Randomized Double Blind Trial of an Extract from the Pentacyclic Alkaloid-Chemotype of Uncaria tomentosa for the Treatment of Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate safety and critical efficacy of a plant extract from the pentacyclic chemotype of Uncaria tomentosa (UT) in patients with active rheumatoid arthritis (RA).

M*ethods*. Forty patients undergoing sulfasalazine or hydroxychloroquine treatment were enrolled in a randomized 52 week, 2 phase study. During the first phase (24 weeks, double blind, placebo controlled), patients were treated with UT extract or placebo. In the second phase (28 weeks) all patients received the plant extract.

R*esults*. Twenty-four weeks of treatment with the UT extract resulted in a reduction of the number of painful joints compared to placebo (by 53.2% vs. 24.1%; p=0.044). Patients receiving the UT extract only during the second phase experienced a reduction in the number of painful (p=0.003) and swollen joints (p=0.007) and the Ritchie Index (p=0.004) compared to the values after 24 weeks of placebo. Only minor effects were observed.

Conclusion. This small preliminary study demonstrates relative safety and modest benefit to the tender joint count of a highly purified extract from the pentacyclic chemotype of UT in patients with active RA taking sulfasalazine or hydroxychloroquine. (J Rheumatol 2002;29:678-81)

Key Indexing Terms:
RHEUMATOID ARTHRITIS **UNCARIA TOMENTOSA**
CLINICAL TRIAL **COMPLEMENTARY MEDICINE**

Uncaria tomentosa (Willd.) DC. is a giant vine of the Rubiaceae family, Cinchonoidae subfamily, growing in the rain forest of Peru. Because of its curved thorns, this vine, together with 16 other different species of plants, has also been called "uña de gato" in Spanish and "cat's claw" in English. Scientific and commercial interest in Uncaria tomentosa (UT) was aroused by reports of miraculous cures of diseases like arthritis, cancer, asthma, stomach ulcers, inflammation of the urinary tract, abscesses, and disorders of wound healing.

Attempts to extract potentially therapeutic components from this plant led to the discovery of 2 chemotypes of UT with a different pattern of tetracyclic (TOA) or pentacyclic oxindole alkaloids (POA)[1]. Quinovic acid glycosides, sterols, epicatechine, and other ubiquitous components were found in both chemotypes. The POA were found to have immune modulatory effects. Besides enhancing phagocytosis, as reported for other plant derived immune modulators[2], POA were shown to inhibit proliferation of highly activated lymphocytes while stimulating proliferation of resting or weakly activated lymphocytes. These effects were antagonistically inhibited by TOA[3].

UT derived preparations are already used as complementary medication, without, however, sufficient clinical evidence of safety and efficacy. We initiated a randomized, double blind, placebo controlled study to evaluate the effects of a well characterized and standardized TOA-free UT extract in patients with active rheumatoid arthritis (RA) treated with sulfasalazine or hydroxychloroquine.

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MATERIALS AND METHODS

Patients. Forty patients aged 20 years or more who fulfilled the American College of Rheumatology criteria for RA[4] with Steinbrocker functional class II or III[5] were enrolled in the study. Disease was considered active when 3 of the following 4 criteria were fulfilled: $\geq$ 6 painful joints, $\geq$ 3 swollen joints, morning stiffness

> 30 min. erythrocyte sedimentation rate (ESR)>25 mm/h, or C-reactive protein (CRP) > 20.0 mg/I. All patients had been treated with sulfasalazine or hydroxychloroquine for a period of at least 6 months; in the 6 week prior to enrollment in the study, patients had to take stable doses of these drugs. Nonsteroidal anti-inflammatory drugs (NSAID) and prednisolone up to 10 mg/day or its equivalent were permitted.

Patients with coexisting hematologic, renal, hepatic, cardiovascular, neurologic, or psychological diseases were excluded. Chronic infection or a neoplastic event in the medical history were considered reasons for exclusions. Patients with a history of alcohol or drug abuse and those with known poor compliance were excluded. In the 4 weeks before and during the course of the study, patients were not permitted to have intraarticular, intramuscular, and soft tissue steroid injections. Pregnant women and nursing mothers were not enrolled in the study. The study was approved by the local ethics commission and written informed consent was obtained from all patients.

