

Steroid-sparing effect of wormwood (*Artemisia absinthium*) in Crohn's disease: A double-blind placebo-controlled study

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Abstract

In this double-blind study carried out at five sites in Germany, 40 patients suffering from Crohn's disease receiving a stable daily dose of steroids at an equivalent of 40 mg or less of prednisone for at least 3 weeks were administered a herbal blend containing wormwood herb (3×500 mg/day) or a placebo for 10 weeks. Besides steroids, 5-aminosalicylates, if dose remained constant for at least 4 weeks prior to entering the trial and/or azathioprine, stable dose for at least 8 weeks, or methotrexate, stable dose for at least 6 weeks, were permitted as concomitant medications. The recruited 40 patients – 20 in each treatment group, were evaluated with the help of a Crohn's Disease Activity Index (CDAI) questionnaire, an Inflammatory Bowel Disease Questionnaire (IBDQ), the 21-item Hamilton Depression Scale (HAMD) and an 8-item Visual Analogue Scale (VA-Scale) in 2-week intervals during the first 10 study weeks, and then at week 12, 16 and 20, which were the trial-medication free observation periods. The initial stable dose of steroids was maintained until week 2, after that a defined tapering schedule was started so that at the start of week 10 all the patients were free of steroids. At the end of week 10 the trial medication was also discontinued. The concomitant medications were maintained at the same dose levels till the end of the observation period that was the end of week 20.

There was a steady improvement in CD symptoms in 18 patients (90%) who received wormwood in spite of tapering of steroids as shown by CDA-Index, IBDQ, HAMD, and VAS. After 8 weeks of treatment with wormwood there was almost complete remission of symptoms in 13 (65%) patients in this group as compared to none in the placebo group. This remission persisted till the end of the observation period that was week 20, and the addition of steroids was not necessary. In two (10%) patients did the re-starting of corticoids become necessary? On the other hand, the CD conditions of the patients who received the placebo deteriorated after the tapering of steroids, and re-starting steroids became necessary in 16 (80%) patients in this group after week 10. These results strongly suggest that wormwood has a steroid sparing effect. The improvements in HAMD scores indicate that wormwood also has an effect on the mood and quality of life of CD patients, which is not achieved by other standard medications.

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Introduction

Herba *Artemisia absinthium*, also known as wormwood, is described in pharmacopoeia books in many countries around the world. It is known by a variety of names, depending upon the country. Wormwood enjoyed a wide spread use and held a high reputation in medicine among the ancients (Weis, 1988; *Encyclopaedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics*, 1996). For medicinal purposes, leaves and stems not thicker than 4 mm are used. The dry leaves and stems contain, among others, 0.25–1.32% essential oil, absinthin, anabsin, anabsinthin, artabsin and matricin. The essential oil contains thujone and thujyl alcohol and other terpene-derivatives, which are neurotoxic. The herb is usually standardised based on absinthin. High-quality wormwood should contain at least 0.2% absinthin (List and Hörhammer, 1973). Thujones are considered to be the major toxic agents present in the wormwood oil; α -thujone being more toxic than β -thujone (Chaisson et al., 2000).

The Crohn's disease (CD) is usually treated with 5-aminosalicylates, mostly in combination with steroids. Azathioprine, and sometimes, methotrexate is added to more severe cases. Side effects occur frequently, particularly during the co-treatment with steroids. Low-dose corticosteroids and alternate day corticosteroids are not effective steroid-sparing alternatives. Azathioprine, 6-mercaptopurine, methotrexate and the new anti-tumour necrosis factor monoclonal antibody infliximab are steroid sparing therapies, but these agents have their own side effects, which are also serious (Hanauer et al., 2002; Sandborn et al., 2000; Feagan et al., 1995). Therefore, a good therapy of CD must take into account the side effects caused by standard medication and must be able to reduce the use of steroids to a minimum.

The etiology and pathogenesis of CD is poorly understood. CD may be a primary autoimmune disease due to pathogenic effect of cytokines, but intestinal vasculitis has also been implicated. Recent studies have shown that a high prevalence of herpes virii such as CMV, HHV6 and EBV in CD patients (Wakefield et al., 1992; Berk et al., 1985). Yanai and his colleagues (1999) detected EBV in tissues of CD (63.8%) and ulcerative colitis (60%) and none in the non-inflammatory areas of colon specimen. These experiments suggested that all these viruses might be playing a significant role in the pathogenesis of CD.

