The efficacy of Ginkgo special extract EGB 761 in patients with tinnitus

C. Morgenstern and E. Biermann
Allgemeines Krankenhaus St. Georg, Hamburg

Abstract. Objective: The objective of the present study in 60 patients with chronic tinnitus auralium was to confirm the efficacy of oral treatment with 2 × 80 mg Ginkgo special extract EGB 761 per day subsequent to 10-day EGB 761 infusion treatment. Methods: Patients with chronic tinnitus auralium underwent 10 days of in-patient infusion treatment with 200 mg/day EGB 761, after which they were randomized to double-blind, oral out-patient treatment with either 2 × 80 mg/day EGB 761 or placebo, given over a scheduled treatment period of 12 weeks. The primary outcome measure was the change in tinnitus volume in the more severely affected ear during randomized treatment. Results: Fifty-two of 60 patients (89.7%) completed the infusion treatment; complete sets of data were available for 40 (66.7%), 30 (50.0%) and 22 (36.7%) patients after 4, 8 and 12 weeks of randomized treatment, respectively. For the primary outcome measure, significant superiority of EGB 761 over placebo was demonstrated in the intention-to-treat analysis data set after 4, 8 and 12 weeks of out-patient treatment (p < 0.05, 1-tailed), although the absolute treatment group difference was moderate. The results were supported by the secondary outcome measures for efficacy (e.g. decreased hearing loss, improved self-assessment of subjective impairment). During out-patient treatment, there were no attributable adverse events under EGB 761. Conclusions: A combination of infusions therapy followed by oral administration of Ginkgo special extract EGB 761 appears to be effective and safe in alleviating the symptoms associated with tinnitus auralium.

Introduction and objectives

The importance of an effective therapy for tinnitus is evident not only from the high incidence of this disturbance in the population [Axelsson and Ringdahl 1987], but also from the steady increase in prevalence in older people (up to 35%; see [Ross et al. 1991]).

Tinnitus does not present as an independent clinical picture, but is symptomatic of a disturbance in the peripheral and central auditory apparatus. The objective manifestations of tinnitus can be assessed diagnostically by the investigator by using suitable procedures; in most cases, they respond well to treatment. Subjective ear noise, however, are only experienced by the person suffering [Wilhelm et al. 1998] and are therefore much more difficult to assess.

Due to a lack of suitable and objective assessment techniques, the neural mechanisms which result in the phenomenon of ear noise without any external acoustic stimulus have not yet been clarified [Lockwood et al. 1998]. Rheological infusion therapy, which aims at improving the perfusion in the inner ear, has resulted in cure or alleviation in patients with acute symptoms, so that life with tinnitus is bearable in over 80% of the patients. Other therapeutic options include various drugs such as calcium antagonists, anticonvulsants or antidepressants as well as psychophysiological, psychotherapeutical and apparative techniques, although no gold standard for tinnitus treatment has been established to date. In more severe chronic sufferers, however, symptom relief has only been achieved in about one fourth of the patients [Wilhelm et al. 1998].

Many of the drugs that are effective in tinnitus treatment have the disadvantage of quite frequent and partly severe and impairing side effects. Since tinnitus often requires prolonged treatment, a well tolerated (and therefore well accepted) treatment regimen is essential. Phytopharmaceutical drugs based on extracts isolated from the leaves of the
Ginkgo biloba tree have been used successfully in this indication for many years. Except for very rare cases of allergic skin reactions, headache or gastrointestinal complaints, no side effects have been reported for them. Despite these favorable prerquisites, remarkably few randomized, controlled clinical trials investigating the efficacy and safety of Ginkgo biloba extracts in tinnitus have been published. Following extensive literature search, Ernst and Stevinson [1999] identified 4 randomized trials that compared Ginkgo biloba extracts either to placebo or to another drug known to be effective in tinnitus treatment [Holgers et al. 1994, Meyer 1986a,b, Morgenstern and Biermann 1997], which fulfilled the authors’ entry criteria for their review (in addition, the authors identified 5 uncontrolled and 3 controlled, but not randomized trials with Ginkgo biloba extracts in the same indication). The studies reported by Meyer [1986a,b] and by Morgenstern and Biermann [1997] included a total of 461 patients suffering from persistent tinnitus, who underwent between 1 and 3 months of investigational treatment, with daily doses of Ginkgo biloba between 120 and 160 mg. Using different criteria for therapeutic efficacy (severity score, specialist’s evaluation, tinnitus loudness measured by audiology), these trials demonstrated superiority of Ginkgo biloba extract over placebo, nicergoline or amitrine-raubasine. Comparable results were also reported by Eckmann and Schlag [1982], Halamia et al. [1988] and in a preclinical trial by Jastreboff and Sasaki [1986].