Study design. The study was carried out in 2 phases at the Rheumatological Outpatient Unit of Innsbruck University Hospital. In the first phase of 24 weeks, the study was designed to be randomized, double blind, and placebo controlled. During this period, patients received one capsule of the plant extract or placebo 3 times daily while continuing their antirheumatic therapy. In the second phase, all patients received the plant extract.

Clinical assessment, was always performed by the same investigator (EM) at the beginning of the study and at 4, 8, 16, 24, 36 and 52 weeks thereafter. The number of swollen (out of 66) and painful joints (out of 68) and the Ritchie Index[6] were determined, and patients were asked to assess pain and disease activity with a visual analog scale (VAS). Morning stiffness was measured on a 5 step scale (0= no morning stiffness, 1 = < 30 min, 2= 30-60 min., 3= 1-2 h, 4= 2-4 h, 5=>4 h). At the start of the study, at 24 weeks thereafter, and at the end of the study, patients' functional capacity was determined with the Health Assessment Questionnaire (HAQ)[7]. Safety was monitored by physical examination, blood pressure, pulse rate, and body temperature and body weight measurements. Laboratory studies included ESR, CRP, rheumatoid factor (RF), antinuclear antibodies, complete blood count, and hepatic and renal variables.

Study medication. Krallendorn® capsules (Immodal Pharmaka GMbH. Volders, Tyrol, Austria) contained 20 mg of an aqueous acid-extracted dry extract of Radix Uncariae tomentosae (Willd.) DC. mod. pent., with 14.7 mg/g POA and no TOA. Lactose 130 mg and ascorbic acid 200 mg per capsule were used as filler. With the exception of the active ingredient, the placebo had the same ingredients.

Statistical analysis. An intent-to-treat analysis was performed. Descriptive statistics included mean values with standard deviations. For comparison of dependent variables at different times the nonparametric Wilcoxon and the Friedman test were used; the Mann-Whitney test was applied for comparison between the UT extract and placebo group. A p value < 0.05 was considered significant. Statistical calculations were performed with SPSS version 9.0.

RESULTS

Demographic data. Patients' characteristics are presented in Table 1. There was no statistical difference between the 2 groups with regard to sex, duration of disease, medication, intake of corticosteroids, and clinical and laboratory values, with the exception of CRP (higher values in the placebo group).

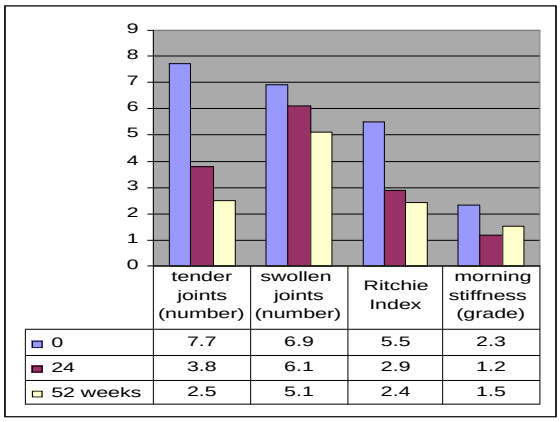
Out of 40 subjects, 19 were randomized to the placebo and 21 to the UT extract group. During the study, one patient from each group dropped out because of adverse events, and one patient from the plant extract withdrew after one month of treatment with the UT extract because of inefficacy of the drug.

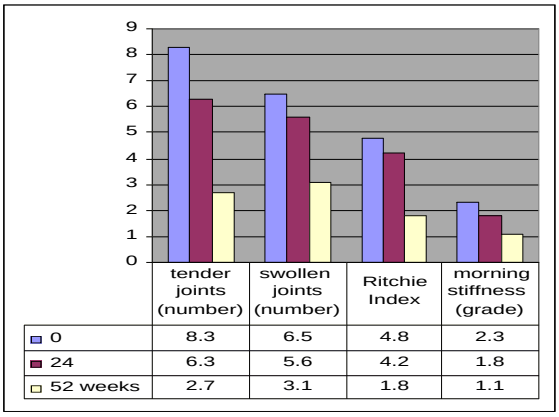
Clinical efficacy. Phase 1 (UT extract or placebo). Comparison of the 2 groups at the end of the first phase of study showed that patients in the plant extract group had fewer painful joints than those of the placebo group (reduction by 53.2 vs 24.1%; p=0.044). No differences were observed between the 2 groups for the other variables.

