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Efficacy of artichoke leaf extract in the treatment of patients with functional dyspepsia: a six-week placebo-controlled, double-blind, multicentre trial

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SUMMARY

Background: This study aimed to assess the efficacy of artichoke leaf extract (ALE) in the treatment of patients with functional dyspepsia (FD).

Methods: In a double-blind, randomized controlled trial (RCT), 247 patients with functional dyspepsia were recruited and treated with either a commercial ALE preparation (2×320 mg plant extract t.d.s.) or a placebo. The primary efficacy variable was the sum score of the patient's weekly rating of the overall change in dyspeptic symptoms (four-point scale). Secondary variables were the scores of each dyspeptic symptom and the quality of life (QOL) as assessed by the Nepean Dyspepsia Index (NDI).

Results: Two hundred and forty-seven patients were enrolled, and data from 244 patients (129 active treatment, 115 placebo) were suitable for inclusion in the statistical analysis (intention-to-treat). The overall symptom improvement over the 6 weeks of treatment was significantly greater with ALE than with the placebo (8.3 ± 4.6, vs. 6.7 ± 4.8, $P < 0.01$). Similarly, patients treated with ALE showed significantly greater improvement in the global quality-of-life scores (NDI) compared with the placebo-treated patients (-41.1 ± 47.6 vs. -24.8 ± 35.6, $P < 0.01$).

Conclusion: The ALE preparation tested was significantly better than the placebo in alleviating symptoms and improving the disease-specific quality of life in patients with functional dyspepsia.

INTRODUCTION

Dyspepsia is highly prevalent in the population, but underlying structural (or organic) lesions are found in only a minority of patients. Dyspepsia in the absence of a clinically identifiable structural lesion causing symptoms is referred to as functional dyspepsia.[1, 2] Because a structural explanation is lacking, disturbed gastrointestinal function (GI) is believed to play a role in the development of symptoms.[3] Pharmacological treatment for patients with functional dyspepsia remains unsatisfactory.[4] Some controlled trials have demonstrated that H_2-receptor antagonists[5] and proton-pump inhibitors[6] are better than a placebo, but the benefits have been modest. Several randomized controlled trials (RCTs) have demonstrated the superiority of cisapride over a placebo, but although this has been confirmed in systematic reviews and meta-analyses[7–9] its use is now restricted in most countries because of rare cardiac side-effects. While eradication of *Helicobacter pylori* has been advocated for the treatment of patients with functional dyspepsia, the results of such eradication studies have been generally disappointing and any long-term benefit is debatable.[10] Finding convincingly effective treatment options thus continues to be an important goal.

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Artichoke (*Cynara scolymus*) leaf extracts have traditionally been used to treat dyspeptic symptoms, and it is now believed that the bitter compounds, such as cynaropicrin, are responsible for the beneficial effects. Artichoke leaf extract (ALE) increases bile flow[11] and is thought to exert hepatoprotective[12] lipid-lowering[13] antioxidant and antispasmodic effects.[14–16]

To date, placebo-controlled studies on the effects of ALE in the treatment of patients with functional dyspepsia are lacking. However, observational data for the artichoke leaf extract tested (ALE LI 220) from more than 1300 patients[17, 18] have shown clear improvement of symptoms during treatment. While this beneficial effect might be due to a placebo effect or spontaneous fluctuation of symptom intensity, placebo-controlled trials are clearly needed to substantiate the efficacy of ALE. For this reason, we aimed to assess the efficacy of a commercially available ALE in the treatment of patients with functional dyspepsia with respect to the intensity of dyspeptic symptoms and the improvement of disease-specific quality of life.