In the placebo-controlled crossover trial published by Holgers et al. [1994], 20 patients received 29.2 mg/day of the investigational preparations for a period of 2 weeks. The main evaluation criterion for efficacy was the patients’ selection which of the 2 preparations they preferred. Differences in preference between Ginkgo biloba extract and placebo could not be demonstrated. Among other factors, the study by Holgers et al. [1994] is different from the above-mentioned trials by its smaller sample size, the shorter duration of treatment and the type of main outcome measure employed. In addition, according to today’s knowledge, the investigational drug was relevantly underdosed, which could account for the study’s divergent results.

The objective of the present study was to investigate the influence of an initial 10-day infusion therapy with 200 mg/day Ginkgo special extract EGB 761 on the success of subsequent oral treatment with 2 × 80 mg EGb 761 per day in patients with chronic tinnitus aurium. The infusion therapy was introduced in order to initiate the therapeutic effect of subsequent oral treatment, which was in accordance with the standards for tinnitus therapy at the time the investigation was designed.

Patients and methods

**Trial site/ethical conduct**

The double-blind, randomized, placebo-controlled, monocentric study was conducted in an ear/nose/throat (ENT) out-patient unit at the St. Georg General Hospital in Hamburg, Germany. Sixty patients (2 × 30) were to be enrolled in the double-blind phase of the study. Treatment allocation was achieved by means of randomization. Study preparation, execution and analysis were carried out in accordance with ethical, regulatory and legal requirements (AMG = German Drug Act, GCP guidelines, Declaration of Helsinki) and the protocol was reviewed by an independent Ethics Committee.

**Inclusion and exclusion criteria**

Patients included into the trial had to be at least 18 years old and were required to declare their informed consent to participate in writing. To assess the patients’ eligibility for the trial, pure tones with frequencies of 0.125, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, and 8.0 kHz were applied to both ears. Normal hearing capacity was defined as a hearing loss of no more than 10 dB compared to the age norm. Eligible patients had to demonstrate normal hearing capacity over at least 3 adjacent frequencies in the audiogram and had to be suffering from chronic tinnitus for at least 2 months. The protocol required that tinnitus was to be reproducible, could be defined tonally and could be masked by means of noise applied to the patient’s ear. Patients who fulfilled 1 of the following exclusion criteria
were not allowed to participate in the study:
- presence of objectively audible noises or middle ear diseases,
- reproducibility of the otoacoustic evoked emissions in the initial examination ≤ 85%,
- absence of stapedius reflex,
- latency between the brain stem potentials J1 - V of both ears > 0.5 ms.

Furthermore, severe organic diseases, decompensated coronary insufficiency, heart attack within the past 4 weeks, alcohol or medication abuse, pregnancy or participation in another trial within the past 4 weeks were criteria for study exclusion.

**Study schedule and medication**

The study started with a 10-day open in-patient phase during which all study participants received daily infusions of Ginkgo extract. This initiation phase was followed by 12 weeks of double-blind out-patient treatment with either Ginkgo extract or placebo, both of which were administered orally. Following a screening examination to determine the patients' eligibility for trial participation, further visits were held at days 1, 5, 10 and 12 of the in-patient phase as well as after 4, 8 and 12 weeks of out-patient treatment (Figure 1 for details).

