study was performed in accordance with the requirements of good clinical practice.

Study Design

The trial was a double-blind, placebo-controlled, parallel group study conducted at 6 centres in Germany. The patients were randomly assigned to receive a new generation macrolide antibiotic, such as roxithromycin, clarithromycin, azithromycin together with Esberitox N or placebo administered as a solution for 28 days. The dosage of Esberitox N was 50 drops 3 times a day, corresponding to 8.8 ml/day. 1 ml Esberitox N contains 0.43 ml of an alcoholic-aqueous extract (1:11) which corresponds to 4 mg *Herba Thujae occidentalis* (white cedar leaf), 15 mg *Radix Echinaceae* (cone flower root; E. purpureae/pallida 1 + 1) and 20 mg *Radix Baptisiae tinctoriae* (wild indigo root).

Patients were evaluated at baseline, day 3 (optional), day 10, day 28 and month 3 as a late follow-up. In this pilot study, a sample size of 53 patients was considered to be sufficient for obtaining first estimates of the effect of the study drug on the primary endpoint in order to plan a subsequent large-scale trial.

Efficacy Assessments

The primary objective of the study was to investigate the improvement of FEV_1 at day 10 compared with FEV_1 measured at baseline. Secondary objectives were to compare both treatment groups regarding profile analysis of FEV_1 at different time points as well as other parameters of lung function [vital capacity (VC), forced vital capacity (FVC)] and the re-infection rate in the time following the treatment with antibiotics during the late follow-up period. Patients were also examined in a subgroup analysis according to age, whether they were or had been smokers, according to their staging of severity and the duration of chronic bronchitis.

Safety Assessments

The safety of treatment was monitored on the basis of physical examination, vital signs, global impression of tolerability and the occurrence of adverse events.

Statistical Analysis

The primary objective variable (FEV_1) was analyzed in a confirmatory manner in a mixed model using the baseline values as a covariate factor. The performed analysis of covariance (ANCOVA) was tested one-sided on a significance threshold of $\alpha = 0.05$. In addition, non-parametric tests on the differences from baseline were presented. Each patient who had received Esberitox N or placebo was considered as enrolled in the study and was evaluated according to the intention-to-treat principle. The per protocol collective was defined as all patients receiving study treatment and following all instructions outlined in the protocol. Minor deviations did not lead to exclusion from the per protocol collective. All patients treated with study medication were included in the assessment of safety and tolerability parameters.

According to the protocol the intention-to-treat collective was analyzed for all efficacy parameters. Additionally an analysis considering the per protocol collective as subgroup was performed to confirm the results.

Results

The study was performed between September 1999 and May 2000. A total of 53 patients were enrolled in the study, 25 randomly assigned to the treatment group and 27 to placebo group. 1 patients was lost to follow-up after visit 1 and excluded from analysis. Baseline demographic and clinical characteristics were similar in both treatment groups, especially for the COPD stage and Winnipeg criteria (see table 1). All patients received the study drug Esberitox N or placebo for 28 days as outlined in the protocol. Antibiotic treatment for almost all patients was azithromycin (n = 51) which was taken for 5 days (500 mg once a day at the first day, then 250 mg once a day according to the summary of product characteristics). Therapeutic failure on day 10 was assessed in 2 Esberitox N patients versus 3 placebo patients. At follow-up the condition of 1 additional patient in both groups had worsened. The use of concomitant treatment during the study was comparable in both treatment groups.

