Reduction of Acute Relapses in Patients with Chronic Recurrent Hypertrophic Sinusitis during Treatment with a Bacterial Immunostimulant (*Enterococcus faecalis* Bacteria of Human Origin – a Medical Probiotic)

Werner Habermann[a], Kurt Zimmermann[a], Horst Skarabis[b], Rudolf Kunze[c], and Volker Rusch[a]

Institute for Microoecology[a], Herborn-Hörbach (Germany), Affina Immuntechnik GmbH[b], Berlin (Germany), and Free University of Berlin, Institute for Empirical Methods and Statistics[c], Berlin (Germany)

Summary

A double-blind, placebo-controlled, multicenter study in 157 patients with chronic recurrent sinusitis investigated the occurrence of acute relapses during treatment of patients with a bacterial immunostimulant (3 × 30 drops/day), comprised of cells and autolysate of human *Enterococcus faecalis* bacteria (Symbioflor® 1, n = 78), in comparison with placebo (n = 79). The study included a treatment period of 6 months and a follow-up period of 8 months. On active drug, the occurrence of relapses (50 incidents) was about half (56 %) the number observed on placebo (90 incidents). In the Kaplan-Meier test the active drug preparation emerged as significantly superior (p = 0.045, log rank test) compared to placebo. This superiority of the verum preparation was found during the treatment period with 17 vs. 33 relapses (p = 0.019) as well as during the follow-up observation with 33 vs. 57 relapses (p = 0.013). The time interval to the first relapse was clearly longer under verum (513 days) than under placebo (331 days). The relative risk for a relapse with the test preparation compared with placebo was 49.0 % during treatment and 55.8 % during the follow-up period. Severity of the acute relapses was comparable in both groups. However, antibiotic therapy was only required in 2 patients treated with active drug compared with 6 patients in the placebo group. Both study medications were well tolerated and serious side effects did not occur in either group. No changes in laboratory tests – haematology and clinical chemistry – were observed. Potential immunomodifying effects of the verum preparation are discussed in view of the significant reduction in relapses.

Key words

- Cytokines
- *Enterococcus faecalis*
- Immunomodulation
- Medical probiotic
- Sinusitis, chronic recurrent hypertrophic, reduction in relapses
- Symbioflor® 1

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1. Introduction

Chronic recurrent hypertrophic sinusitis is a common disease in the field of ENT [1] and originates from a lot of predisposing factors [2–4]. While the acute form of sinusitis is dominated by viral pathogens, chronic sinusitis is mainly caused by bacterial superinfections contributing finally to an exacerbation of the disease [5]. As a result, chronic recurrent inflammatory processes of the mucosa are increasingly superimposed by mixed infections due to an impaired resistance against infections. At this stage of the disease the original cause of the chronic sinusitis is often no more detectable making a successful therapy quite difficult. Acute disease exacerbations are often treated with antibiotics, whose application increasingly raises serious concerns [6–8]. In chronic recurrent courses, an impairment of the host local and peripheral defence mechanisms has been suggested [9, 10]. Therapeutic interventions in the immunopathogenesis of local inflammatory processes led to a marked improvement of symptoms as well [11]. Overall these studies indicate, that changes in the immune system play a crucial role, illustrating that conservative medicine pays more and more attention to these microbiological preparations being classified as so-called immunostimulants. The test preparation used here has been on the market since 1954 and was shown to be effective in the improvement of clinical symptoms in two recent clinical trials [12, 13]. The multicentre study presented here was designed to extend and accomplish these study results. To this end, the influence of a 6-month treatment with the test preparation on the frequency of relapses during treatment (6 months) as well as in a follow-up period (8 months) was investigated compared to placebo. In addition tolerability and safety of the test preparation and its effect on clinical and haematological parameters was examined. After approval by the Ethics Committee of the regional General Medical Council in Frankfurt (Hessen), the study was performed in accordance with the EC Good Clinical Practice (EC-GCP) guidelines and the German Medicines Act. Altogether, 24 general practitioners participated in this study. Most of these GPs were from Frankfurt, three were located near Wiesbaden and two were in Ginsheim-Gustavsburg (Hessen).[1)]

2. Patients, material and methods

2.1. Patients

153 patients of both sexes with clinically established chronic recurrent hypertrophic sinusitis entered the study. The clinical history had to confirm at least 4–6 attacks of sinusitis over at least one year with the typical clinical symptoms [14]. Patients with chronic atrophic sinusitis or chronic recurrent sinusitis, due to congenital malformations, verified by differential diagnosis using x-ray examination, were excluded from the study. Women known to be pregnant or breast-feeding as well as patients with allergic rhinitis, severe allergic diathesis and other severe diseases were also excluded.

