Efficacy and Tolerability of Myrtol Standardized in Long-term Treatment of Chronic Bronchitis

A double-blind, placebo-controlled study

Rolf Meister[a], Thomas Wittig[b], Norbert Beuscher[b], and Christian de Mey[C]
on behalf of the Study Group Investigators')

Marienkrankenhaus[a], Bad Lippspringe (Germany), G. Pohl-Boskamp GmbH & Co.[b], Hohenlockstedt (Germany), Applied Clinical Pharmacology Services[c], Mainz-Kastel (Germany)

Summary

This multicenter, placebo-controlled, double-blind, randomized parallel-group trial was conducted to investigate the efficacy and tolerability of myrtol standardized (MYS, Gelomyrtol® forte, 3 x 300 mg) in the long-term treatment of patients with chronic bronchitis during the winter. 246 patients received the investigational treatments (MYS: 122, placebo: 124) for at least 1 month; 215 subjects (110 under MYS and 105 under placebo) were evaluable in terms of efficacy (exacerbation rate, the need for antibiotics, symptom scores and general well-being) for the protocol-defined 6 months of treatment.

Statistically significantly ($p < 0.01$) more patients remained without acute exacerbation in the myrtol standardized group (72 %) compared to the placebo group (53 %). In the placebo group, there was an evident peak in the incidence of exacerbations during the third month of treatment, which was not observed in the active treatment group. In the MYS group, 5 1.6 % of the patients with an acute exacerbation required antibiotics vs. 61.2 % under placebo. 62.5 % of the patients treated with anitbiotics in the MYS group required them for $\leq$ 7 days, whereas 76.7 % of the patients in the placebo group treated with antibiotics for exacerbation needed antibiotics for > 7 days. Well-being (assessed in terms of general health and health impairment by cough and expectoration) was significantly better under treatment with MYS. The overall therapeutic efficacy evaluation scored higher for MYS.

Therefore, it is concluded that long-term treatment with MYS is equally well tolerated as placebo but is clearly superior in efficacy in terms of protecting against acute exacerbations in patients with chronic bronchitis: it reduces the frequency and intensity of acute exacerbations, the need of antibiotics for them and the health impairment by cough and expectoration.

Zusammenfassung

Wirksamkeit und Verträglichkeit von Myrtol standardisiert bei der Langzeitbehandlung der chronischen Bronchitis / Plazebo-kontrollierte Doppelblindstudie

In der vorliegenden, randomisierten, multizentrischen, Plazebo-kontrollierten Doppelblindstudie im Parallelgruppenvergleich wurde Myrtol standardisiert (MYS, Gelomytrol® forte, 3 x 300 mg) bei Patienten mit chronischer Bronchitis untersucht. Ziel der Studie war, Wirksamkeit und Verträglichkeit von MYS in der Langzeitbehandlung während der Winterzeit zu überprüfen und mit Plazebo zu vergleichen.

Insgesamt 246 Patienten (MYS: 122, Plazebo: 124) erhielten die Studienmedikation für den Zeitraum von mindestens einem Monat. Die Daten von 215 Patienten (MYS: 110, Plazebo: 105) konnten hinsichtlich der Wirksamkeit (Exazerbationsrate, Antibiotikabedarf, Symptome-Scores und Lebensqualität) am Ende der protokoll-definierten Behandlungsdauer von 6 Monaten ausgewertet werden.

Verglichen mit Plazebo blieben in der Patientengruppe, welche MYS erhalten hatte, statistisch signifikant mehr Patienten ohne akute Exazerbation (MYS: 72 %, Plazebo: 53 %, $p < 0.01$). Das Auftreten der akuten Exazerbation über die Studiendauer zeigte in der Plazebo-Gruppe einen ausgeprägten Exazerbationsgipfel im dritten Behandlungsmonat, der in der MYS-Gruppe nicht vorhanden war. Die Antibiotika-Therapie aufgrund einer akuten Exazerbation wurde bei insgesamt 51.6 % der Patienten (MYS) bzw. bei 61.2 % der Patienten (Plazebo)

[1)] See appended list (section 5.).

notwendig. Bei Myrtol stand. behandelten Patienten wurden Antibiotika wegen einer Exazerbation in 62.5 % der Fälle für die Dauer von ≤ 7 Tagen verabreicht, während 76.7 % der Plazebo behandelten Patienten die Antibiotika länger als 7 Tage erhielt.

Die Lebensqualität (beurteilt anhand des Allgemeinbefindens und der Beeinträchtigung durch Husten und Auswurf) verbesserte sich unter der Behandlung mit MYS deutlich. Dieselbe Tendenz wie bei der Beurteilung des Allgemeinbefindens ist such für die Wirksamkeit der Prüfmedikation zu sehen, welche eindeutig höher für MYS bewertet wurde.

Somit ist MYS in der Langzeitbehandlung von Patienten mit chronischer Bronchitis ebenso gut verträglich wie Plazebo, jedoch überlegen wirksam was die Prophylaxe akuter Exazerbationen im Winter betrifft: Intensität und Häufigkeit der Exazerbationen, sowie Antibiotikabedarf und die Beeinträchtigung der Lebensqualität durch Husten und Auswurf werden durch MYS statistisch signifikant und in einem klinisch relevanten Ausmaß gesenkt.