PATIENTS AND METHODS

Patients

Two hundred and forty-seven patients (aged between 18 and 75 years), with persistent or recurrent pain or discomfort centred in the upper abdomen and a diagnosis of functional dyspepsia, were recruited by general practitioners in private practice. Prior to enrolment in the trial, a physical examination, laboratory testing (full blood count, sedimentation rate, fasting blood glucose, liver function tests), an abdominal ultrasound and upper gastrointestinal endoscopy were performed to exclude a structural cause for the symptoms. Colonoscopy was performed in all subjects over the age of 45 years or with symptoms referred to the lower gut.

Functional dyspepsia was diagnosed if the subjects had upper abdominal pain or discomfort (an unpleasant sensation not reaching the level of pain characterized by one or more of the following symptoms: early satiety, postprandial fullness, bloating and nausea) for at least 2 months without an identifiable underlying structural or biochemical cause. Marked reflux symptoms (retrosternal pain, burning and regurgitation) were considered to be associated with gastro-oesophageal reflux disease rather than with functional dyspepsia. Patients with mainly or purely reflux symptoms and patients whose symptoms were predominantly those of irritable bowel syndrome were not eligible to take part in the study. Concomitant medication acting on or influencing the gastrointestinal system (e.g. proton-pump inhibitors, H_2 blockers, cholagogues, prokinetic agents, NSAIDs, theophylline) was not allowed, and patients taking such medication were not eligible for enrolment into the study.

Materials

The medication tested was a commercially available preparation containing 320 mg artichoke leaf extract LI 220 (HeparSL® forte, Sertürner Arzneimittel GmbH, Berlin, Germany) or placebo. The dried extract (consisting of leaves and not flowering heads; draft monograph in Pharmacopeia Europaea) had been eluted with water. The resulting dry extract had a drug-to-extract ratio of 3.8–5.5 : 1. Main substance classes are caffeoyl quinic acids, flavonoids and sesquiterpene lactones (bitters). Patients were asked to take two capsules of artichoke or placebo three times a day. This dose is the recommended daily dose according to the German Commission E monograph for cynarae folium.

Randomization and blinding

Randomization was done electronically with 'Rancode' (idv GmbH, Germany) assigning patient numbers to either ALE or placebo (1:1) in ascending order. Placebo capsules were identical in appearance, smell and taste to the test drug but without pharmacologically active ingredients. Neither the patient nor the physician were aware of the randomization as active or placebo. Test medication and placebo were produced according to good manufacturing practice (GMP).

Study design

This clinical trial was performed as a prospective, multicentre, double-blind, randomized, placebo-controlled, parallel-group comparison of ALE and the placebo over a period of 6 weeks.

The primary outcome variable was the sum score of the patient's rating of the overall change in dyspeptic symptoms, assessed each week. This measurement provided an index for the global response over the 6-week treatment period. Patient ratings were ascribed

to one of four categories (0 = not improved; 1 = slightly improved; 2 = markedly improved; 3 = completely improved), giving a theoretical sum score range from 0 to 18. The category 'not improved' includes worsening of symptoms. This measure with predefined categories of constant intervals allows sufficient distinction between ratings, and is validated for many other verbal four-point rating scales.

Secondary outcome variables were the course of overall changes in individual dyspeptic symptoms during treatment, the sum score of the patient's self-rating of intensity of each dyspeptic symptom, the sum score of differences to baseline and improvement of health-related quality of life as assessed using the Nepean Dyspepsia Index (NDI),[19, 20] and overall assessments of efficacy by patient and investigator. The intensity of dyspeptic symptoms was rated on a four-point Lickert scale from no symptoms (0 points) to severe symptoms (3 points).

Adverse events, overall assessment of tolerability by both patients and investigators, clinically significant changes in laboratory values, and vital signs were also monitored. In addition, the Bowel Disease Questionnaire[21, 22] (BDQ) was used to assess the symptom pattern.

Visits were scheduled immediately before the start of treatment (baseline), and after 2, 4 and 6 weeks of treatment. Between visits, the overall change and the intensity of individual dyspeptic symptoms were assessed in standardized telephone interviews conducted by the physician or study nurse at each site. Ethics committee approval was obtained prior to commencing the study.