In vitro studies done by Karim et al., from the Department of Biology, University of Minnesota at Duluth showed that water extracts of *Artemisia absinthium* were capable of protecting African green monkey kidney cells (Vero-Cells) and human epithelial type two (HEp-2) cells against herpes viruses at non-cytotoxic concentrations levels. In descending order of susceptibility, the virii against which wormwood extract

exhibited anti-viral activity in vitro were HSV I, VZV, EBV, human herpes virus 6 (HHV6), CMV and HSV 2 virus. Combination of wormwood water extract with cardamom, rose petals fruit water extracts resulted in synergetic or additive effects in in vitro studies (Karim et al., unpublished data). Kojima et al. have described a substance isolated from *Artemisia absinthium* and other plants belonging to artemisia family which induces the production of interferon and is at the same time not toxic to animal cells (German Patent Office 30 00 521; Patent Japan P 1540-79, 1979).

We hypothesised that wormwood, because of its anti-herpes properties may be a useful additive in the standard treatment of CD. The aim of the study was to add wormwood to the medication of CD patients receiving stable doses of corticosteroids, and see if wormwood was capable of reducing the patients' dependence on corticosteroids.

The outcomes in CD clinical trials are traditionally reported in terms of remission and response rates according to the Crohn's Disease Activity Index (CDAI) (Best et al., 1976). However, CDAI does not measure the overall burden of the illness experienced by the patients. CD produces a high psychological burden for the patients and many exhibit symptoms of moderate-to-severe depression. The study of Gregor and his colleagues (1997) underscores the belief that the health-related qualities of life (HRQL) in CD patients is significantly worse than in the general population. Therefore, there is a strong need to find a therapy that also improves the HRQL and possesses some anti-depressant effect. Quality of life can be evaluated using either the Short-Form-36 (SF-36) HRQL rating scale or inflammatory Bowel Disease Questionnaire (IBDQ). HRQL questionnaire not only measures the benefits of the therapy on disease symptoms, but also its impact on the social and emotional lives of the patients. The secondary objective of this study was therefore to find evidence that the addition of wormwood to the standard treatment of CD will not only improve the HRQL but also improve the symptoms of depression (Karim and Omer, 1996). To study this effect, we incorporated 21-item Hamilton's Scale of Depression in our observations.

Materials and methods

Application forms

We used herba *Artemisia absinthium pulvis* (wormwood) capsules being marketed by Noorherbals.com LLC, P.O. Box 758, Hockessin, Delaware, USA under the name of SedaCrohn[®]. Each 400 mg of SedaCrohn[®] capsule contained besides 250 mg of wormwood powder, 100 mg of rose, 40 mg of cardamom and 10 mg of mastic

resin. The placebo were identically looking capsules of the same size and weight (400 mg), containing only the fill substances rose-petals (100 mg), cardamom seeds (40 mg), resin of mastic (10 mg) and starch (100 mg). In vitro trials done by Karim et al. at the Minnesota University, Department of Biology, Duluth, USA, showed that neither roses, nor mastic resin or cardamom or any of their combinations, provided the combinations did not contain wormwood, expressed any anti-viral activity (Karim et al., unpublished data).

Standardisation

The wormwood used in Seda Crohn[®] was cultivated in Germany under standardised biological conditions, and was supplied by Galke Arzneipflanzen, Gittelde, Germany (Control No.: D-NI-LG-12-9304-BC, Code-No.: DE-012-ÖKO, EU regulation No.: 2092/91). Leaves and stems not thicker than 4 mm were used for processing. The herb was air-dried, powdered, mixed with powdered carriers (rose-petals, cardamom seeds and resin of mastic), and finally filled in capsules of the size 00. HPLC fingerprint were obtained using absinthin as marker. According to the data supplied by Noorherbals, Seda Crohn[®] preparation contains 0.2–0.38% absinthin and 0.25–1.52% essential oils, depending upon the batch.

Table 1. Patients disposition, baseline characteristics, concomitant medications

	Group I (wormwood)	Group II (placebo)
Males	12	11
Females	8	9
Age (median)	46 (21–75)	41 (22–67)
Duration of disease (years)	6.1 (3.9–14.2)	4.5 (2.7–11.2)
<i>Involved intestine</i>		
Ileum	3	2
Colon	20	20
Ileum + colon	20	20
Gastro-duodenum	3	5
Resection	17	14
CDAI (median)	298 (240–321)	277 (238–317)
IBDQ (median)	121 (110–152)	125 (123–147)
<i>Concomitant medication</i>		
Glucocorticoids		
Below 20 mg	8	6
Above 20 mg	12	14
5-Aminosalicylates	16	18
Azathiopirines	8	6
Methotrexate	4	2

Demographic and clinical characteristics at baseline figures are numbers, medians and ranges.