Key words Bronchitis, chronic · Gelomyrtol® forte, clinical studies, exacerbation rate, long-term treatment, safety · Mucolytic agents · Myrtol standardized

Arzneim.-Forsch./Drug Res. **49 (I),** 351-358 (1999)

1. Introduction

Chronic bronchitis is defined as an inflammatory disease of the lower respiratory tract characterized by cough and expectoration of sputum on most days during at least three consecutive months in more than two consecutive years (definition according to WHO). Currently, far more than 5 million persons suffer from chronic bronchitis in Germany [1]. During the winter months, patients with chronic bronchitis usually have 1-3 acute exacerbation(s), temporarily deteriorating the state of health drastically.

Treatment of chronic bronchitis should be adapted to the disease's actual severity. Various national or international guidelines are available in this regard [2-5]. Most of these (for instance 'Deutsche Atemwegsliga' [3]) do not favor a general use of mucolytic drugs except for patients with explicit clinical symptoms. Mucolytics in consequence are not part of the routine regime for the long-term treatment of patients with chronic bronchitis.

In Germany, the secretomucolytic phytomedicine myrtol standardized (MYS, Gelomyrtol® forte[2)]) is well established for the treatment of acute and chronic bronchitis and sinusitis. MYS is a phytotherapeutic extract (distillate) and mainly consists of three monoterpenes: (+)α-pinene, d-limonene and 1,8-cineole. Standardization is made up to 15 % (+)α-pinene, 35 % (α-)-limonene and 47 % 1,8-cineole per capsule. In contrast to N-acetylcysteine, MYS is well bioavailable both systemically [16] and at the level of the bronchial secretions. Indeed, after enteric absorption, MYS passes into the bronchial and alveolar lumina to a relevant extent, increases secretion, and stimulates expectoration [17, 18]. In addition to its beneficial effects on mucociliary clearance, MYS is assumed to have antiinflammatory properties. Recently, a steroid-like inhibition of monocyte arachidonic acid metabolism and interleukin 1 β (IL- 1 β) production could be shown in vitro for 1,8-cineole [19]. Additionally, as an antioxidant, MYS acts as a scavenger of free radicals and contributes to the protection against oxidative stress.

Clinically, its therapeutic benefit has been demonstrated in extensive studies in acute sinusitis [20]. Previously, a randomized, double-blind, placebo-controlled, parallel-group study showed that MYS added on to the recommended medication for an acute exacerbation of chronic bronchitis efficaciously reduced its symptoms and intensity [21]. The current study was carried out to investigate whether long-term treatment with MYS rather than merely allowing symptomatic improvement, actually protects against acute exacerbations, similarly as was shown for N-acetylcysteine and ambroxol in the past [6-15].

2. Patients and methods

Nineteen practice-based physicians including 6 specialists in respiratory medicine, 7 specialists in internal medicine, and 6 general practitioners participated in this multicenter study conducted from September 1994 to May 1995. Eligible patients with chronic bronchitis were randomly allocated to parallel groups with a 6 month treatment course with either one capsule of 300 mg myrtol standardized or matched placebo thrice daily. Observers and patients were blinded with regard to treatment.

2.1. Subjects

A total of 272 patients with chronic bronchitis (according to WHO definition) with forced expiratory volume in 1 s (FEV_1) ≥ 50 % of the predicted value, who had experienced at least one acute exacerbation in the previous winter and who had not yet been treated with MYS in the past were considered eligible. 260 subjects were actually enrolled.

[2)] Manufacturer: G. Pohl-Boskamp GmbH & Co., Hohenlockstedt (Germany).

Eventual treatment of bronchitis upon study entry had to be in accordance with current guidelines [2-5] and was kept constant throughout the further course of the study. Concomitant treatment with other mucolytic drugs was not allowed. Patients who had been treated with antibiotics within the last 2 months prior to enrolment were not eligible. Patients with peptic ulcer disease, known hypersensitivity to essential oils, neoplasia and other severe concomitant diseases, pregnancy or lactation were to be excluded. Only patients willing and capable to consent to enrolment after ample information had been provided ('informed consent') were enrolled.

2.2. Ethics

The study was conducted in accordance with the Declaration of Helsinki, the european and international Notes of Guidance regarding Good Clinical Practice and the German Drug Law. The protocol was subject to review and approval by an independent Ethics Commitee.

2.3. Methods

Upon recruitment, the patients' baseline condition and eligibility was evaluated by extensive investigations including demography (age, height, body weight, smoking and alcohol habits), medical history (including previous trial participation, concomitant diseases and medication), physical examination and vital functions (pulse rate, blood pressure, body temperature), spirometric FEV_1 and a laboratory safety screen (hematology, clinical chemistry and urinalysis).

