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CASE REPORT

Report of 12 cases of ankylosing spondylitis patients treated with *Tripterygium wilfordii*

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Abstract
Objective Description of the clinical response of 12 consecutive cases of disease-active ankylosing spondylitis (AS) treated with the herbal medicine *Tripterygium wilfordii* Hook f (TwHf; lei gong teng, thunder god vine), which has been reported in controlled studies to be effective in rheumatoid arthritis (RA).
Methods The clinical status of 12 patients with active AS who were started on 60 $mgday^{-1}$ of a commercial tablet preparation of TwHf extract. were monitored at weeks 1, 3, and 6.
Results Compared to baseline, there was significant improvement in mean values of physician assessment, Bath ankylosing spondylitis disease activity index (BASDAI), Bath ankylosing spondylitis functional index (BASFI), and Bath ankylosing spondylitis global score (BAS-G) at weeks 3 and 6, with no changes in liver enzymes or complete blood count (CBC).
Conclusion A placebo-controlled double-blind study for *Tripterygium* is warranted. Until then, this particular report should be considered as case reports and not an endorsement of the use of *Tripterygium* in clinical practice.

Keywords Ankylosing spondylitis · Lei gong teng · *Tripterygium wilfordii* Hook f

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Introduction

One of the medicinal herbs widely used used in China for the treatment of autoimmune and inflammatory diseases is the vine *Tripterygium wilfordii* Hook f (TwHf), also known by the descriptive names lei gong teng, thunder god vine, and seven-step vine [1–3]. A rapid pubmed search for the keywords "*Tripterygium*" plus "inflammatory" yields a total of 120 publications, while a search for "*Tripterygium*" and "lupus" yields 30 publications. More than 21 autoimmune and inflammatory diseases have been reported to have been treated with extracts of *Tripterygium*. At least five pharmaceutical companies in China are marketing extracts of *T. wilfordii* in tablet forms and have been approved by the China State Food and Drug Administration for use in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and ankylosing spondylitis (AS). They are being used by many rheumatologists and nephrologists who practice traditional medicine in China [1–3]. For example, for the Jiangsu Province Hospital of Traditional Chinese Medicine in Nanjing, the number of tablets of *T. wilfordii* prescribed in 2008 was 620,000, the average per month in 2009 has been about 50,000. At least

three controlled double-blind studies for RA with promising results have been reported, one carried out in China and the others in North America [4–7]. Beneficial effects were observed in RA as early as 4 weeks after initiation of *Tripterygium*. In vitro and animal model studies suggest that *Tripterygium* is anti-inflammatory and immunosuppressive, partly by suppressing the generation of proinflammatory cytokines (reviewed in Ref. [1]).

However, no pubmed abstract-available studies have been reported on AS. Search for literature in a Chinese language database showed that the earliest report of the use of *T. wilfordii* in AS was in 1981 [8]. Since then, at least four other Chinese language papers have been published, comprising a total of 175 AS patients (reviewed in Ref. [3]). The efficacy of *T. wilfordii* was broadly described as being nearly 90% effective. However, none of these Chinese language papers assessed patients with internationally standardized evaluation instruments. AS is an inflammatory arthritis affecting mainly the axial skeleton. Like RA, AS also respond to treatment by nonsteroidal anti-inflammatory drugs (NSAID), sulfasalazine, and, more dramatically, to tumor necrosis factor (TNF) blockers. Unlike RA, there is no good evidence that it responds well to methotrexate, leflunomide, or hydroxychloroquine [9, 10]. This paper describes 12 consecutive disease-active AS patients who were started on *Tripterygium* and evaluated with internationally approved evaluation instruments. This paper is a case report and not a randomized placebo-controlled study. In our analysis, we attempted to evaluate the possible significance of response to *Tripterygium* by comparing the *Tripterygium* results to those of 26 AS patients on placebo in a controlled study for etanercept.