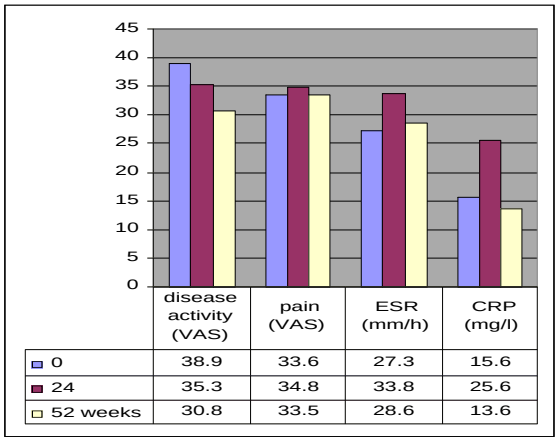
In patients given the plant extract there was a reduction in the number of tender joints (p-0.001), Ritchie Index (p=0.002), and duration of morning stiffness (p=0.002) after 24 weeks compared to the

Table 1. Patient demographics at study entry.

	UT Extract n=21	Placebo Group, N=19
Age, mean ± SD, yrs	53.1 ± 13.4	54.9 ± 13.5
Female/male	20/1	15/4
Disease duration, mean ± SD, yrs	6.1 ± 5.7	7.9 ± 8.3
Tender joints, mean ± SD	7.9 ± 3.0	8.4 ± 4.4
Swollen joints, mean ± SD	7.0 ± 4.2	6.3 ± 2.8
Morning stiffness, mean grade	2.3	23
ESR, mm/l h, mean ± SD	27.3 ± 19.4	30.1 ± 19.7
CRP, mg/l, mean ± SD	15.6 ± 16.9	28.1 ± 25.3
RF positive	10	8
Sulfasalazine/hydroxychloroquine	18/3	17/2
Patients taking prednisolone	7	8







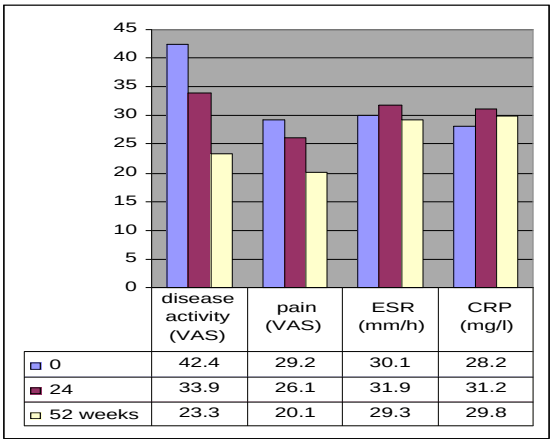


Table 1. Mean outcome measures at 0, 24 and 52 weeks after onset of treatment with UT extract.

Table 2. Mean outcome measures at 0, 24, and 52 weeks in patients receiving placebo from Week 0 to Week 24 and treatment with UT extract from Week 24 to 52.

baseline valued, whereas in the placebo patients the number of tender joints, Ritchie Index, and duration of morning stiffness were not significantly reduced (Figures 1 and 2). No changes were detected for the number of swollen joints, patient assessment of disease activity, subjective assessment of pain, and the laboratory variables except for an increase in the level of RF in the placebo group (p=0.041).

Phase 2 (UT extract). Further intake of the UT extract resulted in a reduced number of tender joints ($p < 0.001$), Ritchie Index ($p = 0.001$), and duration of morning stiffness ($p = 0.004$) compared with the baseline values at Week 0 (Figure 1). No changes were found for the other clinical variables and the laboratory values.