Eligible patients fulfilling the criteria to enrolment were then randomly allocated to treatment with either MYS or matched placebo. Follow-up visits were scheduled every month in order to assess well-being (including exacerbations) during the previous month, compliance, comedication (including eventual treatment with antibiotics) and adverse events. In-between these visits, the patients were ambulatory. Daily cough frequency of sputum and difficulty of expectoration were to be recorded in the patient's diary by means of a visual analogue scale (VAS); at the end of each treatment month they were to evaluate the overall treatment experience during the past month in terms of efficacy and tolerability.

At the final visit, the subject's participation was formally concluded (incl. physical examination and laboratory safety screen).

Incidents meeting the following criteria were considered an 'acute exacerbation' [8, 10, 12]:

1. Mucopurulent or purulent sputum and cough of recent onset or - if pre-existing - increasing considerably plus
2. at least one of the following symptoms: increased sputum thickness, increased difficulty of expectoration, breathlessness, impairment of the general state of health, common coldlike symptoms; body temperature > 38.0 °C

This diagnosis of exacerbation was mainly based on clinical criteria that are evaluable by the individual patient after appropriate training. Ancillary criteria such as accelerated respiratory and/or cardiac rate, edema, cyanosis, use of accessory muscles and loss of alertness were not taken into account as they proved either unreliable if they were to be assessed and/or reported by the patient.

Intercurrent exacerbation-like fluctuating changes were only considered as separate attacks if they were separated by at least 2 weeks during which the patient was symptom-free. The evaluations for the first week of treatment during the first month were discarded from analysis.

Eventual concomitant treatment was graded as follows [2]:

0: No additional medication
1: β_2-sympathicomimetics
2: β_2-sympathicomimetics plus parasympathicolytics
3: β_2-sympathicomimetics plus parasympathicolytics and/or theophylline or plus inhaled corticosteroids.
4: β_2-sympathicomimetics plus parasympathicolytics and/or theophylline plus inhaled corticosteroids plus oral corticosteroids.

Subgroups were furthermore defined according to specialisation of the care-providing physician:

1. subjects treated by Specialists in Respiratory Medicine (n = 79)
2. subjects treated by Specialists in Internal Medicine (n = 90)
3. subjects treated by General Practitioners (n = 77).

2.4. Statistical analysis

The intent-to-treat data-set (ITT) consisted of all evaluable patients who were treated for at least 1 month. The per-protocol data-set (PP) for the efficacy analysis consisted of all patients treated for 6 months and in whom no relevant protocol violation occurred that otherwise would have confounded the efficacy evaluation.

The treatment groups (MYS/placebo) were evaluated for baseline pre-treatment comparability with regard to demographic data, vital signs, risk factors, physical findings, history, concomitant diseases and duration of chronic bronchitis (t-test or Fisher's exact test, respectively).

They were also compared in terms of the exacerbation rate (number of exacerbation-free subjects relative the total number of subjects exposed) and the progression thereof during treatment (two-sided Fisher's exact test). Subgroup-effects were evaluated by means of the Breslow-Day test.

The secondary efficacy criteria (general state of health, impairment by cough/expectoration and overall treatment efficacy) were categorized (positive and negative categories). The treatments were compared in an exploratory way in their regard by means of Fisher's exact tests.

Similar exploratory analyses were carried out with regard to the antibiotic treatment categories ($\leq$ 7 days / > 7 days; confined to antibiotics used explicitly for exacerbation).

3. Results

3.1. Drop-outs and reasons for withdrawal

A total of 260 patients was exposed to the study medication at least once. Forty-two patients (16 %) discontinued the study prematurely. There was no treatment difference in this regard (Table 1). Eight

Table 1: Reasons for premature discontinuation – multiple listings possible.

Reason for withdrawal	MYS	Placebo
Adverse events	8	10
Patient's decision	4	4
Insufficient co-operation	2	0
Patient did not return	4	2
Insufficient efficacy	1	2
Other reasons	5	10

Table 2: Demographic data, FEV_1, smoking habits of the patient population (x ± SD).

	Treatment group	
	MYS	Placebo
Sex n (%)		
Males	58 (47.5 %)	51 (41.1 %)
Females	64 (52.5 %)	73 (58.9 %)
Ethnic group n (%)		
White	119 (97.5 %)	118 (95.1 %)
Other	3 (2.4 %)	6 (4.8 %)
Age (years)		
Males	61.4 ± 10.8	62.6 + 14.7
Females	52.5 ± 14.4	54.7 ± 17.1
Height (cm)		
Males	174.8 ± 5.9	173.0 ± 6.7
Females	163.8 ± 7.1	162.9 ± 6.3
Weight (kg)		
Males	80.9 ± 11.6	78.3 ± 12.6
Females	69.5 ± 11.1	66.6 + 11.6
FEV_1 (% of predicted)		
Males	75.1 ± 18.6	72.9 ± 14.9
Females	79.7 ± 20.1	83.7 ± 24.9
Smoking habits (%)		
Smokers	44 (36 %)	37 (30 %)
Ex-smokers	26 (21 %)	28 (23 %)
Non-smokers	52 (43 %)	59 (48 %)

patients on MYS and 10 on placebo were discontinued because of adverse events (see below). One patient on MYS and two on placebo were discontinued because of cinically relevant lack of efficacy. 246 patients had been treated for at least 1 month (ITT-data-set): 122 on MYS and 124 on placebo. 215 patients were included in the 'per protocol' data-set for efficacy analysis (PP-data set): 110 treated with MYS and 105 treated with placebo.