During hospitalization, all patients received 1 infusion/day with Ginkgo special extract EGb 761 (batch number: 5242) over 30 – 60 minutes (1 dry vial in 500 ml isotonic saline). The dry vials contained 200 mg of dry extract from Ginkgo biloba leaves (drug-extract ratio 50 : 1), standardized to 48 mg Ginkgo flavone glycosides and 12 mg terpene lactones (ginkgolides, bilobalide); 26 mg disodium hydrogen phosphate: 12 H₂O in 3 ml solution served as the solvent.

In the randomized, double-blind outpatient phase, the patients received 2 × 1 film-coated tablet/day of either EGb 761 (batch number: 5558) or placebo (batch number: 5558 P) over a period of 12 weeks. Each EGb 761 tablet contained 80 mg of dry extract from Ginkgo biloba leaves (drug-extract ratio 50 : 1) standardized to 19.2 mg Ginkgo flavone glycosides and 4.8 mg terpene lactones. Accordingly, the total daily dose of EGb 761 during the out-patient phase was 160 mg. The investigational drugs were indistinguishable with regard to all external characteristics (shape, size, color, smell).

Concomitant medication not interfering with efficacy assessment could be maintained at an unchanged dosage if discontinuation was not possible.

**Primary and secondary outcome measures**

The primary outcome measure was the difference in tinnitus volume between day 10 of the in-patient phase and months 3, 2 and 1 of the out-patient phase. Click-evoked otoacoustic emissions, loss of tonal hearing (tone threshold audiometry), number and word comprehension (speech audiometry) and subjective intensity of tinnitus (measured on a 6-point rating scale) were monitored as secondary efficacy parameters. All measures of efficacy were evaluated for the more severely affected ear.

The safety of the investigational products was evaluated by laboratory monitoring (hemoglobin, erythrocytes, leukocytes, differential blood count, fibrinogen) and the documentation of any adverse events.
Examination procedures

Pure-tone audiometry was undertaken by means of the bracketing method [Anon 1981, IOS 1980], using a Bosch Audiometer (Model KSS). Speech audiometry was carried out by means of the Freiburg Speech Test (test in accordance with DIN 45621, Part 1, 1973) using the same type of apparatus, by determining hearing loss (number comprehension) and discrimination loss (word comprehension, Hahlbrock [1970]).

Feldmann's procedures [Feldmann 1971] were used as the basis for tinnitus diagnostics. According to this method, the patient has to compare the ear noise with the frequency and loudness of pure tones and octave band noise. The aim is to measure the volume needed to mask the tinnitus completely. The loudness of the tinnitus is determined by 4 separate measurements in 2 dB steps which approach the actual value using sub-threshold or suprathreshold noise. If the intensities differed by more than 5 dB, the intensity determination was repeated. The intensity of the tinnitus is given by the mean of the separate measurements. If the tinnitus frequency or loudness could not be precisely defined, the patient was not enrolled in the study. All measurements were undertaken by the same audiologist.

The subjective assessment of tinnitus intensity was performed using a 6-point rating scale in which the patient rated his/her perception from "no ear noise" (0) to "continuous ear noise, very obtrusive" [DeFeudis 1991].

Monitoring of otoacoustic emissions (OAE) enables the active biomechanical performance of the outer hair cells to be assessed. The OAE parameters used in this study were reproducibility and response (echo).

Randomization, biometrical planning and analysis

The study participants were allocated symmetrically to the treatment groups according to a randomization schedule created by means of an EDP random number generator, with random block sizes of 2 or 4. The patient numbers were assigned to the patients chronologically in ascending order.

Our working hypothesis predicted superior clinical efficacy of Ginkgo special extract EGB 761 in comparison to placebo, as measured by a decrease in tinnitus volume in the more severely affected ear during out-patient treatment. Confirmatory tests for treatment group differences were conducted for the changes in tinnitus volume between the end of the in-patient phase (examination 4 in Figure 1) and the examinations after 12, 8 and 4 weeks of out-patient treatment. The corresponding null hypotheses were arranged in advance in the specified sequence, by descending order of importance.