2.2. Treatment of patients

The test preparation[2)] (*Enterococcus faecalis* bacteria of the serological group D, common part of the normal physiological intestinal flora) consisted of cells and autolysate at a concentration of 1.5–4.5 × 10^7 bacteria/ml. A starch suspension diluted in isotonic saline solution served as placebo. In a randomised double-blind comparative study design, all patients received 30 drops of active drug (= 11.25–33.75 × 10^7 bacteria/day) or placebo t.i.d. Accompanying treatments with immunosuppressants, systemic corticosteroids, local or systemic antibiotics as well as mouth and throat disinfectants were not allowed during the study. In the case antibiotics were indicated for treatment of a relapse, their use was monitored as secondary objective of the study.

2.3. Objectives

Primary objective was the frequency of relapses during treatment with active drug compared to placebo and during the follow-up period. Relapses identified by the clinical findings (eg spontaneous pain, pain on palpation or percussion, changes of the nasal mucosa or the paranasal sinuses, nasal respiration and temperature) were recorded. The severity of the relapse was assessed by a three-rank score as follows:

Mild: Daily living habits not impaired Moderate: Impairment of daily living habits in spite of using decongestants and antibiotics.

Severe: More than two days of bed rest plus antibiotic treatment.

At the beginning and at the end of the 6-month treatment period, a complete blood count and examination of clinical parameters was performed. At each examination patients were asked about adverse events. The patients' examinations were performed one or four weeks after the beginning of the treatment and thereafter at monthly intervals.

2.4. Statistical analysis

A prospective, randomised, double-blind, multicentre trial with parallel groups was regarded to be adequate determining the efficacy of the test preparation compared with placebo with respect to the frequency of relapses in patients with chronic sinusitis.

Due to the lack of comparable data concerning the relapse rates, estimates on patients number based upon an assumed success rate of 80 % (with active drug) and 50 % (with placebo) for the improvement of the mucosal changes. Calculations according to Fisher's exact (X^2) test with α = 5 % and β = 20 % resulted in 45 patients per group. A raise of this patient collective by 40 % to compensate for drop-outs and including an additional patient per centre (for the analysis of center effects), resulted finally in an estimate of 70 patients per group. The primary objective – reduction of acute relapses – was first calculated with Fisher's exact test, which however requires the time period patients reside in the study to be identical for both

[1)] A list of the names of all participating investigators can be obtained from the correspondence author, Dr. Zimmermann.

[2)] Manufacturer: SymbioPharm GmbH, Herborn (Germany).

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Table 1: Demographic data of sinusitis patients in the verum group and the placebo groups (mean ± SD).

	Active drug	Placebo
Age (years)	40.4 ± 12.4	42.2 ± 12.8
Height (cm)	169.8 ± 8.9	170.0 ± 8.7
Weight (kg)	68.6 ± 11.3	69.7 ± 11.8

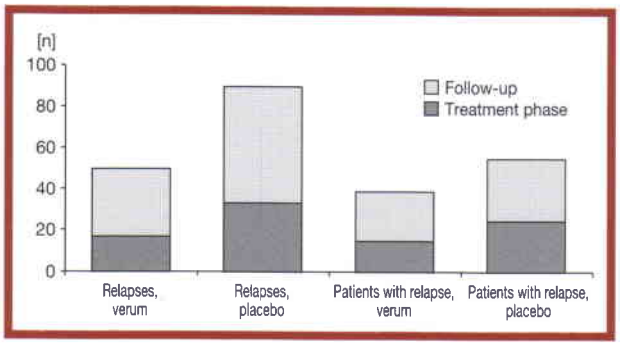

Fig. 1: Absolute frequency of relapses under active drug or placebo, as well as the number of patients with sinusitis in the respective treatment group, separately calculated for the 6-month treatment period and the 8-month follow-up.

groups. In order to take into account the fact that patients remained in the trial for different time periods, the percentage of patients being free of relapses upon examination was estimated using the Kaplan-Meier method and compared for both treatment groups.

3. Results

3.1. Patients

Table 1 illustrates the demographic data for the two treatment groups. All 157 patients (age: 18–70 yrs, m 46, f 111, n = 78 for verum, n = 79 for placebo) were used for the analysis of efficacy and safety. The two treatment groups were comparable considering the demographic and medical history data (Table 1). With about 95 % of patients, the clinical history revealed 4–6 attacks of sinusitis and an abnormal picture of the nasal mucosa, followed by events where abnormal findings include paranasal sinuses with opacification (50–70 %).