3.2. Comparison of the two treatment groups

The treatment groups were well comparable with regard to demographic data, FEV_1, smoking habits (Table 2), vital signs, history, and concomitant diseases. Several patients had concomitant treatment for chronic bronchitis, less often (41 %) when treated by Specialists in Internal Medicine or General Practitioners (care-providers subgroups 2 and 3) compared to those treated by Specialists in Respiratory Medicine (subgroup 1: n = 79 %). In total, 46 % (56/122) of the patients on MYS and 48 % (60/124) of the patients on placebo had no concomitant treatment for chronic bronchitis. There was no difference between the treatment groups in this regard nor with regard to the type associated treatment (graded therapy schemes as defined above) (Table 3).

3.3. Effect of therapy on exacerbation

For the 'per protocol' data-set, 79/110 (71.8 %) of the patients treated with MYS and 56/105 (53.3 %) of the patients on placebo remained free of acute exacerbations during the 6 month observation ($p < 0.01$). This is in accordance with the observations for the ITT-data-set: 89/122 (73 %) patients on MYS and 72/124 (58 %) on placebo did not experience an exacerbation ($p < 0.05$).

The course of the monthly exacerbation rate and the cumulative number of patients with at least 1 acute exacerbation is shown in Fig. 1a-lb. There was a remarkable time effect (Fig. la): under MYS, the number of patients with an acute exacerbation was between 7-8/month during the first 5 months and 3 during the last month; in the placebo group, the number patients with an acute exacerbation increased from 5 during the 1st treatment month up to 18 during the third and then decreasing again to 7 over the 6th month of treatment.

There was a significant Center-treatment interaction: the superiority of MYS vs. placebo was not equally evidenced in all centers. Further analysis revealed that whilst the exacerbation rate under MYS was independent of the specialization of the care-providing physician, more patients remained exacerbation-free under placebo when treated by a Specialist in Respiratory Medicine (Fig. 2). This difference was associated with an evident distinction in the comedication pattern: patients in sub-

Table 3: Number (percentage in parentheses) of patients in different subgroups (stratified according to care-providing physician) with the respective basic therapy (ITT-data set; for grades, see text).

	No therapy n (%)	Graded therapy scheme[a]				Other therapy n (%)	Total n (%)
		Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)		
	Specialist in Respiratory Medicine (subgroup 1; n = 79)						
MYS	7 (18)	3 (8)	10 (26)	5 (13)	9 (24)	4 (11)	38 (100)
Placebo	10 (24)	8 (20)	8 (20)	5 (12)	9 (22)	1 (2)	41 (100)
Total	17 (21)	11 (14)	18 (23)	10 (13)	18 (23)	5 (6)	79 (100)
	Specialist in Internal Medicine (subgroup 2; n = 90) and General Practitioners (subgroup 3; n = 77)						
MYS	49 (58)	15 (18)	14 (17)	4 (5)	0 (0)	2 (2)	84 (100)
Placebo	50 (60)	13 (16)	10 (12)	7 (8)	0 (0)	3 (4)	83 (100)
Total	99 (59)	28 (17)	24 (14)	11 (7)	0 (0)	5 (3)	167 (100)

[a] Number of patients in different subgroups treated according to graduated therapy scheme.
[b] Patients who did not receive any parasympatholytic drug in Grade 3 were also included in this group.

group 1 (treated by Specialists in Respiratory Medicine) more frequently had concomitant medication than those in subgroups 2 and 3; in subgroup 1, 35 % of the patients were treated with corticosteroids (oral and/or inhaled), whereas no patients in the subgroups 2 and 3 received such treatment. Patients in centers with relatively small differences between the treatments tended to have higher average FEV_1-values (74-101 %) than patients in centers with clearly less placebo response (FEV_1: 66-78 %).

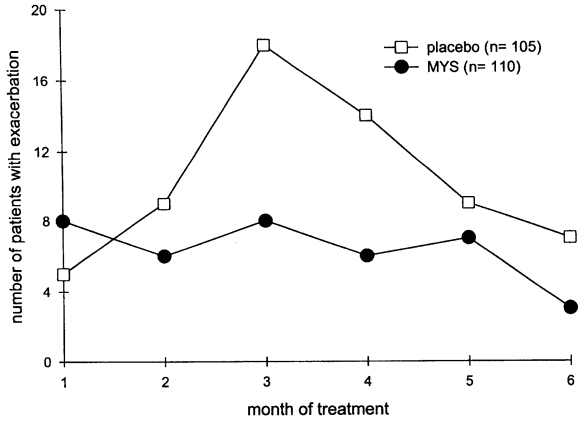

Fig. 1a: Number of patients (pts) with exacerbations for each month during the 6-month treatment with MYS or placebo ('per-protocol' data-set).