Materials and methods

Patients receiving *Tripterygium* were those attending the Jiangsu Province Hospital of Traditional Chinese Medicine, Jiangsu, Nanjing, China. The study and informed consent followed the guidance of the Hospital Institutional Research Board (approval ref. no. 2009NL-1501). The study was designed to arbitrarily include all consecutive patients within a period of 4 months who satisified the following criteria: They satisfied the 1984 Modified New York Criteria for AS [11]. Their pelvis X-ray showed a sacroiliitis score of ≥4 when combining scores of both right and left sides. Their scores for Bath ankylosing spondylitis disease activity index (BASDAI) and for spinal pain were ≥40 on a scale of 0 to 100. They had failed NSAID. Of the 12 patients, eight had failed ≥ 1 month NSAID, while 8/12 had also failed ≥3 months of at least one disease-modifying antirheumatic drugs (DMARD). All prospective patients were advised of the antifertility effect of *Tripterygium*. Following the standard practice in this institute, excluded from *Tripterygium* treatment, were those patients with potential family planning, or being positive for hepatitis antigens, or showed elevated liver enzymes in blood tests. A general evaluation was also carried out to exclude those with significant co-morbidities. None of the AS patients in this case report had psoriasis or active uveitis or had used corticosteroids within the past 1 month. Patients who were on NSAID and DMARD were allowed to continue their medications with no increase in dosages. The *Tripterygium* used in these 12 patients was manufactured by the Zhe Jiang De En De Pharmaceutical (Zhejiang, China), the supplier for this institute. The lot number of the tablets was 0802102. The dose of the *Tripterygium* was 20 mg 3 times daily. Evaluations were carried out at entry of study as well as at weeks 1, 3, and 6. After finishing the 6 weeks of observation, patients were followed by their own personal physicians and not by the investigators.

The placebo patients were derived from a randomized double-blind controlled study of etanercept carried in the Chinese PLA General Hospital, Beijing, China. Placebo was administered subcutaneously twice a week. The selection of patients according to their disease severity was similar to those of the *Tripterygium* patients in that the BASDAI score at baseline should be ≥40 (scale 0–100). Details were similar to those of another placebo/etanercept study carried out also in the Chinese PLA General Hospital reported recently [12]. This study also followed the guidelines of the local and national Institutional Review Boards.

Evaluations included physician and patient self-assessment (Bath ankylosing spondylitis global score, BAS-G) over the past week, joint count for swelling, BASDAI, Bath ankylosing spondylitis functional index (BASFI), and ranges of motion included in the Bath ankylosing spondylitis metrology index (BASMI) [13–16]. Endpoints of clinical response were expressed as ASAS20 and ASAS40 [17]. Blood tests included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count (CBC), and liver tests. For assessment of possible side effects, in addition to laboratory tests and general review of systems, also was enquired patients' own assessment of possible side effects.

For statistical evaluations, the overall significance of each parameter of clinical response was first tested by the Friedman test. Those with p values<0.001 were further evaluated by the Wilcoxon signed-rank test. Other statistical tests used were the t test for unequal variances and the chi-square test. All p values were corrected for multiple testing by multiplying the values with 20 (Bonferroni factor for these data sets). Values were considered significant if the corrected p values were ≤ 0.05. One evaluation datum was missing and was carried forward from the previous week. Because 8 of the 12 *Tripterygium* patients were on

DMARD, no analysis was carried out to compare effect of *Tripterygium* on patients on DMARD to those not on DMARD.

Results

The demographics and clinical characteristics of the 12 patients were listed in Table 1. The mean age was 36.2± 10.9 years, mean duration of disease 6.8±4.3 years, and mean BASDAI value 52±11.4 (0–100 scale). While all patients complained of spinal pain, swollen joints were detected in only three. HLA-B27 was tested in ten patients and was positive in nine. All patients were carefully followed up for 6 weeks, except patient #6 who did not return for the 6th week apparently because of lack of response. Patient numbering was consecutive except #5 which did not exist.

By week 3 of treatment, the percent of patients showing ASAS20 and ASAS40 response were 91.7% and 33.3%, respectively. These appeared to be sustained to week 6 (Fig. 1). Statistically significant improvement as assessed first by Friedman test ($p<0.001$), followed by Wilcoxon signed-rank test, followed by correction for multiple testing was observed with BAS-G, BASDAI, and BASFI starting at week 1 (Fig. 2). For BAS-G and BASDAI, the improvement at week 6 exceeded those at week 3. Statistically significant improvement for physician assessment was observed at weeks 3 and 6. Although there was improvement in BASMI, it was not statistically significant after correction for multiple testing. At week 6, the ESR decreased from 26.8±16.7 at week 0 to 9.8±5.8 ($p=0.007$ before Bonferroni correction). The decrease in CRP became statistically significant at week 6 ($p=0.04$ after Bonferroni correction; Fig. 2).