According to the data analysis, the assumption that the analysis samples came from a normally distributed population was not justified. Therefore, the Mann-Whitney U-test procedure was applied for confirmatory testing using a multiple Type 1 error of $\alpha = 5\%$ (1-tailed test). The application of the corresponding multiple test procedure, according to which lower-ranked hypotheses are only tested after all higher-ranked null hypotheses have been rejected, ensures the control of a multiple level of $\alpha$ [Maurer et al. 1995]. The confirmatory hypothesis tests were based on all patients who had been randomized, had completed the in-patient phase and had received double-blind treatment with either EGB 761 or placebo at least once (intention-to-treat population). An additional per protocol analysis was performed to assess the stability of the results.

In case of missing data in the primary outcome measure, the last valid observation was carried forward (LOCF), beginning with day 5 of the in-patient phase (i.e. in a patient with valid observations at day 1 of the in-patient phase, but missing data for all subsequent visits, these missing data were replaced by the value for day 1). To assess the influence of missing data replacement considering a large rate of premature study terminations (see results section below), supplementary analyses were performed in which the starting point for the replacement of missing data was shifted systematically towards the end of the trial period, i.e. replacement was restricted to data missing at visits after days 5 or 10 of the in-patient phase, or after month 1 of the outpatient phase. These analyses showed that the differences between the treatment groups with regard to the study's primary outcome
Table 1. Hearing loss (in dB) for the more severely impaired ear, screening examination (mean, standard deviation, 2-tailed U-test p value).

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Placebo (n = 29)</th>
<th>EGB 761 (n = 31)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>0.125 kHz</td>
<td>14.8</td>
<td>11.8</td>
<td>12.7</td>
</tr>
<tr>
<td>0.25 kHz</td>
<td>15.0</td>
<td>10.1</td>
<td>15.0</td>
</tr>
<tr>
<td>0.5 kHz</td>
<td>16.2</td>
<td>11.7</td>
<td>15.8</td>
</tr>
<tr>
<td>1.0 kHz</td>
<td>17.2</td>
<td>12.3</td>
<td>18.1</td>
</tr>
<tr>
<td>1.5 kHz</td>
<td>18.9</td>
<td>13.5</td>
<td>19.4</td>
</tr>
<tr>
<td>2.0 kHz</td>
<td>22.9</td>
<td>12.5</td>
<td>22.6</td>
</tr>
<tr>
<td>3.0 kHz</td>
<td>32.6</td>
<td>17.0</td>
<td>29.2</td>
</tr>
<tr>
<td>4.0 kHz</td>
<td>40.9</td>
<td>20.0</td>
<td>36.8</td>
</tr>
<tr>
<td>6.0 kHz</td>
<td>39.1</td>
<td>19.8</td>
<td>35.7</td>
</tr>
<tr>
<td>8.0 kHz</td>
<td>35.5</td>
<td>18.2</td>
<td>35.3</td>
</tr>
</tbody>
</table>

The secondary parameters were analyzed descriptively [Abt 1987]. All patients included into the trial were considered in the analysis.

The statistical analyses were conducted using SAS data analysis software, version 6.12.

Results

Unless explicitly specified otherwise, the results presented in the following sections refer to the intention-to-treat population (treatment efficacy) or to all patients included (all other parameters).

Patients and baseline status

A total of 60 patients was included into the trial; 31 of them were randomly assigned to out-patient treatment with EGB 761 and 29 to placebo. The 2 treatment groups were homogeneous with respect to demographic data, previous and concomitant illnesses and physical findings: 15 of the 29 placebo patients (51.7%) and 19 of 31 EGB 761 patients (61.3%) were male. The median age of the patients was 45 years in the EGB 761 group and 47 years in the placebo group.

At the time of study enrolment, the patients in both treatment groups had been suffering from tinnitus for an average of approximately 3 years, with the medium 50% of the study population between 3 months and 3.5 years. Table 1 shows that the extent of the patients' hearing loss at screening was comparable in both treatment groups over the entire auditory field, and that hearing loss was strongest in the area of 4 kHz and above. The extent of hearing impairment evident in the word and number comprehension tests was also comparable between the treatment groups.