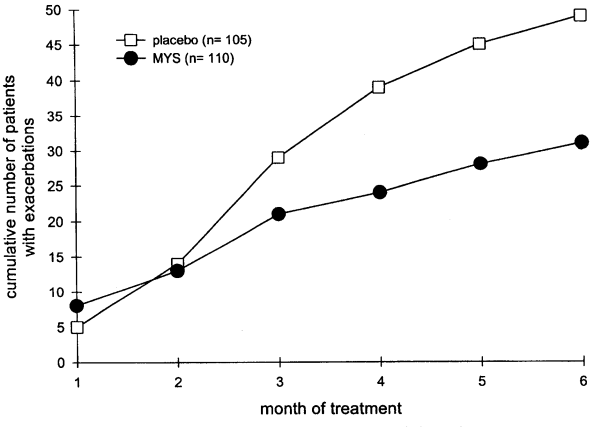

Fig. 1b: Cumulative number of patients with a least one acute exacerbation during the 6-month treatment in the MYS and the placebo group ('per-protocol' data-set, $p < 0.05$ for the treatment effect beyond the 3rd month of treatment).

3.4. Effect of therapy on the need of antibiotics

The need for systemic antibiotic therapy is a further indicator of the prominence of acute exacerbations. In the MYS group, 16 (51.6 %) of the 31 patients with an acute exacerbation required antibiotics vs. 30 (61.2 %) of the 49 patients with exacerbations under placebo. Under placebo, the antibiotic treatment courses lasted longer: 10/16 (62.5 %) of the patients treated with antibiotics in the MYS group required them for ≤ 7 days, whereas 23/30 (76.7 %) of the patients treated with antibiotics for exacerbations in the placebo group needed them for > 7 days (Fig. 3).

3.5. Subjective assessment of the course of the disease and the treatment efficacy

Disease related health impairment by cough and expectoration was assessed by means of the daily VAS-records. Assessments were summarized at the end of each month. Markedly and significantly more patients under MYS reported 'no' or 'rare' health impairment by cough and expectoration (Fig. 4a). Markedly and significantly more patients under MYS reported 'very good' or 'good' general health compared to those under placebo (Fig. 4b). Markedly and significantly more patients and physicians characterized the overall efficacy as 'good' or 'medium' for patients treated with MYS compared to those treated with placebo (Fig. 4c): after 6 months of treatment, approximately 75 % of the patients and physicians graded the overall efficacy of MYS as 'very good' or 'good' vs. only approx. 40 % for placebo; actually, almost 24 % of the patients and 30 % of the physicians graded the efficacy under placebo as 'not satisfactory' or 'not efficacious'.

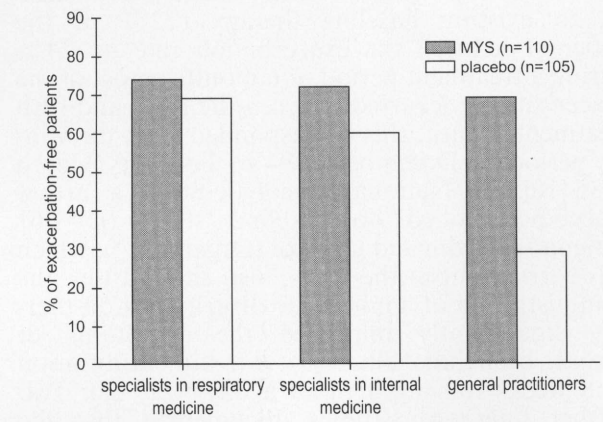

Fig. 2: Percentage of exacerbation-free patients during the 6-month treatment with MYS or placebo in the three subgroups stratified according to care-providing physician ('per-protocol' data-set; difference between MYS and placebo: $p < 0.01$ for the pooled data-base and General Practitioners' Subgroup).

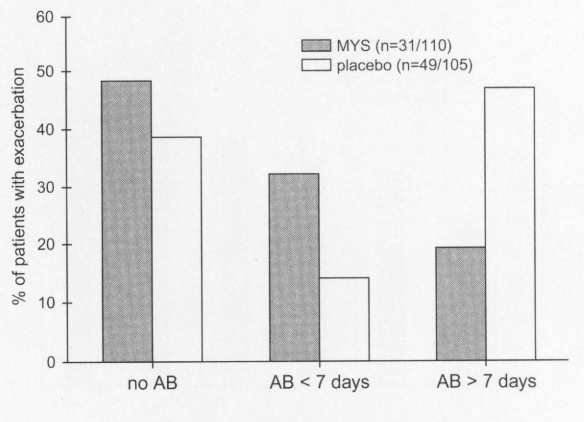

Fig. 3: Percentage of patients with exacerbations who either received or did not require antibiotic therapy (AB) during the 6-month treatment with either MYS or placebo ('per protocol' data-set; $p = 0.01$ for the difference between MYS and placebo among the groups who received antibiotics).