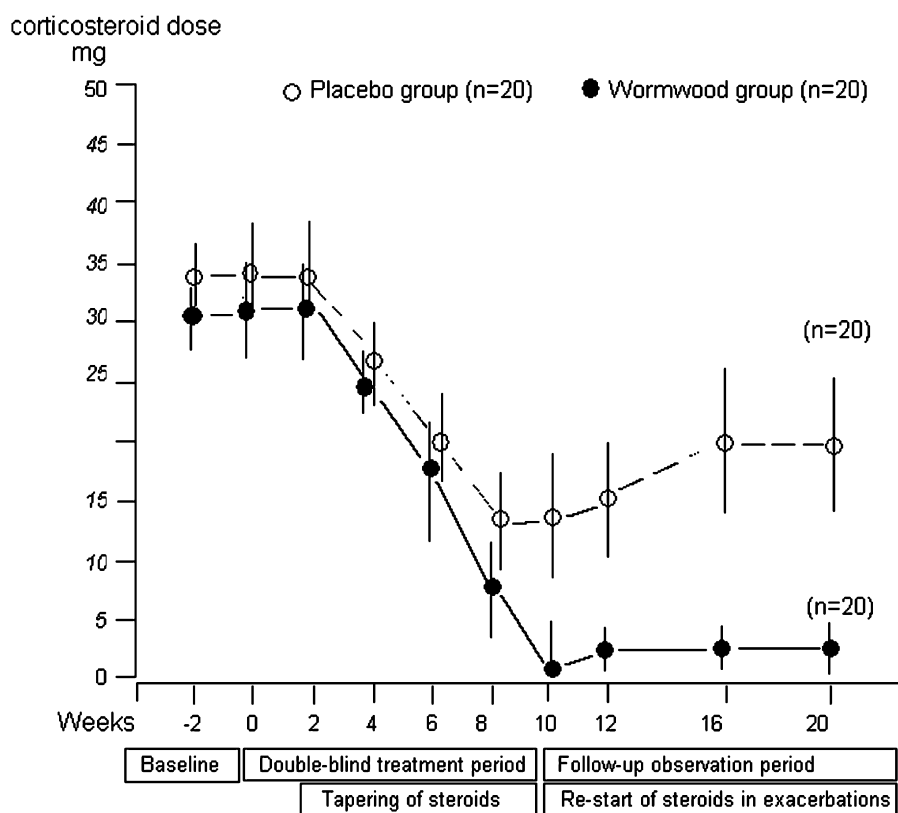


Fig. 1. Patients receiving corticosteroids maintained a stable dose until week 2, after that tapering of steroids started and completed at week 10. In the placebo-group 80% of the patients were unable to discontinue with corticosteroids without disease exacerbation, whereas there were only 10% such patients in the group receiving wormwood.

Toxicity data

In 1979, the FAO/WHO Codex Committee on Food additives restricted the use of α - and β -thujones to the maximum levels in final products ready for consumption: 0.5 ppm in food. In the capsules used in our study, the thujone contents were less than 5 ppm. They were estimated according to the Official Methods of Analysis of the Association of Official Analytical Chemists, 13th Ed., 1980, Section 9.129 (Data provided by Noorherbals.com). The amount of absinthin present in the trial batch was 0.37% as required by Deutsches Arzneibuch (DAB VII) for a good medicinal wormwood (Data provided by Noorherbals.com).

Acute (24 h), sub-acute (4 weeks) and chronic (6 months) toxicity data of the above composition in powder form was provided by LiTaka Pharmaceutical Laboratories, Pune, India. In acute toxicity studies done 5 doses ranging from 0.575 to 5.812 g/kg were administered. No mortality in mice was observed. For sub-acute

(4 weeks) toxicity 10 albino rats were fed with 45 mg/100 g and 90 mg/100 g rats daily for 4 weeks. There was a significant gain in weight at the end of 4 weeks feeding. In 6 months toxicity studies same doses as for sub-acute toxicity were given for 6 months. Body weight, organ weights and hematological findings did not show signs of toxicity. Teratogenic studies on rats after 6 months feeding of the above-mentioned dose did not show any changes in uterus, ovaries and corpora lutea and there were no dead fetes or reabsorbed embryos (unpublished data of Li Taka Pharmaceuticals). This laboratory has been assigned the Labeler Code No. 58317 by the Department of Health and Human Services, Food and Drug Administration, Rockville, MD, USA).