Before the start of study treatment, the patients' tinnitus was audible at frequencies ranging from 125 Hz to 12 kHz, with mean values of 5.3 kHz (SD = 3.0 kHz) for EGB 761 and 4.4 kHz (SD = 3.2 kHz) for placebo. During the screening examination, the average loudness of tinnitus was determined as 44.2 dB (SD = 21.2 dB) in the EGB 761 group and 43.7 dB (SD = 19.9 dB) in the placebo group (absolute values). For both parameters, the differences between the treatment groups were statistically negligible (p > 0.15, U-test). In 28 of the 29 patients in the placebo group and in 29 of the 31 study participants randomized to EGB 761 the subjective ear sound was audible permanently. Nineteen patients in the placebo group (65.5%) and 22 in the EGB 761 group (70.2%) characterized the sound as subjectively annoying or very annoying.

According to anamnestic information obtained from the patients, the disturbance was attributable to the following causes (number of patients for placebo/EGB 761, respectively): sudden deafness (7/6), noise (3/5), blast trauma (0/2), other reasons (6/5), cause unknown (15/13) (multiple reasons possible).

During the open in-patient phase, the patients awaiting randomized treatment with EGB 761 and placebo showed comparable decreases of tinnitus volume by mean values of 8.5 and 7.4 dB, respectively (Table 3 below). The group means determined at day 10 of in-
The efficacy of Ginkgo special extract EGb 761 in patients with tinnitus

Figure 2. Disposition of patients and reasons for premature withdrawal.

Table 2. Difference in tinnitus volume (in dB) between the end of in-patient treatment and subsequent visits (ITT; last observation carried forward).

<table>
<thead>
<tr>
<th>Difference vs.</th>
<th>Placebo (n = 27)</th>
<th>EGb 761 (n = 30)</th>
<th>U-test p value (1-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Week 4</td>
<td>0.0</td>
<td>17.7</td>
<td>-5.8</td>
</tr>
<tr>
<td>Week 8</td>
<td>-1.3</td>
<td>16.2</td>
<td>-3.0</td>
</tr>
<tr>
<td>Week 12</td>
<td>-1.9</td>
<td>17.3</td>
<td>-3.5</td>
</tr>
</tbody>
</table>

Negative means denote tinnitus volume decrease.

Fusion treatment, which served as the baseline values for the double-blind phase, were 34.8 ± 22.9 dB for EGb 761 and 33.7 ± 23.2 dB for placebo, respectively (mean ± SD), so that baseline comparability of the treatment groups was ensured.

Figure 2 shows the accountability of the 60 patients included into the trial. Out of the 58 study participants included into the in-patient phase, 6 were withdrawn during EGb 761 infusion treatment, so that 52 patients (EGb 761: 29; placebo: 23) entered the double-blind out-patient phase. In both treatment groups, fewer than half of the patients completed randomized treatment after 12 weeks. Six patients in each treatment group left the trial before the first follow-up visit at month 1. Together with those already withdrawn during in-patient treatment, last observations originating from a visit during (or at the end of) hospitalization had to be carried forward in 7 patients randomized to EGb 761 and in 11 randomized to placebo.

Five study participants randomized to EGb 761 (17.3% of those included into dou-
Table 3. Difference in tinnitus volume (in dB) between screening and subsequent visits; ITT analysis data set with and without missing data imputation.