There were no clinically significant changes in CBC and liver function tests. None of the patients reported of any side effects such as headache or abdominal discomfort.

In a separate study, a total of 26 patients were given placebo in a randomized double-blind controlled study for etanercept. In this placebo group, NSAID, DMARD, and corticosteroids were also maintained at the same doses as in the baseline. The mean age of these patients was 30.1±7.7 years, and the mean duration of disease was 9.7±6.1 years. Out of 26 patients, 25 were male. The mean BASDAI, BASFI, and BAS-G values are shown in Table 2. At the entry of study, there were no statistically significant differences between this placebo group and the *Tripterygium* group in age, duration of disease, BASDAI, and BASFI. In the placebo group, after 6 weeks, even on placebo, there were 10–20% decrease in the values of BASDAI, BASFI, and BAS-G. These decreases were statistically significant in BASDAI and BAS-G ($p=0.0001$ and 0.01), but not BASFI ($p=0.09$; Table 2). The decreases in values of BASDAI, BASFI, and BAS-G at week 6 of the *Tripterygium* group were about 60%, and compared to the corresponding values of the placebo group, they were significantly lower in the *Tripterygium* group ($p=0.0001$ for all three parameters; Table 2 and Fig. 1). At week 6, the percent of patients in the placebo group who achieved ASAS20 and ASAS40 were 30.8% and 3.8%, respectively. These were significantly less than the corresponding values in the *Tripterygium* group ($p<0.01$ and <0.001, respectively).

Discussion

Extracts of *T. wilfordii* are being distributed in tablet form as patent medicines by at least six pharmaceutical companies in China. The cost is about US $0.50 per day, which is much lower than that of the biologics. They are widely used by physicians practicing traditional medicine and accepted by patients in China as standard treatment for several inflammatory and autoimmune diseases, especially RA, AS, SLE, and nephritis. A large number of publications, mostly in the Chinese language, have been reported [2–4, 6]. It is also being used for AS. A total of 175 AS patients treated with *T. wilfordii* have been reported in Chinese language papers [3]. None of them used internationally standardized evaluation instruments. Nevertheless, the drug was reported as being 90% effective. Since a major side effect of this drug is antifertility in male and amenorrhea in female, and because many AS patients are in the reproductive age, it is imperative to understand the risk/benefit ratio more precisely before continuing such indiscriminate use [18]. Although the Jiangsu Province Hospital of Traditional Chinese Medicine has been using this drug routinely for AS resistant to conventional therapies, this study is also the first in this institute to use internationally standardized evaluation instruments to describe 12 consecutive disease-active AS patients. The particular commercial preparation used in this study was one which has been used in this hospital for the past 5 years. The compilations of results of these 12 patients do show significant improvement in BAS-G, BASDAI, BASFI, and physician assessment. One needs to be cautioned that all these are subjective parameters. Since these are case reports, no placebo-controlled data were collected. In a recent placebo-controlled study of etanercept in AS, also carried out in China, data are available from 26 patients who received 6 weeks treatment with placebo. At week 6, only 31% of those placebo-treated patients showed an ASAS20 response. The results from three separate published placebo-controlled study for TNFα carried out in Caucasian countries also showed that the ASAS20 response for placebo at weeks 4–8 are about 20%

Table 1 Demographics and patient characteristics at entry

Designation	Age	Gender	Years of AS	DMARD
Patient 1	31	F	2	Methotrexate (MTX)
Patient 2	42	M	13	Sulfasalazine
Patient 3	30	M	6	MTX + sulfasalzine
Patient 4	28	M	8	
Patient 6	57	M	15	
Patient 7	31	M	3	
Patient 8	30	M	3	MTX + sulfasalzine
Patient 9	30	M	5	MTX
Patient 10	27	M	10	MTX
Patient 11	34	F	1.1	
Patient 12	35	F	8	Sulfasalazine
Patient 13	59	M	7	Sulfasalazine + thalidomide
Mean	36.2		6.8	
SD	10.9		4.3	
Median	31.0		6.5	