In patients who received the plant extract only during the second phase, there was a reduction in the number of painful joints ($p = 0.003$), number of swollen joints ($p = 0.007$), and Ritchie Index ($p = 0.004$) compared to the values observed at the end of their placebo treatment (Figure 2). There was a decrease in the intensity of pain and disease activity as assessed by the patients and the duration of morning stiffness; none of these changes, however, reached statistical significance. Among the laboratory values there was a reduction in the RF from 135 to 32; this too, along with the other laboratory measures, was not statistically significant.

There was no change of the HAQ in either group compared to baseline values or the end of the first phase.

Table 2. Adverse events. Relation to treatment: 1 = definitely not, 2 = probably not, 3 = possibly, 4 = probably, 5 = definitely

	UT Extract		Placebo	
	No. of Patients	Relation to Treatment	No. of Patients	Relation to Treatment
Dyspepsia	2	2;2	2	2;4
Respiratory infection	2	2;3	1	2
Dermatitis	0	--	2	2;3
Pruritus	2	2;2	0	--
Conjunctivitis	1	2	1	2
Influenza	1	2	1	2
Gastritis	1	2	1	3
Herpes zoster	1	2	1	2
Urinary tract infection	1	2	0	--
Fatigue	1	2	0	--
Diarrhea	0	--	1	4
Headache	0	--	1	2
Toothache	0	--	1	2

Safety. During the first phase, adverse events occurred in 12 patients of each group (Table 2). One patient taking the UT extract withdrew from the study owing to gastritis and one patient from the placebo group because of diarrhea. In the second phase, 7 other side effects were seen, none that could be clearly attributed to the drug intake. No major side effects were seen in the active and the placebo group.

DISCUSSION

An increasing number of patients with RA are skeptical about conventional antirheumatic medication. It has been reported that up to 40% of rheumatology patients visit a complementary medicine practitioner in the course of their disease[8]. Failure of orthodox drugs to bring sufficient relief of symptoms and concern about potential side effects are the main reasons patients turn to complementary approaches[9].

Many patients believe that plant derived drugs have less side effects, but at least some efficacy. Thus extracts from a variety of plants are widely used by patients with rheumatic diseases, although the efficacy of the majority of these preparations has not been substantiated with adequate evidence. In addition, some herbal therapies were reported to have clinically relevant side effects. Taking these facts into consideration there is a demand for research on the efficacy and safety of this kind of complementary medicine[10-12].

Selected plants of Uncaria tomentosa have a long tradition in the Ashaninka Indians of Peru as a remedy for rheumatic diseases[1]. *In vitro*, a UT plant extract containing POA revealed an immunomodulatory effect, which is antagonistically inhibited by TOA[3]. An alkaloid-free extract from UT was shown to enhance DNA repair[13]. Another UT extract containing POA has been reported to inhibit production of tumor necrosis factor-_ and to have antioxidative effects[14]. Information on the clinical efficacy of UT in patients with rheumatic diseases, however, is quite sparse.

This study demonstrates that a TOA-free extract from the pentacyclic chemotype of UT, in combination with sulfasalazine or hydroxychloroquine, has some favorable clinical effect on RA disease. At the end of the placebo controlled phase of the study, the number of painful joints was reduced in patients treated with the UT extract compared to the placebo group, whereas the number of swollen joints, the Ritchie Index, and morning stiffness were not affected. Followup of patients treated over a total period of 52 weeks revealed continuing clinical improvement, with a reduction in the number of tender joints, the Ritchie Index, and morning stiffness compared to baseline. These results suggest that this TOA-free extract from the pentacyclic chemotype of UT has a clinically relevant adjunctive therapeutic potential when combined with conventional disease modifying drugs, corticosteroids, and NSAID. The daily dosage of 60 mg of an aqueous acid-extracted dry TOA-free extract of UT can be considered well tolerated and safe. There were no side effects clearly attributable to the UT extract and both the number and quality of the side effects of the UT extract were comparable to placebo. Whether and to what extent variations in the doses applied lead to changes in toleration and efficacy needs to be examined in larger placebo controlled double blind trials.