<table>
<thead>
<tr>
<th>Placebo</th>
<th>EGb 761</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last observation</td>
<td>Last observation</td>
</tr>
<tr>
<td>carried forward (n = 27)</td>
<td>carried forward (n = 30)</td>
</tr>
<tr>
<td>No missing data</td>
<td>No missing data</td>
</tr>
<tr>
<td>imputation (n = 23/17/12/9)</td>
<td>imputation (n = 29/23/18/13)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Difference vs.:</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>-7.4</td>
<td>20.5</td>
<td>-9.1</td>
<td>20.2</td>
<td>-8.5</td>
<td>24.0</td>
<td>-9.1</td>
<td>24.6</td>
</tr>
<tr>
<td>Week 4</td>
<td>-7.4</td>
<td>22.4</td>
<td>-8.5</td>
<td>24.3</td>
<td>-14.3</td>
<td>25.6</td>
<td>-22.9</td>
<td>24.3</td>
</tr>
<tr>
<td>Week 8</td>
<td>-8.7</td>
<td>24.5</td>
<td>-13.8</td>
<td>31.2</td>
<td>-11.5</td>
<td>27.1</td>
<td>-13.9</td>
<td>31.3</td>
</tr>
<tr>
<td>Week 12</td>
<td>-9.3</td>
<td>25.8</td>
<td>-21.1</td>
<td>34.5</td>
<td>-12.0</td>
<td>27.3</td>
<td>-23.5</td>
<td>24.5</td>
</tr>
</tbody>
</table>

Negative means denote tinnitus volume decrease.

It was possible for the study medication to be administered prematurely because their tinnitus symptoms had subsided completely. In the placebo group, 1 patient refused further treatment due to lack of efficacy. The majority of study non-completers in both groups, however, failed to attend any further visits at some point during out-patient treatment (these individuals were lost to follow-up, so that their motivation for leaving the trial remained unknown).

Two study participants (1 in each treatment arm) attended only the screening examination and were withdrawn from the trial without ever receiving any study-specific medication. One additional patient randomized to placebo suffered from chills after the first infusion and was withdrawn without any further testing, so that only his screening data were available. Since the last observation for the assessment of treatment efficacy was carried forward from the visit at day 1 of infusion treatment on, these 3 patients were not evaluable. The number of patients analyzed according to intention-to-treat (ITT) was therefore 30 and 27 for EGb 761 and placebo, respectively.

In addition to premature study discontinuation, relevant protocol violations were detected in 3 study completers randomized to placebo and in 1 from the EGb 761 group. As a consequence, the sample sizes for the per protocol (PP) analysis of efficacy were 6 and 12 patients for EGb 761 and placebo, respectively.

**Primary outcome measure**

Following the decrease in tinnitus volume during initial infusion treatment (cf. previous section), the study participants randomized to placebo showed no further symptom improvement during the first 4 weeks of double-blind treatment. Between weeks 4 and 12 (or treatment end), an average decrease by 1.9 dB was observed (Table 2). The mean tinnitus levels at baseline and week 12 were 33.7 ± 23.2 dB and 31.9 ± 24.4 dB, respectively (means ± SD). The patients in the EGb 761 group showed an average decrease in tinnitus volume by 5.8 dB, during the first 4 weeks of randomized out-patient treatment. Although these improvements were not fully preserved until the end of the period of observation, there was still a decrease of tinnitus volume by an average of 3.5 dB at treatment end, with mean values (± SD) of 34.8 ± 22.9 dB at baseline and 31.3 ± 24.6 dB at week 12. The comparatively large standard deviations associated with these means indicate that there were considerable inter-individual differences regarding the degree of response to EGb 761 within the treatment groups (due to the preceding infusion treatment, this applies to the placebo group as well).

Table 2 also shows that for all 3 follow-up examinations, the differences in tinnitus decrease between the 2 treatment groups were associated with p values below the nominal level of α = 0.05. Hence the 3 associated null hypotheses were rejected and the trial demon-
The efficacy of Ginkgo special extract EGb 761 in patients with tinnitus

Table 4. Difference in hearing loss (in dB) by frequency; comparison between baseline and week 12 (ITT; last observation carried forward).

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Placebo (n = 27)</th>
<th>EGb 761 (n = 30)</th>
<th>U-test p value (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0 kHz</td>
<td>3.7 ± 7.7</td>
<td>-0.5 ± 7.1</td>
<td>0.04</td>
</tr>
<tr>
<td>4.0 kHz</td>
<td>4.3 ± 9.8</td>
<td>-4.8 ± 11.4</td>
<td>0.002</td>
</tr>
<tr>
<td>6.0 kHz</td>
<td>1.7 ± 6.4</td>
<td>-1.8 ± 13.8</td>
<td>0.27</td>
</tr>
<tr>
<td>8.0 kHz</td>
<td>1.7 ± 3.9</td>
<td>-2.2 ± 12.0</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Negative means denote decrease in hearing loss (i.e. improved hearing).