Statistical analysis

All analyses were done in concordance with current good clinical practice-guidelines. A two-sided *t*-test for independent samples was used for the analysis of the primary and secondary outcome variables. In case of a deviation from the normal distribution the Wilcoxon *U*-test was used instead of the *t*-test.

The intention-to-treat (ITT) analysis was the primary analysis to test the efficacy of ALE. The ITT set includes all patients who had received study medication and had at least one value for the primary efficacy variable. Missing values were carried forward by the last value (LOCF). Values for patients who had dropped out were continued as zero points (no improvement). Analysis was also done in the per protocol sample (PPS). This analysis set was mainly characterized as patients having one missing value for the primary efficacy variable and minor protocol deviations only.

The sample size of each treatment group (≥ 115 evaluable cases) was sufficient for testing with 90% power at the 5% alpha level on the basis of a 15% difference between the treatment groups. For the power calculation, the placebo response was assumed to be 40%.

RESULTS

Study population

The study was conducted with outpatients seen by 30 general internists and general practitioners in primary care settings in Germany. Two hundred and forty-seven patients with functional dyspepsia were enrolled in the study. Data from 244 patients were eligible for ITT analysis (Figure 1). The two treatment groups were similar with respect to the distribution of demographic parameters and the pattern of symptoms (Table 1).

Disease characteristics

Functional dyspepsia is classified into three types according to the Rome II criteria.[2] The distribution of symptom types was similar in the two treatment groups ($P > 0.91$), with dysmotility-like functional dyspepsia being the most frequent in both groups (Table 1).

Overall change in dyspeptic symptoms

At each point in time, the overall change in self-rated intensity of dyspeptic symptoms compared to baseline was numerically greater in the ALE group than in the placebo group (Figure 2). The sum score of the self-rating of the overall change in dyspeptic symptoms (primary outcome variable) was significantly greater in the ALE group than in the placebo group, resulting in differences of 1.6 sum score units in the ITT analysis ($P = 0.007$) and 1.7 units in the analysis of patients treated according to protocol ($P = 0.006$) (Table 2).

During the study, the proportion of patients with complete resolution of symptoms increased. However, in the ALE study group this proportion was always numerically greater, and increased from one patient at the first visit to six, 12, 15, 31 and 32 at the follow-up visits. In patients treated with placebo a smaller number

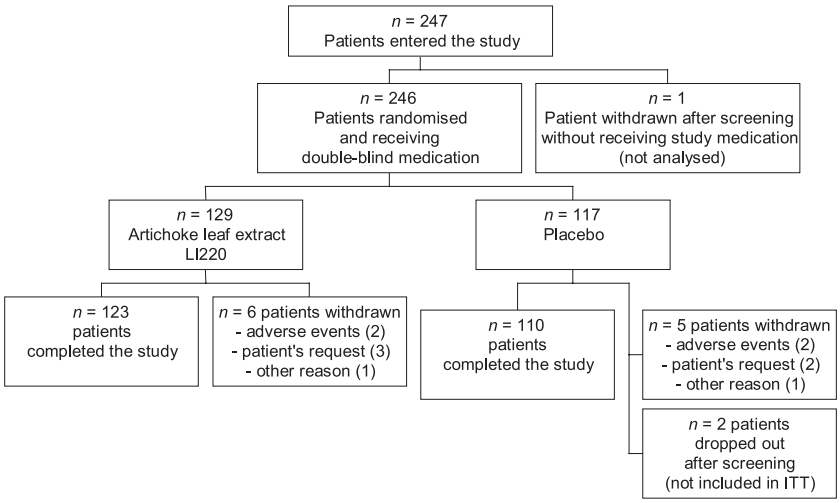

Figure 1. Patient randomization, allocation and drop-outs.