The two groups differed only marginally (Table 1) with regard to the time span between the two last relapses before the study. The median time for relapse-free intervals was 88 days in the verum group and 92 days in the placebo group. Vital parameters and clinical laboratory findings showed no abnormalities at baseline and did not change significantly during the study period.

3.2. Relapse rates

Fig. 1 shows the frequency of relapses in the two treatment groups during treatment and during the follow-up period.

With 50 relapses under active drug (56 %), the number of relapses was only about half the number of relapses observed with placebo, reaching 90 relapses. This kind of difference was found both during the treatment period with 17 to 33 relapses and in the follow-up period with 33 to 57 relapses (Fig. 1). Thus, absolute numbers were higher during the follow-up period, which can only partially be explained by its longer duration. The number of patients with relapses was markedly lower in the active drug group than in the placebo group. The relative risk to get at least one relapse under verum was 0.49. Hence, this was only half the risk calculated for placebo, and with 0.56 it remained almost unchanged in the verum group during the follow-up. These differences were statistically significant in both phases with $p = 0.019$ and $p = 0.013$ (each two-sided), respectively. The frequency of multiple relapses was markedly more in the placebo group, summarized in Fig. 2.

Accordingly, more than 2 relapses were recorded in one patient in the verum group during or after treatment but in 8 patients in the placebo group. On active drug, at least 15 patients experienced one relapse compared to 25 patients treated with placebo. During follow-up, the frequencies (24 compared with 30) again illustrate the superiority of the active drug. When the relapse rate was analysed according to the Kaplan-Meier method which, unlike Fisher's exact test takes into account the real observation time period for each individual, the frequency of relapses was significantly lower during treatment with the test preparation compared to placebo ($p = 0.045$; log rank test). These results are presented in Fig. 3.

Fig. 3 depicts the time span from the beginning of the study to the first relapse in the two treatment groups (placebo: median 311 days, active drug: median 513 days). An identical analysis for the time span passed before the second relapse ocurred, showed similar marked differences between the treatment groups. The median duration was 703 days (active drug) and only 413 days in the placebo group ($p = 0.03$; log rank test). The number of months with and without relapse as well as the relative risk and the odds ratio calculated from these data are summarized in Table 2.

Compared with placebo, the relative risk and the odds ratio in the verum group was only half as high as under placebo and this effect remained almost unchanged during the 8-month follow-up. Data for severity of relapses were available for all 50 relapses on active drug, but for only 72 of the 90 relapses after placebo treatment. These results are shown in Fig. 4.

No difference between the two treatment groups considering the severity of the relapses was observed. An additional treatment with antibiotics was necessary in 6 patients receiving placebo (and in only two patients under verum). No changes in the blood count or clinical laboratory findings were seen during the treatment period. In both treatment groups adverse events oc-

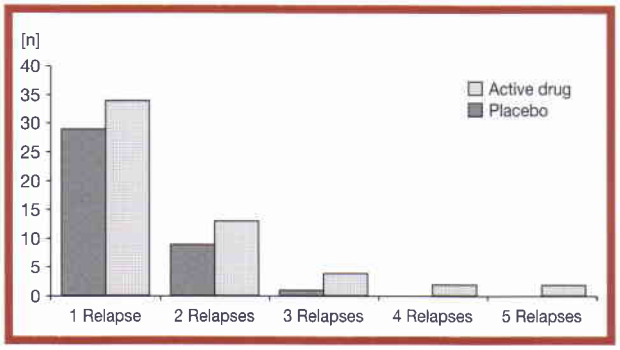

Fig. 2: Number of patients with one or more relapses.

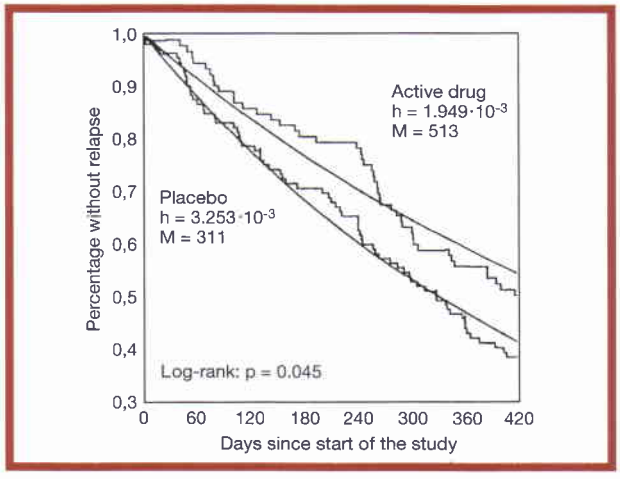

Fig. 3: Time span from the beginning of the study to the first relapse, after active drug and placebo, respectively.