Designation	BASDAI	BASFI	BASG	Physician assessment	Spinal pain
Patient 1	49.5	43	50	54	62
Patient 2	45.4	30.8	45	50	48
Patient 3	49.07	30.4	46	50	72
Patient 4	44.75	42.5	57	60	45
Patient 6	44.65	42.7	45	50	58
Patient 7	54.4	41.2	50	54	65
Patient 8	70	45.1	45	50	65
Patient 9	45.8	53.9	72	60	64
Patient 10	80.4	59.3	85	82	82
Patient 11	46.25	34.5	35	35	0
Patient 12	48.5	31.9	31	30	75
Patient 13	44.9	59.5	72	70	70
Mean	52.0	42.9	52.8	53.8	58.83
SD	11.4	10.3	16.0	13.9	21.28
Median	47.4	42.6	48.0	52.0	64.5

Designation	ESR	CRP	Swollen joints	Tragus to wall distance	Schober test
Patient 1	15	4.2	0	20	3
Patient 2	46	13.09	0	17	2
Patient 3	16	6.02	0	17	2.5
Patient 4	58	26.6	0	15	2.5
Patient 6	10	1	0	14	2.5
Patient 7	8	6.33	1	10	4
Patient 8	43	10	0	10	2.5
Patient 9	10	8.7	2	18	1
Patient 10	14	11.2	1	15	1
Patient 11	33	5.1	6	10	4.5
Patient 12	34	6.07	0	12	3.5
Patient 13	34	6.07	0	10	2
Mean	26.8	8.7	0.83	14.00	2.58
SD	16.7	6.5	1.75	3.57	1.06
Median	24.5	6.2	0	14.5	2.5

There is no patient #5. Units of measurements are in text.

MTX was at 10 mg $week^{-1}$, sulfasalazine at 1.5 $g day^{-1}$, and thalidomide at 100 mg day^{-1}.

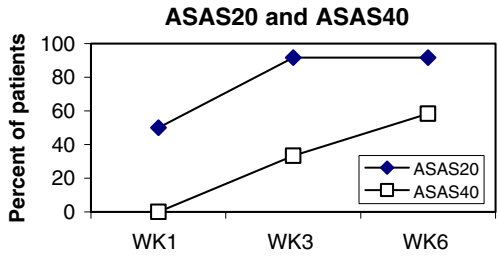

Fig. 1 Percent of patients achieving ASAS20 or ASAS40 in response to treatment by *Tripterygium*

[19–21]. Hence, the observation that about 90% of patients on *Tripterygium* achieved ASAS20 at week 6 is very encouraging. Because such comparisons across studies provide very little degree of confidence, we also attempted to document the response to *Tripterygium* more objectively using the acute phase reactants. There appears to be statistically significant improvement in the serum CRP, with some suppression also in ESR, although not to a statistically less significant degree.

Table 2 Changes in disease status in patients on placebo

	Week 0	Week 6
BASDAI	57.3±11.2	44.7±17.4
BASFI	50.4±21.1	45.1±24.8
BAS-G	72.8±21.1	60.3±19.4

Scores are in scale 0–100

Changes in BASDAI and BAS-G were statistically significant

Each of our patients was also questioned for possible drug-related side effects. Surprisingly, none of the patients complained of side effect, perhaps because this drug is widely accepted by patients as a standard therapy in a traditional medicine hospital. Also, perhaps because of the short duration of the study, none of the three female patients reported the expected amenorrhea. From numerous reports in Chinese journals, the most serious side effect of *Tripterygium* is that on fertility. In one study of 97 women treated for dermatological diseases, hypomenorrhea was observed in 39 patients, and amenorrhea in 9. There are less