Table 1. Demographic data and type of functional dyspepsia (ITT)

	ALE ($n = 129$)	Placebo ($n = 115$)	*P*-value
Sex [*n* (%)]			
Male	44 (34.1)	46 (40.0)	$P > 0.8$
Female	85 (65.9)	69 (60.0)	$P > 0.8$
Age (years), mean ± s.d.	48.5 ± 13.3	46.1 ± 13.3	$P > 0.8$
Body mass index (kg/m^2), mean ± s.d.	25.2 ± 4.4	25.2 ± 3.5	$P > 0.8$
Type of dyspepsia			$P > 0.8$
Ulcer-type [*n* (%)]	18 (14.0)	18 (15.7)	$P > 0.8$
Dysmotility-type [*n* (%)]	74 (57.4)	66 (57.4)	$P > 0.8$
Unspecified [*n* (%)]	37 (28.7)	31 (27.0)	$P > 0.8$

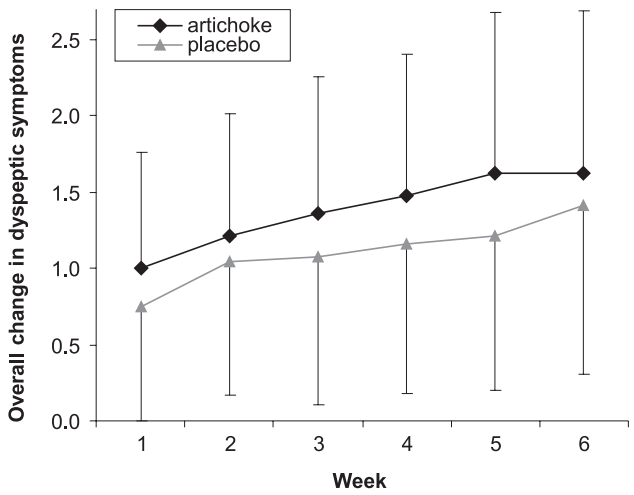

Figure 2. Change of the self-reported intensity of dyspeptic symptoms after 1, 2, 3, 4, 5 and 6 weeks of treatment (mean values for each visit, ±SD, ITT population).

Table 2. Sum scores of the patient self-rating of the overall change in dyspeptic symptoms (primary variable of this trial)*

	Group comparisons		
Analysis group	ALE	Placebo	*P*-value
ITT	8.3 ± 4.6	6.7 ± 4.8	0.0069†
Mean ± s.d. (range; *n*)	(0–17; 129)	(0–18; 115)	
PPS	8.5 ± 4.6	6.8 ± 4.9	0.0064†
Mean ± s.d. (range; *n*)	(0–17; 115)	(0–18; 102)	

* Data for the intention-to-treat (ITT) and per protocol sample (PPS).
† *t*-test.

of patients reported complete resolution of symptoms (from one patient to two, 10, 8, 12 and 23 during the follow-up visits). Interestingly the patients in the ALE group reported an immediate response to medication after one week.

For the interpretation of treatment efficacy, the number needed to treat (NNT) is a further important parameter to compare different therapeutic options for a disease. Assessing patients who rated the categories 'markedly' or 'completely' improved, the NNTs for the 4-, 5- or 6-week treatment were 8.1, 6.8 or 11.5, respectively.

Sub-group analysis

The analysis of two subgroups defined by specific questions out of the Bowel Disease Questionnaire revealed considerable differences between the groups. Patients without additional irritable bowel symptoms ($N = 159$) gained much more benefit from ALE

treatment than patients with additional irritable bowel syndrome ($N = 78$) (data not shown). The sum score of the overall change of dyspeptic symptoms in patients without concomitant irritable bowel syndrome symptoms was 9.0 ± 4.6 units, whereas in patients with irritable bowel syndrome symptoms 6.32 ± 4.9 sum score units were reached ($P < 0.001$).