Table 2: Number of months with or without relapse during the 6-month treatment period and the 8-month follow-up as well as the resulting relative risk and the odds-ratio for treatment with the study medications

	Treatment period		Follow-up period	
	Active drug	Placebo	Active drug	Placebo
Months with relapse	17	33	33	57
Months without relapse	411	382	529	485
Months total	428	415	562	542
Relative risk	49.0 %		55.8 %	
Odds ratio	47.9 %		53.8 %	

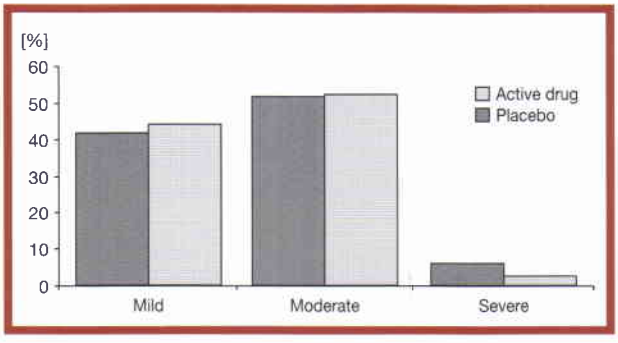

Fig. 4: Severity of relapses in the verum group compared to the placebo groups, respectively.

curred with equal distribution. Hence, 12 patients under verum and 13 patients receiving placebo reported adverse events such as disgust, nasty taste of the study medications, nausea, vomiting and meteorism. Severe adverse events did not occur in either group.

4. Discussion

The clinical study presented here demonstrated, that patients with chronic recurrent sinusitis treated with a bacterial immunostimmulant showed a statistically significant reduction in the relative risk for a relapse to approximately 49 % during treatment ($p = 0.019$) and approximately 56 % during the follow-up period ($p = 0.013$), compared with placebo. Because such a marked reduction in the frequency of relapses can be regarded to be medically relevant, the question on the underlying mechanisms of action of the applied bacterial preparation arise. First, it is well known that the inflammatory process underlying chronic recurrent hypertrophic sinusitis is superimposed in most cases by a mixed bacterial infection. Second this requires the use of more and more potent antibiotics enhancing the risk of growing bacterial resistance [15–17]. On the other hand, the aim of a microbiological therapy is to strenghten the patient's immune system in order to reduce the number of relapses and therefore the prescription of antibiotics. Whereas this therapy just a few years ago still based on clinical experience, there are in the meantime several clinical studies with other bacterial immunomodulators demonstrating their clinical relevance for the treatment of recurrent infections of the upper and lower respiratory tract [18–23]. Some of these preparations of bacterial origin not only cause an antigen-specific immune response, e.g. passive vaccination against those bacterial strains in the preparations [21–23], but also a stimulation of antigen-nonspecific mechanisms operating in the immune system [24], due to an increased activity of macrophages or neutrophil granulocytes. Obviously, the peroral application route resulted in a primary stimulation of the mucosa-associated immune system of the gastro-intestinal tract [23, 25], as some studies also report an effect of these preparations on the production of secretory IgA. Those experimental studies that have been performed so far with the test preparation used in this study also point to interactions with the immune system being in accordance with a stimulation of non-specific immune mechanisms, induced by such bacterial preparations and resulting in an overall increase in the functions of monocytes and granulocytes. Thus, recently performed animal experiments with the test preparation of this study showed an increased resistance of mice against experimentally induced infections [26]. Further studies with minipigs demonstrated a stimulation of secretory immunity, following the peroral administration of human Enterococcus faecalis bacteria [27] resulting in a significant increase in saliva IgA-antibodies of the animals. These

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results clearly reflect the stimulation of the mucosa-associated immune system whose essential role in local defense of pathogens can be considered as established meanwhile [28, 29]. To extend these studies, in vitro experiments with human leukocytes showed an influence of the present test preparation on the release of cytokines such as interleukin-I, interleukin-2 and interferon-γ [30]. These cytokines investigated in this study play an important role in the regulation and induction of cell-mediated immunity [31, 32], so that changes at the level of the "communication signals" of the immune system inevitably should affect the defense mechanisms of the body by stimulating the activity of CD4 T-helper-cells (by IL-1, IL-2) and macrophages (by interferon-γ). Despite studies on the underlying mechanisms of action of the test preparation used here have shown immunomodulatory effects in vitro or in various animal models, there are no detailed studies concerning the direct influence of the preparation on the immune system of human patients so far, although the results shown here, demonstrating a reduction in the frequency of relapses being a clinically detectable and relevant parameter, still indicating possible effects on the patients' immune system.