Table 4 demonstrates the superiority of EGb 761 over placebo for the primary outcome measure after 12, 8, and 4 weeks of randomized out-patient treatment.

In the per-protocol population, the decrease in tinnitus volume during in-patient infusion treatment (approximately 16 dB on average) was almost twice as large as in the intention-to-treat data set. The treatment group differences in tinnitus change at months 1 and 2 were larger (in favor of EGb 761) than in the intention-to-treat analysis, but smaller at month 3. The per-protocol results must be interpreted with consideration, however, due to the small PP sample size (EGb 761 n = 12; placebo n = 6).

The impact of premature treatment terminations on the primary efficacy measure can also be assessed by comparing the results obtained by applying the LOCF method to those without missing data imputation (i.e. to those patients who were actually still in the trial at a particular visit). Table 3 displays the changes in tinnitus volume between the pre-infusion screening visit and subsequent visits starting with baseline. At all visits (including the baseline of the double-blind phase that followed EGb 761 infusion treatment), the patients in both treatment groups who were still in the trial consistently showed larger improvements in tinnitus versus screening, which might suggest an interaction between (insufficient) tinnitus volume decrease and premature study termination. During subsequent out-patient treatment, the differences between the 2 groups of patients still in the trial were comparable to those between data sets in which the last observations of terminating patients were carried forward. The results therefore do not indicate a systematic influence of premature study terminations on the treatment group differences observed during the double-blind phase of the trial.

Secondary outcome measures of efficacy

A reduction of hearing loss was observed for all frequencies during the open in-patient phase with EGb 761 infusion treatment. In the double-blind phase, the patients in both treatment groups showed no further changes regarding hearing loss at lower frequencies (0.125 – 2.0 kHz). At frequencies of 3.0 kHz and above, further improvements in the patients’ audition were observed in the EGb 761 group, while the patients in the placebo group showed an average deterioration of their power of hearing (Table 4).

According to the descriptive p values shown in Table 4, the between-group differences were most pronounced at 4 kHz, followed by 3, 8, and 6 kHz.

In the course of the trial, both treatment groups showed no relevant changes regarding word and number comprehension. The same applied to changes in tinnitus frequency, where there were also no interpretable between-group differences.

In the patients’ self-rating of tinnitus intensity, the fraction of patients with permanently audible and annoying or very annoying subjective ear sounds decreased from 58.6% of the assessable patients in the EGb 761 group at baseline to 37.9% at treatment end. The values for placebo were 43.4% and 47.8%, respectively, pointing to a mild deterioration of self-assessment during randomized out-patient treatment.

Safety

During initial in-patient treatment, 10 adverse events were reported by 9 patients. In 5 events (4 patients), a causal relationship with the EGb 761 infusion was assessed as unlikely, but could not be excluded entirely. These events were chills (possibly related to concomitant infection), phlebitis (possibly caused by insufficient wound sanitation), vertigo (2 x), and nausea. The remaining events were evidently attributable to causes other
than the study drug. All events during inpatient treatment were mild or moderate in intensity and subsided without sequels.

In the randomized out-patient phase, 2 adverse events (iron deficiency and common cold) were reported by 2 patients treated with EGB 761. For both events, the intensity of which was assessed as mild and moderate respectively, a causal relationship with the study drug was excluded, as other causes were evident. In the placebo group, 3 patients reported 5 adverse events.

During the entire study period, serious adverse events (i.e., events that were life-threatening or fatal, led to permanent disability, necessitated or prolonged hospitalization, or caused congenital abnormal development or malignancies) were not observed.