Efficacy of Treatment

A statistically significant difference was found for the main outcome variable to be in favour of those patients receiving Esberitox N compared to placebo. Table 2

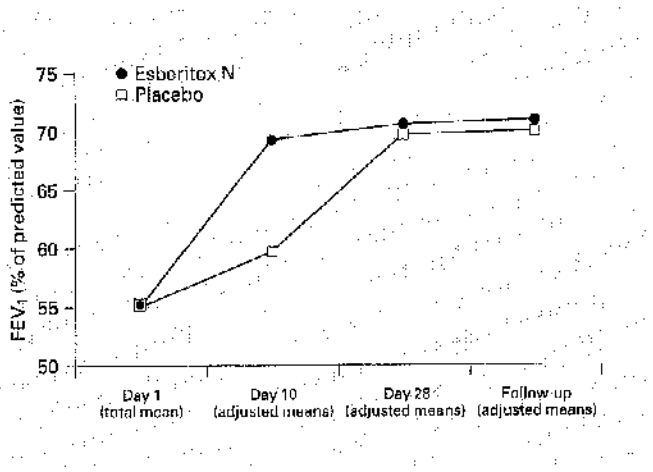

Fig. 1. Comparison of FEV_1 (%) values measured at day 1 and adjusted values at day 10, 28 and at the follow-up visit (means in % of predicted value, intention-to-treat collective).

Table 1. Age, height, weight and COPD of all enrolled subjects (intention-to-treat collective)

		Total	
		Esberitox N (n = 25)	placebo (n = 27)
Age, years	Mean	44.24	45.67
	SD	14.90	14.38
Height, cm	Mean	169.04	166.30
	SD	10.22	9.06
Weight, kg	Mean	75.80	74.54
	SD	15.77	17.85
COPD (stage)	I	20	21
	II	4	6
Anamnestic FEV_1, %[a]	Mean	64.68	60.52
	SD	12.48	10.90

[a] % of the predicted value.

shows the improvement of the FEV_1 (%) for both treatment groups. The baseline-adjusted means on day 10 were 68.7% for the Esberitox N group and 59.2% for the placebo group. The difference between the two treatment groups was 9.57% (standard error = 4.98%) and was statistically significant (ANCOVA; p = 0.0303, one-sided). The one-sided 95% confidence interval for the difference of the adjusted means was 1.21%, ∞ and indicated that the lower bound was >0. In addition, the non-parametric Kruskal-Wallis test on the difference from baseline supports the results from the ANCOVA with a significant result of p = 0.0277. Measured in absolute volume (FEV_1, ml) the baseline-adjusted means on day 10 were 2,141 ml for the Exberitox N group and 1,873 ml for the placebo group (see table 3) and reached statistical significance in the non-parametric test (p = 0.04991).

Figure 1 shows that the mean baseline-adjusted FEV_1 percent values measured at day 1, 10, 28 and at follow-up visit showed a faster improvement of the Esberitox N group compared to placebo at day 10. Apart from FEV_1 measurement other parameters for lung function, such as VC and FVC, were measured at every visit of the subjects. However, these parameters did not show any relevant differences between the two treatment groups, most probably due to the small sample size. Subgroup analysis was performed regarding change of FEV_1 value for some factors. No statistically significant influence could be found for sex, age and duration of chronic bronchitis. A treatment by factor interaction might exist for patients' age (p = 0.2564), for the stage of COPD (p = 0.0368) and was found regarding smoking habits (p = 0.016).

In detail, a higher difference between treatment groups at day 10 (percent mean 17.89 ± 8.37) could be observed in those patients older than 50 years when compared to all patients (percent mean 9.53 ± 4.98). Patients with a diagnosis of chronic bronchitis of less than 48 months seem to benefit to a greater extent from Esberitox N treatment. The difference in means is 12.2 (± 6.5) compared to 5.2 (± 8.02) for those suffering from chronic bronchitis for more than 48 months. Patients with COPD stage II (35–50%) showed an improvement of the FEV_1 value (baseline adjusted) of 73.2%, and the difference to the placebo group was 30.7%. It seems that smokers benefit from additional treatment with Esberitox N to a greater extent. A mean difference in FEV_1 (%) of 25.40 ± 7.93 was calculated for smoking subjects, whereas for non-smoking subjects there was no difference between the treatment groups (see table 4).