So far, cost aspects should not be underestimated for the treatment of chronic sinusitis concerning the therapeutic use of this bacterial immunomodulator compared to standard therapies with antibiotics. According to Ray et al. [33], alone the treatment of chronic sinusitis in the USA cost 5.8 million US-$ in 1996. Likewise according to Adams et al. [34], an estimated 12 % of the American population at the age of 45 years suffer from the symptoms of chronic sinusitis. In the context to this study presented here l on the effects of the bacterial immunostimulant on the relapse rate in chronic sinusitis patients, a first approximation estimates the frequency of relapses in the verum group to be half of those of the placebo group, corresponding to a decline for a lost time from work, which has to be calculated against the corresponding treatment costs.

Even though, for a final analysis of the cost-benefit ratio the overall efficacy of the prophylactic treatment with this bacterial preparation should be known, the cost savings for this trial period of 14 months are really very promising. To summarize, the present placebo-controlled, multicenter study further points to the immunomodulatory effects of this bacterial preparation, being demonstrated by the clinically relevant reduction in the frequency of relapse rates. More detailed investigations considering the immune system enhancing effects of this bacterial immunostimulant should accomplish and extend for example the promising results of the cytokine modulating capacity of the preparation.

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Correspondence:
Dr. Kurt Zimmermann,
Institut für Mikroökologie,
Auf den Lüppen 8,
35745 Herborn (Germany)
e-mail: kurt.zimmermann@mikrooek.de

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ERRATUM

In the article by Habermann W. et al. entitled “Reduction of acute recurrence in patients with chronic recurrent hypertrophic sinusitis by treatment with a bacterial immunostimulant (Enterococcus faecalis Bacteriae of human origin [Verminderung der Rezidivhaufigkeit bei Patienten mit chronisch rezidivierender hypertrophischer Sinusitis unter Behandlung mit einem bakteriellen Immunostimulans (Enterococcus faecalis-Bakterien humaner Herkunft], published in **Arzneimittelforschung 52 (8)**: 622-627, 2002, the colours of the bar diagrams Figure 2 and Figure 4 have been reversed due to a technical fault. We apologize for this error.

Concerning the statistical calculations presented in Table 2 please note that the number of relapses (17 vs 33 during treatment; 33 vs 57 follow-up) account for number of patients/per month and NOT for the absolute time span! The correct figures are shown below.

Fig. 2: Number of patients with one/more than one relapse

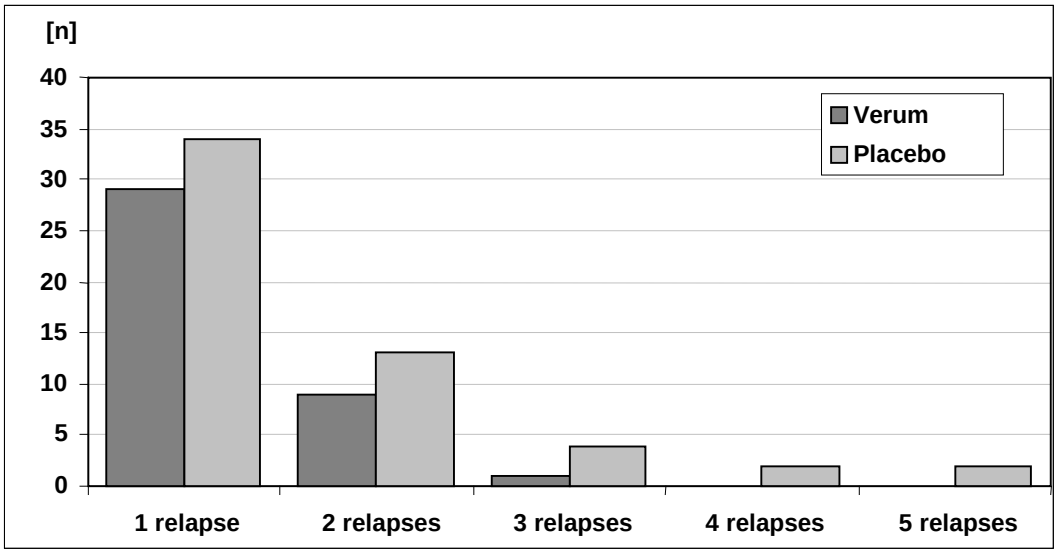

Fig. 4 : Severity of relapses under Verum vs Placebo