Examination of the ratings by category for the overall change of dyspeptic complaints shows huge differences between the subgroups. In the non-irritable bowel syndrome sub-group the rating category 'completely improved' was fulfilled from 27 (33.3%) patients of the ALE treatment but only from 14 (17.9%) patients treated with placebo. In contrast, the situation differed in the patient group with additional irritable bowel syndrome symptoms. Here only four (8.9%) patients with ALE treatment but nine (27.3%) patients with placebo rated 'completely improved' (both at visit 6). Additionally, the same contrary picture was seen when the category 'not improved' was reviewed.

Intensity of individual dyspeptic symptoms

Table 3 summarizes the sums of differences from baseline for the main dyspeptic symptoms of fullness, flatulence, early satiety, nausea, vomiting and epigastric pain. The mean values of all symptoms were improved during the 6 weeks of treatment in all patients, but always with better improvement in patients with ALE treatment compared to placebo. Significantly better responses for the ALE group were found for the ease of symptom fullness, early satiety and flatulence (all $P < 0.05$). Improvement in pain, nausea or vomiting was not significantly different. Figure 3 presents the means of ratings for the dyspeptic symptoms rated for both treatment groups.

Table 3. Intensity of dyspeptic symptoms (ITT)*

Sum of difference to baseline mean ± s.d.	ALE ($n = 129$)	Placebo ($n = 115$)	P-value (t-test)
Fullness	6.6 ± 5.6	4.5 ± 5.8	0.0050
Flatulence	6.6 ± 5.8	4.7 ± 5.5	0.0112
Early satiety	5.3 ± 5.9	3.1 ± 5.8	0.0032
Nausea	4.3 ± 5.1	3.9 ± 5.2	0.5029
Vomiting	1.0 ± 2.6	1.0 ± 3.0	0.8369
Epigastric pain	7.7 ± 5.5	6.7 ± 5.7	0.1786

* A sum of difference to baseline score of −18 indicates maximum deterioration, while +18 indicates maximum improvement.

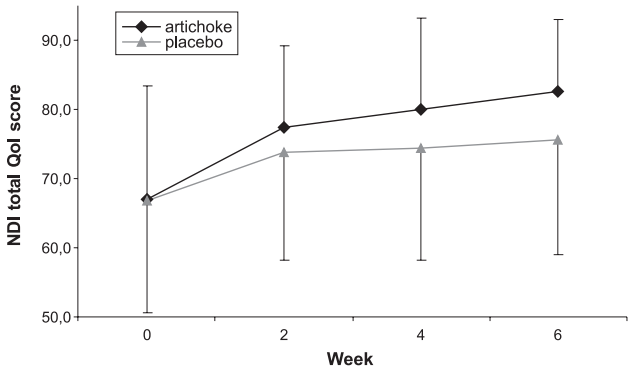

Figure 3. NDI total quality of life score during the study, by treatment group (mean values for each visits, ±SD).

Health-related quality of life

Like the severity ratings for dyspeptic symptoms, the mean NDI total symptom score improved in both treatment groups. The sums of differences from baseline for NDI total symptom scores were 89.6 ± 95.8 for ALE and 67.5 ± 77.3 for the placebo ($P = 0.05$) and for the NDI total quality of life score −41.1 ± 47.6 and −24.8 ± 35.6, respectively ($P < 0.01$), as shown in Figure 3.

Global efficacy rating by the physician and patient

The investigators rated the efficacy of treatment as satisfactory, good or very good in 84.7% of patients treated with ALE. Patient assessments yielded a similar result (85.5%). In the placebo group, efficacy was considered satisfactory or better in 69.6% of cases (patient assessments 68.7%). Thus, both investigator ($P = 0.02$) and patient ratings ($P < 0.02$) showed the superiority of active treatment with ALE in comparison with placebo.