The positive overall result can be clarified by the analysis of the time to half maximal improvement when calculated by linear interpolation. Time to half maximal improvement was 5.7 days for the Esberitox N group compared to 12.8 days for the placebo group (fig. 2).

Table 2. Improvement of FEV_1 (% of the predicted value) on study day 10 compared to study day 1 (intention-to-treat collective)

	Day 1	Day 10	Adjusted values day 10
Esberitox N			
Number	25	25	25
Mean	57.76	69.56	68.72
SD	21.96	15.82	3.57[a]
Minimum	15.00	42.00	56.77
Median	57.00	75.00	69.33
Maximum	130.00	110.00	91.16
Placebo			
Number	27	27	27
Mean	52.33	58.37	59.15
SD	19.10	20.92	3.44[a]
Minimum	7.00	12.00	44.81
Median	54.00	59.00	58.87
Maximum	74.00	95.00	64.85
Difference in means			9.57 (4.98)[a]

[a] Standard error; the values at day 10 were ANCOVA-adjusted for the values at day 1.

Table 3. Improvement of FEV_1 (ml) on study day 10 compared to study day 1 (intention-to-treat collective)

	Day 1	Day 10	Adjusted values day 10
Esberitox N			
Number	25	25	25
Mean	1,883.60	2,228.44	2,140.54
SD	825.33	690.85	132.15[a]
Minimum	570.00	1,160.00	1,458.35
Median	1,640.00	2,071.00	2,085.63
Maximum	3,990.00	3,720.00	3,463.30
Placebo			
Number	27	27	27
Mean	1,594.81	1,791.85	1,873.25
SD	760.19	884.56	127.08[a]
Minimum	220.00	350.00	985.88
Median	1,560.00	1,810.00	1,771.44
Maximum	3,090.00	3,370.00	2,668.39
Difference in means			267.29 (182.14)[a]

[a] Standard error; the values at day 10 were ANCOVA-adjusted for the values at day 1.

Table 4. Improvement of FEV_1 (% of the predicted value) on study day 10 for smoking and non-smoking subjects (intention-to-treat collective)

	Smoking subjects			Non-smoking subjects		
	day 1	day 10	adjusted mean day 10	day 1	day 10	adjusted mean day 10
Esberitox N						
Number	11	11	11	14	14	14
Mean	50.18	73.36	74.91	63.71	66.57	63.72
SD	20.28	16.98	5.17[a]	22.07	14.77	4.68[a]
Minimum	15.00	48.00	61.95	40.00	42.00	58.88
Median	47.00	75.00	72.33	60.50	72.50	65.53
Maximum	74.00	110.00	81.09	130.00	87.00	88.08
Placebo						
Number	8	8	8	19	19	19
Mean	48.75	47.50	49.51	53.84	62.95	63.30
SD	11.74	23.60	6.08[a]	21.57	18.46	3.92[a]
Minimum	33.00	13.00	42.39	7.00	12.00	47.75
Median	51.00	45.00	48.23	62.00	68.00	65.59
Maximum	68.00	95.00	53.75	74.00	85.00	69.49
Difference in means			25.40 (7.93)[a]			0.42 (6.13)[a]

[a] Standard error; the values at day 10 were ANCOVA-adjusted for the values at day 1.

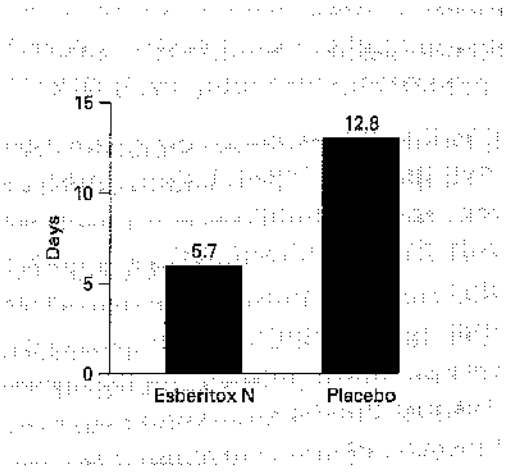

Fig. 2. Time to half maximal improvement.