Study protocol

The protocol of this study was designed to assess the steroid-sparing effect, remission inducing properties and quality of life improving effect of wormwood. It was a

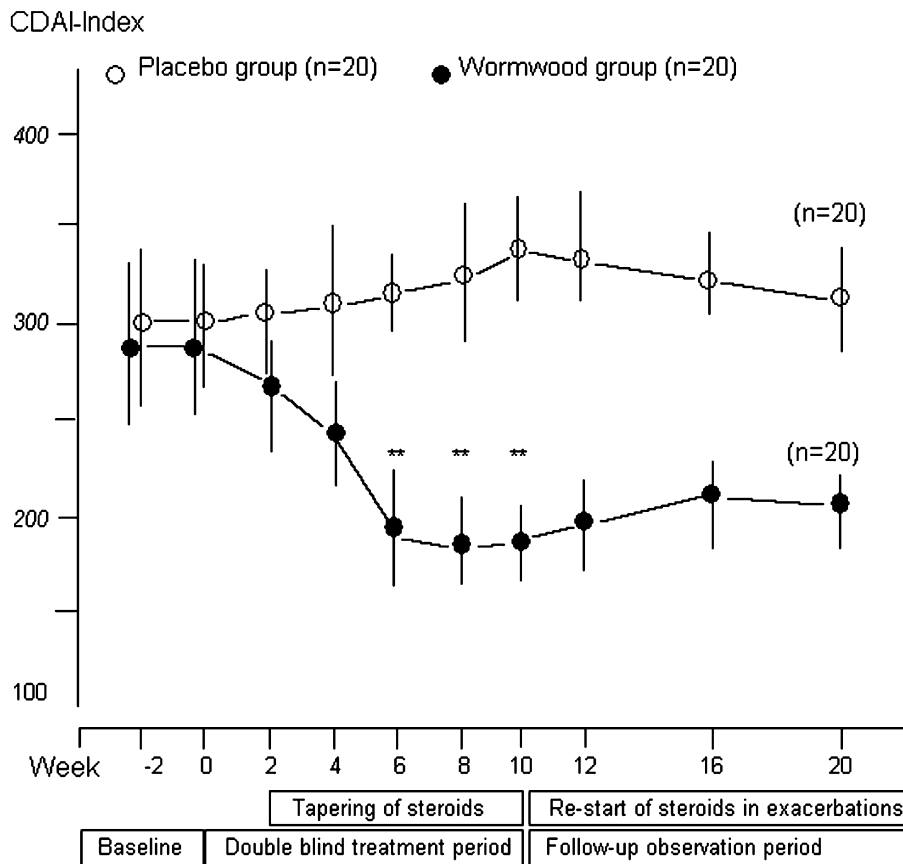


Fig. 2. Total CDA-Index scores over time (means and 95% confidence intervals) are shown. Crohn’s disease (CD) deteriorated as expressed in the CDA-Index scores at week 10 in 16 (80%) patients in the placebo group when all corticosteroids were tapered to zero. This necessitated the restart of corticosteroid treatment in 11 patients, 9 patients tolerated the reduction in steroids but their CDA-Index scores remained unchanged. There is steady improvement in CD in 18 patient of group receiving wormwood in spite of tapering of steroids. After 8 weeks of treatment there was almost complete remission of symptoms in 13 (65%), which was maintained till the week 20 evaluation without the addition of steroids.

multi-centre, randomized, double-blind trial in which patients received either the wormwood powdered herb preparation described above or identically looking placebo for 10 weeks. The study was carried out at five sites in Germany. The protocol of the study was approved by the institutional review boards and the ethical committees of the participating sites. Written informed consent was obtained from all patients.