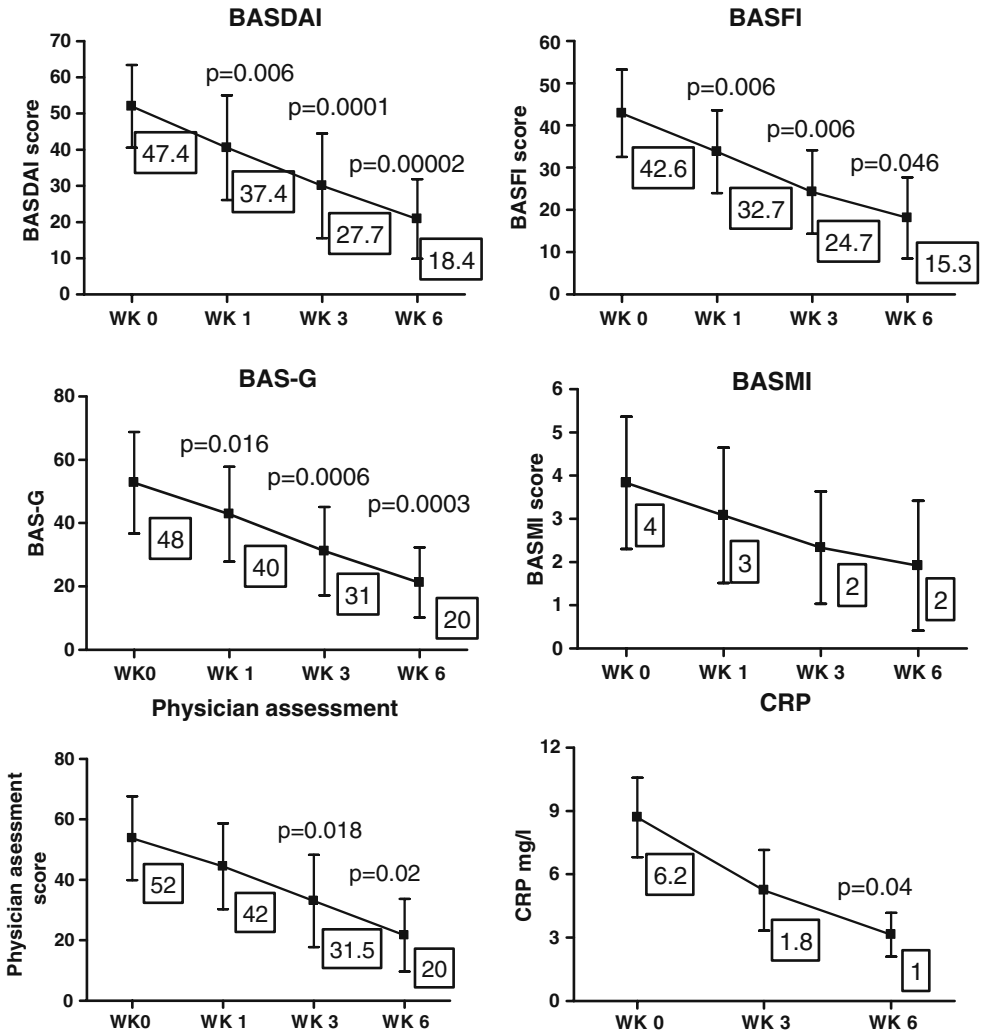

Fig. 2 Changes in parameters in response to *Tripterygium*. *Error bars* represent standard deviations. The *p* values shown are in comparison to corresponding values at week 0. Where *p* values are not shown, they are more than 0.05. All *p* values have been corrected for multiple testing. Numbers inside *squares* represent median values of the corresponding points

documentations of the effect of *Tripterygium* on male fertility. In the same study on dermatological diseases, abnormalities of sperm were detected in 24 of 66 male patients. All these occur within 3–5 weeks after starting *Tripterygium* [22]. There is no assurance that this adverse effect on fertility is not permanent. In addition to adverse effect for fertility, the frequency of liver toxicity has been reported to be as high as 30% and marrow suppression to be 15% [18]. We did not observe these side effects in any of our 12 patients perhaps because of the brevity of the study.

Our results carry a high risk of observer and patient bias. The high degree of response might reflect such errors in a culture where *Tripterygium* has been accepted as standard therapy. Based on the reports on toxicity, *Tripterygium* should not be initiated for any diseases by physicians with no experience with this medication. AS patients should regard the usefulness of *Tripterygium* with skepticism. For it to be continued to be used in AS in any country, a placebo-controlled study should be carried out to evaluate the risk/benefit ratio. At the minimum, our results can provide some basis for power analysis for such future studies.

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Disclosures None

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