3.6. Safety and tolerability of MYS

There was no treatment related change with regard to physical examination, vital functions and laboratory safety during the course of the study. Both treatments were equally well tolerated. The study was conducted under very close medical surveillance. The patients were repeatedly interrogated with regard to their well-being and were actively encouraged to report and change thereof. Any untoward change - irrespective of whether considered to be treatment related - was recorded as an adverse event (AE). 158 of the 260 patients who were at least treated once reported a total of 371 AEs. For 56 (42.7 %) of the 131 patients treated with MYS no AEs were reported vs. 46 (35.7 %) of the 129 patients treated with placebo (Table 4). AEs were usually of mild or moderate intensity, mainly affecting the gastro-intestinal or respiratory tract or the general state of health. There was no evident difference between the treatments in their regard. Usually the AEs were self-limiting and spontaneously regressing without the need to discontinue treatment .

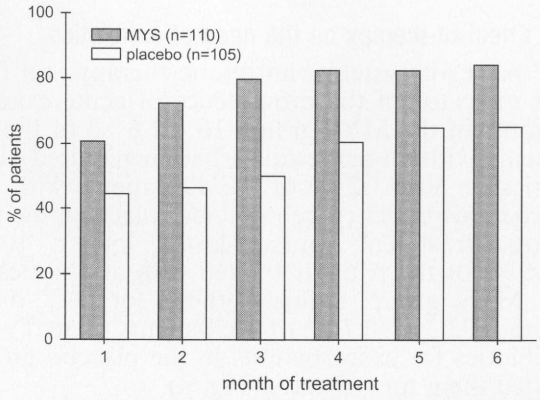

Fig. 4a: Percentage of patients who scored 'rare' or 'no' with regard to the health impairment by cough or expectoration during the 6-month treatment with MYS or placebo ($p < 0.01$ for the difference between MYS and placebo at all time points beyond the 1st month).

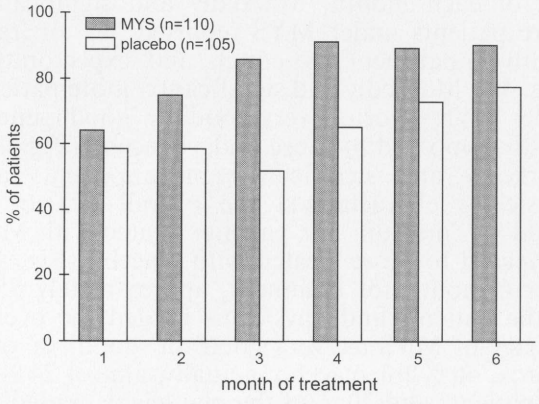

Fig. 4b: Percentage of patients who scored 'good' or 'very good' with regard to the general state of health during the 6-month treatment with MYS or placebo ($p < 0.01$ for the difference between MYS and placebo at all time points beyond the 1st month).

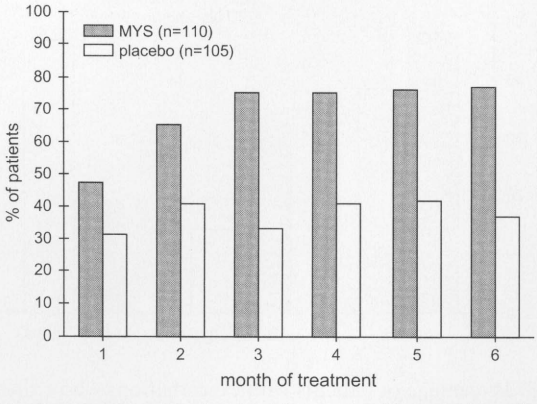

Fig. 4c: Percentage of patients with an overall treatment efficacy scored as 'medium' or 'good' during the 6-month treatment with MYS or placebo ($p < 0.01$ for the difference between MYS and placebo at all time points beyond the 1st month).

4. Discussion

Patients with chronic bronchitis are particularly prone to acute exacerbations especially during the winter. Previously, a placebo-controlled double-blind study had shown that MYS added on to the recommended medication for an acute exacerbation of chronic bronchitis efficaciously reduced its symptoms and intensity [21]. The present study demonstrates that a long-term treatment with MYS clearly reduced the Frequency and intensity (need for antibiotics and extent of health impairment) of acute exacerbations during a 6 months treatment course in the winter. In the patients treated with MYS, the incidence of acute exacerbations did not show its naturally occurring peak between the 2nd and 4th month of treatment (in most patients coinciding with the calendar months December to February) whilst this peak was still evident under placebo (Fig. la).

This result corresponds with previous observations for N-acetylcysteine [6-13] and ambroxol [14, 15]. A double-blind, placebo-controlled, multi-center study in patients with chronic bronchitis demonstrated that N-acetylcysteine retard tablets either as monotherapy (28 % of the patients) or as add-on to existing baseline therapy (72 % of the patients) reduced the exacerbation rate by 24 % during a treatment period of 6 months; most of the exacerbations occurred between the third and fifth treatment month; this corresponded with the winter period of December 1984 to February/March 1985 [10]. The National Mucolytic Study, a further placebo-controlled double-blind study (n = 361 patients) of iodinated glycerol (Organidin®), which was carried out in the USA, also showed that the administration of a mucolytic drug as add-on therapy significantly improved the symptoms of chronic bronchitis, already at a treatment duration of 8 weeks (60 mg 4 times a day) [22, 23]. Two further long-term - studies documented that the regular intake of ambroxol during the winter was protective againstexacerbations of chronic bronchitis [14, 15]. In the present study, MYS also not only reduced the incidence of exacerbations but ra-

Table 4: List of adverse events (more than one report per patient possible) with respect to special organ systems (WHO-classification; total number of exposed population).