The goal was to recruit 40 patients with CD. The CD was to be verified by coloscopy and histology and has to be of at least 3 months duration with a score of 170 or above on CDAI questionnaire (Best et al., 1976). Patients between the age of 18–80, receiving CD treatments with 5-aminosalicylates, if dose remained constant for at least 4 weeks prior to entering the trial and corticosteroids (prednisolone, prednisone or budesonide) at the equivalent of 40 mg/day of prednisone or less, stable dose for 3 weeks, were selected for the trial. Patients receiving azathioprine, stable dose for 8 weeks, or methotrexate stable dose for 6 weeks in addition to corticosteroids and 5-aminosalicylates qualified, however, patients treated with infliximab were excluded from the trial.

Patients were screened for eligibility 2 weeks prior to entering the trial (week-2) based on their medical history, physical examination, routine blood tests, electrocardiogram (ECG), urine analyses, CDI-Index scores and CD medication. For women, pregnancy tests were done at baseline evaluation where appropriate. Patients with serious pathological findings in ECGs, liver, kidney and heart functions, or coexisting organic diseases such as a history of cancer, asthma or other autoimmune disease requiring steroid treatments, were excluded from the trial. Any condition that, in the investigators opinion placed the patient at undue risk by participating in the 5-months study period were also excluded from taking part in the study. The recruited patients were assessed again at week 0 with the help of CDAI questionnaire, an Inflammatory Bowel Disease Questionnaire (IBDQ), a Visual Analogue Scale (VA-Scale) and 21-item Hamilton Depression Scale (HAMD). VA-Scale was an 8-item polar scale, at the positive end was the subjective condition of “Feeling Excellent” and the other negative end was the item “Feeling Worse” than before. The middle point of the scale was “Subjectively Unchanged”. The patients were

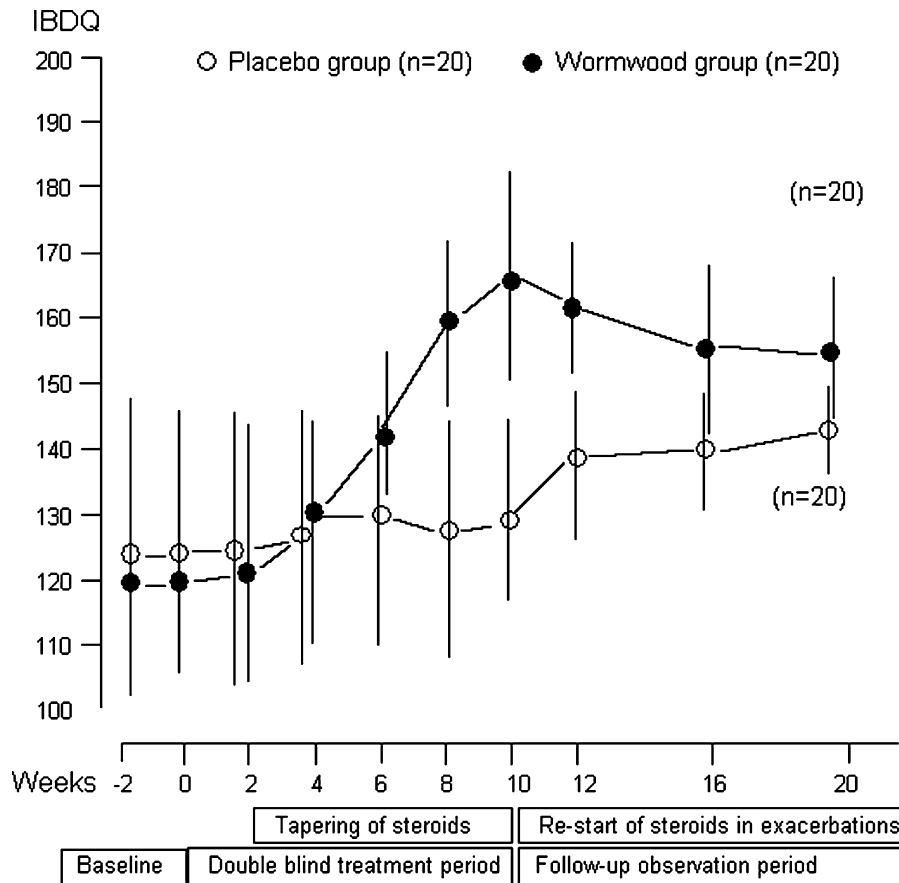


Fig. 3. IBD Questionnaire scores (means and 95% confidence intervals) are shown. Crohn’s disease (CD) deteriorated at week 10 as expressed in the IBD Questionnaire scores in 85% of the patients in placebo group when all corticosteroids were tapered to zero. There is a steady improvement in CD in patient group receiving wormwood in spite of tapering of steroids.