The TOA-free extract from the pentacyclic chemotype of UT administered in this study represents a purified and well defined agent containing a defined and standardized content of POA, whereas many other herbal products lack a clear specification of their ingredients. Indeed, most cat's claw products available in health food stores vary in quality and quantity of their content[15,16]. Both the total alkaloid amount and the percentage of pentacyclic alkaloids vary over a wide range in the undefined UT extracts. Even different batches of the same product may show considerable variations of ingredients[16].

From the phytochemical standpoint plant species are not homogenous sources of raw material. There is variation in components in many plant species depending on external factors like climate or light, whereas heredity may cause the development of different chemotypes, as in UT. In view of these circumstances, high standards of manufacturing and quality control in the production of herbal drugs are necessary to provide herbal remedies with a clear specification of their ingredients. Although there is evidence for the safety and efficacy of some herbal therapies, this kind of treatment can only be accepted for treatment of rheumatic disease when the specific preparation offers a well defined and standardized medication shown to be effective and safe in adequate controlled clinical trials.

Concerning TOA-free extract from the pentacyclic chemotype of Uncaria tomentosa, on the basis of its relative safety and modest benefit to the tender joint count compared to placebo shown in this small preliminary study, a larger longer placebo controlled double blind trial is recommended.

REFERENCES

1. Keplinger K, Laus G, Wurm M, Dierich MP, Teppner H. Uncaria Tomentosa (Willd.)DC -Ethnomecial use and new phamaceutical, toxicological and botanical results. J Ethnopharmacol 1999;64:23-34.
2. Wagner H, Krntzkamp B, Jurcic K. Die Alkaloide von Uncaria tomentosa and the Phagozytose-steigrnde Wirkung. Planta Med 1985;51:419-23.
3. Wurm M, Kacani L, Laus G, Keplinger K, Dierich MP. Pentacyclic oxindols alkaloids from Uncaria tomentosa induce

human endothelial cell to release a lymphocyte-proliferation-regulating factor. Planta Med 1998;64:701-4.
4. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis, Arthritis Rheum 1988;31:315-24.
5. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. JAMA 1949;140:659-62.
6. Ritchie DM, Boyle JA, McInnes JM, et al. Clinical studies with an articualr index for the assessment of joint tenderness in patients with rheumatoid arthritis. Q J Med 1968;37:393-406.
7. Fries JF, Spitz P. Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.
8. Vecchio PC. Attitudes to alternative medicine by rheumatology outpatient attenders. J Rheumatol 194;21:145-7.
9. Vincent C, Furnham A. Complementary medicine: A research perspective. Chichester: Wiley & Sons;1997.
10. Little C. Parsons T. Herbal therapy for treating rheumatoid arthritis (Cochrane Review). Cochrane Database Syst. Rev 2001;1CD002948.[abstract:hap//209.242.147.2/Abs/ab002948.htm]
11. Klepser TB, Klepser ME. Unsafe and potentially safe herbal therapies. Am J Health Syst Pham 1999;56:125-38.
12. van Haselen RA. Research on complementary medicine in rheumatic diseases: the need for better quality studies and reproduction of claimed positive results. Rheumatology 1999;38:387-90.
13. Sheng Y, Bryagelsson C, Pero RW, Enhanced DNA repair, immune function and reduced toxicity of C-MED-100, a novel aqueous extract from Uncaria tomentosa. J Ethnopharmacol 2000;69:115-26.
14. Sandoval M, Charbonnet RM., Okuhamma NN et al. Cat's Claw inhibits TNF alpha production and scavenges free radicals: role in cytoprotection. Free Radic Biol Med 2000;29:71-8.
15. Reinhard RH, Uncaria tomentosa (Willd.) DC:Cat's Claw, uña de gato, or saventaro. J Altern Complement Med 1999;5:143-51.
16. Laus G, Keplinger K, Wurm M, Dierich MP, Pharmacological activities of two chemotypes of Uncaria tomentosa (Willd.) DC [abstract]. In: Jurenitsch J, Kopp B, Kubelka W, editors. Proceedings of the 46th Annual Congress of the Society for Medical Plant Research 1998, Aug. 31-Sept. 4. Vienna: Society for Medical Plant Research; 1998:J61.