	Gastrointestinal tract	Respiratory tract	Skin allergies	General indisposition	Other systems	Total
MYS	30	30	7	24	110	201
Placebo	24	26	9	37	74	170
Total	54	56	16	61	184	371

ther than merely blunting the seasonal peak, actually seemed to abolish it.

These observations and those of the present study convincingly endorse the value of chronic mucolytic therapy either alone or as add-on to the individually optimized baseline treatment to protect patients with chronic bronchitis against acute exacerbations, in the winter in particular. The subgroups stratified according to the specialization of the care-providing physician showed relevant baseline differences: patients treated by Specialists in Respiratory Medicine (subgroup 1) more frequently had already a baseline treatment (often including inhaled and/or systemic corticosteroids) and tended to have higher FEV_1-values (whilst under such treatment). The percentage of exacerbation-free patients under MYS was not affected by a subgroup effect: MYS had similar protective effects against acute exacerbations in all subgroups. However, less patients of subgroup 1 experienced exacerbations when treated with placebo. In consequence, the add-on value of MYS to the existing baseline therapy (quite often inhaled or systemic corticosteroids) appeared comparably small vs. the evident benefit of MYS relative to placebo in the subgroups with less baseline treatment. This prompts the hypothesis that conventional baseline treatment (with β_2-sympathicomimetics, parasympathicolytics, theophylline, inhaled or systemic corticosteroids) is indeed protective against exacerbations, but, that a similar protective efficacy might have been achieved by including MYS in the baseline therapeutic strategy instead of some of the potentially more aggressive alternatives.

Treatment with MYS in this study reduced the need for antibiotics and the duration of antibiotic treatment could be shortened. This again agrees with the observations for N-acetylcysteine [7-10, 12] and ambroxol [14, 15]. As with other mucoactive drugs [7, 13, 14, 22], the long-term therapy with MYS in the present study also improved the patients' general state of health: it reduced their health impairment by cough and sputum expectoration in everyday life and improved their quality of life.

The patients and investigators considered the overall treatment effiacy in the MYS group clearly superior to that in the placebo group. This is in accordance with the observations by Ulmer and Schött [21] who recorded a clearly superior efficacy evaluation vs. placebo already within 2 weeks of the treatment of acute exacerbations with MYS. Furthermore, a six-month treatment course with MYS had a similarly good overall objective and subjective tolerability as placebo. This confirms previous studies [20, 21].

Therefore, it is concluded that long-term treatment with MYS is protective against acute exacerbations in patients with chronic bronchitis, by reducing the incidence and intensity of acute exacerbations, the need of antibiotics for them and the health impairment by cough and expectoration. The treatment is equally well tolerated as placebo, whilst improving overall wellbeing. These observations furthermore encourage to consider mucolytics such as MYS to be made part of the conventional treatment schema for chronic bronchitis.

5. List of investigators

Dr. med. Bannout (Augsburg), Dr. med. A. Bisping-Arnold (Freising), Dr. med. A. Boeltzig (Munich), Dr. med. J. Ebeling (Hamburg), Dr. med. H. Grygier (Bad Homburg), Dr. med. H.-P Haas (Ellwangen), Dr. med. Kratzer (Munich), Dr. med. Krezdorn (Munich), Dr. med. R. Kropp & Dr. med. R. Laumen (Fulda), Dr. med. H.-O. Kühl (Elmshorn), Dr. med. M. Leveringhaus (Bochum), Dr. med. I. Naudts (Dudenhofen), Dr. med. G. Nowack (Dudenhofen), Dr. med. M. Panijel (Frankfurt/Main), Dr. med. K. Pfeiffer (Munich), Dr. med. E. Rieckmann (Cologne), Dr. med. H. Samiri (Frankfurt/Main), Dr. med. M. Schußmann (Todstedt), Dr. med. U. Steinhauser (Sinsheim) (all Germany).

6. References

[1] Nowak, D., in: N. Konietzko (ed.), Bronchitis, pp. 233-253, Urban & Schwarzenberg, München (1995)

[2] Deutsche Liga zur Bekämpfung der Atemwegserkrankungen. Empfehlungen für ein Stufenschema der medikamentösen Langzeittherapie obstruktiver Atemwegserkrankungen. Dtsch. med. Wochenschr. **113,** 1609 (1988)

[3] Wettengel, R., Böhning, W., Cegla, U. et al., Empfehlungen der Deutschen Atemwegsliga zur Behandlung von Patienten mit chronisch obstruktiver Bronchitis und Lungenemphysem. Med. Klin. **90,** 3 (1995)

[4] Celli, B., Snider, G. L., Heffner, J. et al., Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **152** (Suppl.), S77 (1995)