asked to mark with a cross their present subjective feelings at each assessment period. None of the concomitant medications, except that of steroids, already being taken by the eligible patients were increased, decreased or discontinued during the entire study period. At week 0, the eligible patients were assigned to either of the two treatment group: Group I taking wormwood and Group II taking similarly looking placebo capsules under double-blind conditions. Three capsules, containing either wormwood powder or placebo, were to be taken twice a day. This trial medication was given for 10 weeks. Patients were assessed at weeks 2, 4, 6, 8, and 10, and then at weeks 12, 16 and 20 (which was the trial-medication-free observation period) with the help of the scales used at week 0 assessment.

The dose of corticosteroids taken by the patients at baseline (week 0) evaluation was maintained constant until week 2; after that a defined tapering schedule was started. Patients who entered the trial receiving prednisone or its equivalent above 20 mg/day had their treatment tapered at a rate of 5 mg/week. The tapering rate for patients receiving 20 mg prednisone equivalent or less was 2.5–3 mg/week. The tapering rate was selected so that at the start of week 10 all corticosteroids

were tapered and the patients were free of this medication. Aminosalicylates and other immune-modulators were maintained at the same dose level, but the trial medication was discontinued.

Patients were excluded from the study if their CD or general health condition worsened. Worsening was defined as an increase in CDAI score of at least 70 points from the qualifying baseline score. Any condition that necessitated the introduction of a new treatment or additional treatment with corticosteroid also resulted in the removal of patients from the study. Also, hospitalisation for any reason resulted removal from the study. Patients whose CD worsened by less than 70 points on CDAI due to tapering of steroids, were not dropped from the study, but were eligible to restart the steroids after week 10, thereby the same level of steroids was reached as it was before the begin of tapering. All data obtained during treatment with trial medication was included in the safety analyses.

Response to treatment was defined as a decrease in the CDAI score of at least 70 points from the qualifying score, or a decrease in 30% of CDAI score from the baseline score. For the HAMD total score, the primary outcome measure was the absolute decrease of the Hamilton total depression score between baseline

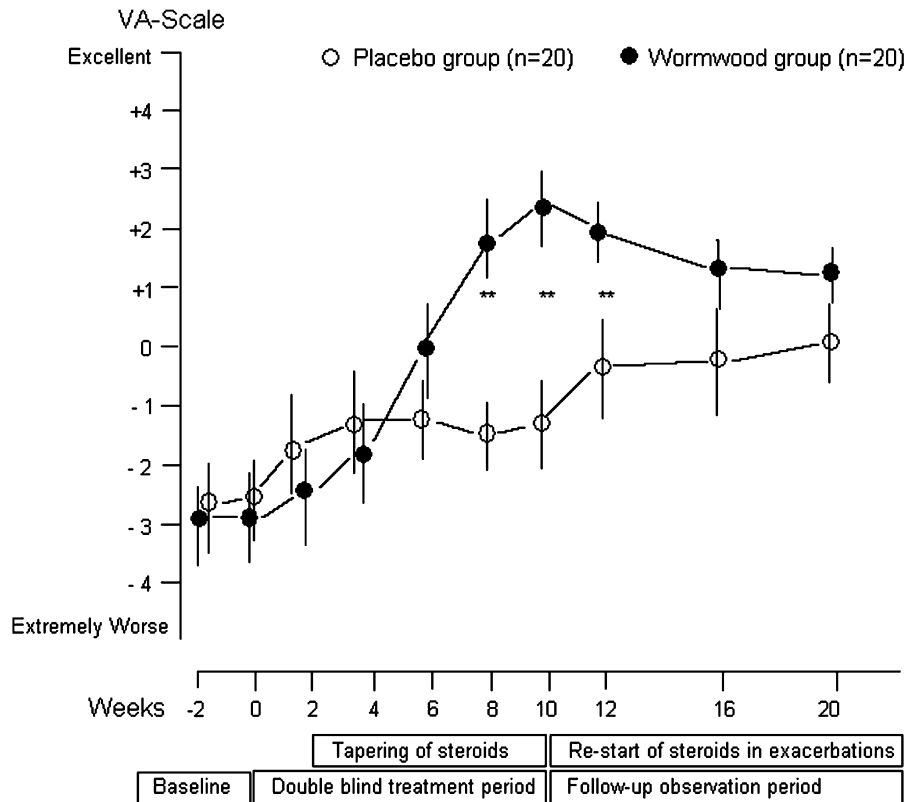


Fig. 4. Subjective feelings, as self-assessed by the patients on 6-item Visual Analogue Scale improved steadily after 4 weeks of treatment in the wormwood group and reached its maximum after 8–10 weeks. In the placebo group there was a trend of deterioration due to tapering of steroids.