Adverse events and tolerability

A total of 70 adverse events occurred during the study. Forty-five adverse events occurred in 29 patients treated with ALE compared with 25 adverse events in 18 patients in the placebo group. Most adverse events were reported for the WHO-ART organ class 'gastrointestinal system' (25.7% of all adverse events) followed by adverse events related to 'body as a whole' (18.6%). An accumulation of adverse events for a specific symptom or disease was not observed. The majority of adverse events were classified as mild or moderate, and

had resolved themselves by the end of the study. Four patients (two patients receiving ALE and two patients in the placebo group) withdrew prematurely because of adverse events.

One serious adverse event (moderate bilateral adnexitis) occurred in the placebo group. The relationship to the study drug was assessed by the investigator as unlikely. The patient recovered completely.

No effects of the study treatment on laboratory values or vital signs were reported. In accordance with these results, the vast majority of patients assessed the tolerability of both study drug and placebo as good or very good (ALE vs. placebo, 93.6% vs. 95.6%).

DISCUSSION

This is the first double-blind, randomized, placebo-controlled study that complies with the established standards for the conduct of studies in patients with functional dyspepsia. Our study demonstrated significantly greater improvement of dyspeptic symptoms during treatment with artichoke leaf extract compared to placebo. In addition, the test medication was superior to the placebo in improving disease-specific quality of life. In our study, the difference in the global response between ALE and placebo approached 15%. This therapeutic gain is within the range that has been observed in previous studies with chemically defined treatments.[8] Interestingly, the greatest group differences were observed for early satiety and fullness, while responses for pain and nausea were not significantly different for ALE and placebo. It appears that ALE exerts defined pharmacological actions that are particularly beneficial in patients with this pattern of symptoms.

The effects on bile secretion that have been found in previous trials[11] may partially contribute to our results. The increase in bile acid secretion is suitable to accelerate gastrointestinal transit and thus may alleviate bloating and fullness. The well known antispasmodic feature of ALE may also add to both effects.

Similar to other studies in this field have shown that there was a remarkable improvement in symptoms during the placebo treatment. While it is sometimes argued that this improvement reflects true placebo effects, it is likely that spontaneous fluctuations of symptom intensity contribute to the improvement seen during the placebo treatment. However, the superiority of active treatment over placebo was convincing and within the range observed in other trials.[8, 23]

In the present study, symptoms were assessed during a 6-week treatment period, as there are as yet no empirical data on the most appropriate duration of trials in patients with functional dyspepsia. On the other hand, some investigators recommend a trial duration of 8–12 weeks.[23] In clinical practice, many patients are treated on an on-demand basis. Thus data from short- rather than long-term trials are important to assess the clinical efficacy of these treatment. Thus we sincerely believe that our 6 week trials provided valuable information regarding the efficacy of ALE.

Patients with predominant irritable bowel syndrome symptoms were not eligible for the trial. However, we observed a trend towards greater improvement of symptoms in patients without concomitant irritable bowel syndrome symptoms (data not shown). While this finding needs replication in future trials, it is well known that ALE influences bowel movements and sometimes causes loose stools. Thus in patients with concomitant diarrhoea-dominant irritable bowel syndrome, symptoms might be aggravated.

The response of the secondary efficacy variables was in line with the primary outcome variable. While there was an overall improvement of symptoms during the course of the study, active treatment with ALE resulted in substantially greater improvement of individual symptoms and disease-specific quality of life.

With strict adherence to good clinical practice, the study was conducted in specific primary care settings so that only patients seen at the primary care level were recruited for this trial. These patients, rather than those seen at secondary referral centres, are most likely to represent typical patients with functional dyspepsia. For this reason, our data should be representative and applicable to the majority of patients with functional dyspepsia treated in similar settings.

In summary, the artichoke leaf extract tested was significantly superior to a placebo in the treatment of patients with functional dyspepsia. The effects of treatment were not simply restricted to an improvement of symptoms but also had a substantial impact on the disease-specific quality of life. Therefore, the artichoke leaf extract LI 220 appears to be an effective therapy for patients with functional dyspepsia. The precise mechanism of action needs to be elucidated.

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