**Discussion**

The study demonstrates superiority of Ginkgo biloba special extract EGB 761 over placebo in the reduction of the loudness of subjective ear sounds (tinnitus) after administration of 2 × 80 mg extract/day. This treatment effect, which was already evident after 4 weeks and persisted until the end of the study after 12 weeks, was evident clinically and was confirmed by statistical significance at all follow-up visits. The results for the primary outcome measure were fully supported by the secondary variables. In particular, the patients' hearing ability was improved during double-blind treatment with EGB 761, but deteriorated under placebo. The study outcome confirms the findings of previous studies [Eckmann and Schlag 1982, Halama et al. 1988, Meyer 1986a, 1986b, Morgenstern and Biermann 1997] which also demonstrated the efficacy of preparations from Ginkgo biloba extracts in tinnitus treatment.

To assess the impact of prior EGB 761 infusion treatment on overall treatment success, the data published by Morgenstern and Biermann [1997], whose trial was identical in design to the one reported here except for the absence of an initial infusion phase, can be consulted for comparison. In Morgenstern and Biermann [1997], the treatment group mean for tinnitus volume decreased from 42.2 dB at baseline to 39.0 dB after 12 weeks in patients treated with 120 mg/day EGB 761 and it increased from 44.3 dB to 45.1 dB in the placebo group. With differences in the mean versus baseline of −3.2 dB for EGB 761 and +0.8 dB for placebo, the results in the previous trial were quite comparable to ours (mean changes of −3.5 dB and −1.9 dB for EGB 761 and placebo, respectively), particularly in the study participants who received the herbal extract during randomized treatment. However, while Morgenstern' s and Biermann' s [1997] baseline volumes of tinnitus differed only marginally from the ones determined in this trial before the beginning of the infusion phase (means around 44 dB for both treatment groups), the means determined at the beginning of double-blind treatment were substantially lower, owing to the beneficial effect of the infusion therapy applied to all patients. The comparison between the 2 trials thus shows that the effects of initial EGB 761 infusion treatment and subsequent EGB 761 oral out-patient treatment were largely additive and that the patients drew a maximum benefit from the combination of both.

As expected, the measured improvement in pure tone threshold did not lead to an improvement in speech comprehension, as this was above the frequency range of the 2nd formants.

Despite abundant research in the area of tinnitus, the exact pathophysiological correlates of the disease are yet unknown, as are the mechanisms by which effective drugs contribute to its alleviation. Poor perfusion of the inner ear is thought to be a possible cause of subjective ear sounds [Holgers et al. 1994, Lenarz 1989]. The known influence of Ginkgo special extract EGB 761 on platelet activation factor antagonism and thromboxan/prostacyclin balance [Ernst and Huber 1991, Ernst et al. 1989], which can affect the microcirculation in the inner ear, may offer an explanation for the efficacy demonstrated in this study.

With fewer adverse events in the EGB 761 group than in the placebo group during double-blind treatment, which were furthermore only mild to moderate in intensity and unrelated to the herbal extract throughout, the tolerability of oral EGB 761 was excellent. Mild vertigo and moderate nausea, which were attributable adverse events during infusion treatment, were not unexpected when considering the drug's side effect profile and
also did not present serious limitations regarding tolerance to the extract. These results are thus in full accordance with the experience with the preparation to date [Commission E monograph 1994, DeFeudis 1991].

The high rate of premature withdrawals from treatment was regrettable, but there were no indications that it was causally related to lack of tolerability, nor that substantially different conclusions would have been reached, had these patients remained in the trial until the scheduled end.

Conclusions

A combination of infusion therapy followed by oral administration of Ginkgo special extract EGB 761 appears to be effective and safe in alleviating the symptoms associated with tinnitus aurium. Owing to the unproblematic tolerability of the oral preparation in particular, this treatment regimen may offer promising perspectives for long-term treatment of this chronic condition.

References

Abit K 1987 Descriptive data analysis: a concept between confirmatory and exploratory data analysis. Meth Info Med 26: 77-88


Ernst A, Hunger O 1991 PAF receptor antagonists influence asphyxia-induced changes of the inner ear. J Lipid Mediat 4: 327-332


Fechtmaur H 1971 Homolateral and contralateral masking of tinnitus by noise-bands and pure-tones. Audiology 10: 138-144

Halebrook KH 1970 Sprachaudiometrie. Thieme, Stuttgart