and the following treatment weeks. We defined response as a decrease in total score of >50% from baseline and remission as a score <10 points. Statistical methods used for comparison of the groups were Student's *t*-test and χ^2 -test. A *p*-value of 0.01 was set to define significance. χ^2 -test compared the patients of the two treatment groups who responded to the study medication during the observation weeks: 2, 4, 6, 8, 10 and then at 12, 14, 16, and 20. Median CDAI, IBDQ and HAMD scores were compared at pre-defined study visits.

Results

Forty patients who fulfilled the inclusion criteria of CD were enrolled in 5 study centres in Germany. Twenty patients were assigned to each treatment group under double-blind conditions. The patient population comprised 42% men and 58% women with a median age of 37 (range 18–82) years. Their baseline disposition, medication and other characteristics are summarised in Table 1.

All patients started with 3 × 2 capsules of wormwood or placebo besides their CD basic treatment at week 0. The CD basic treatment was maintained throughout the clinical trial period of 20 weeks, except that of steroids. Study medication was given, as the protocol required, for 10 weeks. None of the patients discontinued the treatment before the final evaluation at week 20.

Fig. 1 shows the average doses of corticosteroids during the study period. The steroid dose was maintained stable until week 2, after that, tapering off started and was completed at week 10. In the placebo group, 16 patients (80%) showed CD exacerbation due to reduction in steroid dose, whereas there were only two (10%) such patients in the group, which was receiving wormwood. The exacerbation of CD symptoms necessitated the re-start of steroids in 11 patients in the placebo and two from the wormwood group.

Fig. 2 shows the score development on CDA-Index of the two treatment-groups. At week-10, 13 patients (65%) of group I were almost free of CD symptoms and there was no need to restart the steroid treatment in the following follow-up weeks. These patients continued to benefit from the previous wormwood treatment in spite of discontinuation of steroids and wormwood without loss of remission. The worsening of CD severity as indicated by CDA-Index scores was observed only in two patients of this group during the tapering period of steroids. Five patients from this group tolerated the reduction of steroids, but their CDA-Index scores remained almost unchanged during the first 10 weeks, but they gradually improved in the following 10 weeks.

In the placebo group the worsening of CD severity was observed in 16 patients during tapering of steroids

as indicated by increase in CDA-Index scores. In 11 patients (55%) of this group it became necessary to restart the steroid treatment at week 11 onward. Nine patients of this group tolerated the reduction in steroids as indicated by a un-change in their CDA-Index scores. In the following follow-up observation period (week 10–20), 11 patients of this group were still depending on steroids. Already after 6 weeks the number of patients who showed clinical improvement (reduction of CDAI to 70 or more) were significantly higher (*p* = 0.01) in group I as compared to group II. This significant difference continued beyond week-10. The results of the IBD Questionnaire scores were similar to the CDA-Index scores (Fig. 3).

VA-Scale score showed pattern similar to that seen in CDA-Index scores (Fig. 4). There was almost no change in the subjective feelings of illness in self-assessment (VA-Scale) of the patients in the placebo group, whereas in the wormwood group the self-assessment evaluation of the patients indicated significant improvement.

Hamilton total scores decreased by an average of 9.8 (SD 5.8) points for wormwood group and by 3.4 (SD 6.6) points for placebo group. At the end of the acute treatment phase (week 10), 70% of the patients in the wormwood group and none in the placebo group showed remission of depressive symptoms (Fig. 5).

Discussion

A very significant and unexpected finding was that at week 10, 13 patients (65%) of the group that received wormwood were almost free of CD symptoms as compared to none in the placebo group. Moreover, in these patients there was no need to restart corticosteroids in the follow-up weeks, and there was no remission of disease and the patients continued to benefit from 10-week wormwood treatment. This observation suggests that wormwood might be having a kind of “curing” effect on a sub-group of CD patients. This effect can be attributed to the virus elimination by wormwood. As mentioned before, wormwood has anti-DNA virus properties, and there are studies indicating that a DNA-Virus might be playing a role in the CD disease. The registered effect can also be attributed to immune system modulation by wormwood. More in vitro and in vivo trials are to be done in order to understand the observed efficacy of this herb.