Safety

During the study period 19 mild to moderate adverse events (Esberitox N: 8, placebo: 11) in 14 subjects were documented by the investigators. None of them was assessed as serious and no event was classified as an adverse drug reaction.

Discussion

Severe bacterial infections are an increasing cause of significant morbidity. For example, chronic bronchitis – despite treatment – is one of the most common causes of death for patients with COPD [35]. Bacteria frequently isolated after acquired exacerbations include *S. pneumoniae, H. influenzae* and *M. catarrhalis* [36]. Atypical bacterial pathogens are causative in about 10% of all episodes. Viruses are estimated to precipitate exacerbations of chronic bronchitis in approximately 30% of all cases with rhinovirus as the predominant pathogen [37]. Furthermore, quite a number of bacterial exacerbations are secondary infections to those caused by viruses.

For the treatment of infectious exacerbations various strategies have been established in the past. Most commonly, antibiotic therapy is used to treat especially those patients who have an extremely decreased respiratory function (FEV_1 <50%) or who have multiple exacerbations each year [36]. But guidelines derived from evidence-based medicine for an appropriate therapy for acute exacerbation of chronic bronchitis are still being discussed. Unsatisfactory results of routine antibiotic therapy have been attributed to a lack of in vivo activity, virus-induced exacerbations, the development of antibiotic resistance, pharmacokinetic inadequacies and individual patient factors [37]. Furthermore, various degrees of immune impairment add to the inadequacies of fourth generation antibiotics. For example, macrolides themselves have anti-inflammatory properties, leading to corticoid-sparing effects, as was shown for roxithromycin in asthmatic patients [38]. Therefore, it seems promising to supplement the antibiotic therapy with an agent possessing immunomodulating effects in order to enhance the therapeutic benefit of the antibiotic group of newer macrolides.

Esberitox N as an immunomodulating phytopharmaceutical has effects synergistic with antibiotics which are mostly due to the stimulation of the unspecific immune defence probably based on the activation of macrophage functions [23, 24]. Moreover, some activity against viruses could be demonstrated and was also confirmed in clinical studies [22, 28]. Those immunostimulating properties of Esberitox N seem to be an ideal synergistic partner for the treatment of severe bacterial infections such as acute exacerbations in chronic bronchitis.

This rationale made us perform this pilot study combining macrolide treatment with Esberitox® N in patients with chronic bronchitis and suffering from an acute episode of infectious exacerbation. The patients included in the study were staged according to Eller et al. [14]. Only patients with stage I and II were recruited, i.e. patients with an FEV_1 between 35 and 75% of the predicted value measured in the infection-free interval before the start of the study.

FEV_1 is regarded as the most significant correlate of survival in COPD and is used as a measure of disease severity in the staging of COPD [39]. FEV_1 was the most commonly reported outcome variable in clinical studies and the management of COPD, which were selected for the Cochrane reviews [40–42]. In these reviews other parameters of lung function such as VC were not reported as a primary outcome. Therefore, FEV_1 was selected as a primary outcome variable for our study.

It could be demonstrated that the improvement of FEV_1 in the Esberitox N group was significantly higher in percentage and millilitres as compared to placebo. Moreover, the subgroup analyses gave hints for a correlation of stage, age and smoking habits to the improvement in FEV_1. It seems that additional treatment with Esberitox N helps the patients to recover sooner from reduced lung function caused by infectious exacerbation. The findings of this study are clinically relevant. Due to the small sam-

ple size our pilot study might not allow a generalization of the study results, especially concerning the subgroup analyses. Further experience with this combination therapy will show whether it leads to a lower number of exacerbations per year and thus slows down the process of COPD. However, the promising results of this pilot study are another example of the efficacy of this phytomedicine when added to antibiotic therapy of severe bacterial infections.

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