[5] Siafakas, N. M., Vermeire, P., Pride, N. B. et al., Optimal assessment and management of patients with chronic obstructive pulmonary disease (COPD). Eur. Respir. J. **8,** 1398 (1995)

[6] Grassi, C., Morandini, G. C., A controlled trial of intermittent oral acetylcysteine in the long-term treatment of chronic bronchitis. Eur. J. Clin. Pharmacol. **9,** 393 (1976)
[7] Multicenter Study Group. Long-term oral acetylcysteine in chronic bronchitis. A double-blind controlled study. Eur. J. Respir. Dis. **61** (Suppl. 111), 93 (1980)
[8] Boman, G., Backer, U., Larsson, S. et al., Oral acetylcysteine reduces exacerbation rate in chronic bronchitis: report of a trial organized by the Swedish Society for Pulmonary Diseases. Eur. J. Respir. Dis. **64,** 405 (1983)
[9] British Thoracic Society Research Committee. Oral N-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airway obstruction. Thorax 40, 832 (1985)
[10] Meister, R., Langzeittherapie mit Acetylcystein Retard-Tabletten bei Patienten mit chronischer Bronchitis. Eine doppelblinde, placebokontrollierte Studie. Forum Prakt. Allg.-Arzt **25,** 18 (1986)
[11] Parr, G. D., Huitson, A., Oral Fabrol (oral N-acetylcysteine) in chronic bronchitis. Br. J. Dis. Chest **81,** 341 (1987)
[12] Rasmussen, J. B., Gelnnow, G., Reduction in days of illness after long-term treatment with N-acetylcysteine controlled-release tablets in patients with chronic bronchitis. Eur. Respir. J. **1,** 351 (1988)
[13] Hansen, N. C. G., Skriver, A., Brorsen-Riis, L. et al., Orally administered N-acetylcysteine may improve general well-being in patients with mild chronic bronchitis. Respir. Med. **88,** 531 (1994)
[14] Olivieri, D., Zavattini, G., Tomasini, G. et al., Ambroxol for the prevention of chronic bronchitis exacerbations. Long-term multicenter trial. Respiration **51** (Suppl. l), 42 (1987)
[15] Cegla, U. H., Langzeittherapie über 2 Jahre mit Ambroxol (Mucosolvan ®) Retardkapseln bei Patienten mit chronischer Bronchitis. Ergebnisse einer Doppelblindstudie an 180 Patienten. Prax. Klin. Pneumol. **42,** 715 (1988)
[16] Zimmermann, T., Seiberling, M., Thomann, P. et al. Untersuchungen zur Bioverfügbarkeit und zur Pharmakokinetik von Myrtol standardisiert. Arzneim.-Forsch./ Drug Res. **45** (II), 1198 (1995)
[17] Dorow, P., Weiss, T., Felix, R. et al., Einfluß eines Sekretolytikums und einer Kombination von Pinen, Limonen und Cineol auf die mukoziliäre Clearance bei Patienten mit chronisch obstruktiver Atemwegserkrankung. Arzneim.-Forsch./Drug. Res. **37 (II),** 1378 (1987)
[18] Behrbohm, H., Kaschke, O., Sydow, K., Der Einfluß des pflanzlichen Sekretolytikums Gelomyrtol forte auf die mukoziliare Clearance der Kieferhöhle. Laryngo-Rhino-Otol. **74,** 733 (1995)
[19] Juergens, U. R., Stöber, M., Vetter, H., Steroidartige Hemmung des monozytären Arachidonsäuremetabolismus und der IL-l β-Produktion durch 1.8-Cineol. Atemw.-Lungenkrkh. **24,** 3 (1998)
[20] Federspil, P., Wulkow, R., Zimmermann, T., Wirkung von Myrtol standardisiert bei der Therapie der akuten Sinusitis - Ergebnisse einer doppelblinden, randomisierten Multicenterstudie gegen Placebo. Laryngo-Rhino-Otol. **76,** 23 (1997)
[21] Ulmer, W. T., Schött, D., Chronisch-obstruktive Bronchitis. Wirkung von Gelomyrtol forte in einer plazebokontrollierten Doppelblindstudie. Fortschr. Med. **109,** 547 (1991)
[22] Petty, T. L., The National Mucolytic Study. Results of a randomized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. Chest **97,** 75 (1990)
[23] Morgan, E. J., Petty, T. L., Summary of the National Mucolytic Study. Chest **97** (Suppl.), 24 S (1990)

Acknowledgements

The authors wish to thank Dr. rer. nat. Cornelia Schäfer, formerly Innovex (Biodesign) GmbH, Mannheim (Germany), Dr. Thomas Zimmermann, formerly at G. Pohl-Boskamp, and Mrs. Carolin Peiske, G. Pohl-Boskamp, Hohenlockstedt (Germany) for their expert help and contribution.

Correspondence: Prof. Dr. med. Rolf Meister, Marienkrankenhaus Gem. GmbH, Auguste-Viktoria-Allee 2, D-33175 Bad Lippspringe (Germany)