The fact that five patients showed little response to the wormwood treatment, indicate that there is a subgroup of CD patients, which is resistant to wormwood treatment. The five patients from this group tolerated the reduction of steroids, but their CDA-Index scores remained almost unchanged during the first 10 weeks. As these patients gradually improved in the following 10 weeks, indicates that this improve-

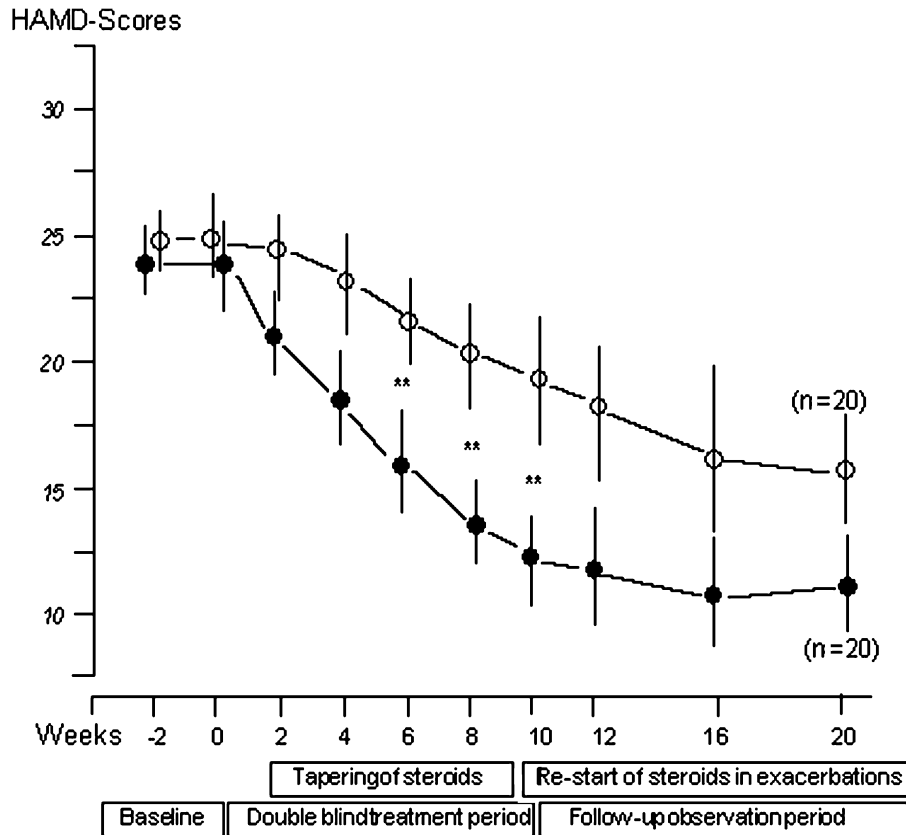


Fig. 5. Total Hamilton depression scores over time (means and 95% confidence intervals) are shown. There is a steady improvement in the depressive symptoms as indicated by decrease in the average HAM-Depression Scores in patient group receiving wormwood as compared to those who received placebo. After 8 weeks of treatment 70% of the patients receiving wormwood, were almost free of accompanying depressive symptoms (total HAM-Score 10 or less).

ment can be attributed to the concomitant basic CD treatment.

CD patients usually suffer from mood disturbance. Hamilton's Depression Scale is a good validated instrument to assess changes in mood. The average baseline scores on this scale showed that CD patients were moderately depressed. Their mood improved gradually and there was a statistically significant difference at week 10 and 12 evaluation. For an anti-depressant drug, these finding will amount to an evidence for an anti-depressant activity. This conclusion cannot be drawn from these finding as the selection of the patients was not based on the depression criteria but on the criteria of CD severity. It is still striking to note that wormwood not only possesses beneficial effects for the patients with CD but also has a significant effect on the quality of life and mood. Very few trials on CD patients have taken into consideration this aspect. From the results presented, a conclusion can be drawn that wormwood has not only steroid-sparing effect on CD patients, but this effect continues for several weeks after the end of the 10-week treatment period. The trial opens new doors to investigate this ancient traditional herb.

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