A Randomized Double Blind, Placebo Controlled Trial of Topical *Tripterygium wilfordii* in Rheumatoid Arthritis: Reanalysis Using Logistic Regression Analysis

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ABSTRACT. ***Objective.*** To assess the efficacy of topical *Tripterygium wilfordii* (TW), a Chinese herbal therapy, in rheumatoid arthritis (RA).

Methods. A 6 week randomized double blind placebo controlled study of 61 patients with RA meeting American College of Rheumatology (ACR) criteria was conducted in China. The primary outcome was a modified ACR-20 response rate, analyzed by logistic regression analysis.

Results. The modified ACR-20 response rate differed significantly (topical TW 58% vs placebo 20%; p = 0.002). There was an 8.1-fold (95% CI 1.9-35.4) increase in the modified ACR-20 response for the TW compared to the placebo group, adjusted for age and erythrocyte sedimentation rate.

Conclusion. Topical TW appears efficacious for the treatment of RA, but larger studies are needed. (J Rheumatol 2003;30:465–7)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
RANDOMIZED CONTROLLED TRIAL
TRIPTERYGIUM WILFORDII
LOGISTIC REGRESSION ANALYSIS

Tripterygium wilfordii (TW), also known as Thunder God vine, is a herbal treatment used in traditional Chinese medicine. It has recently been studied in the treatment of autoimmune conditions[1-9]. Because of frequent and potentially serious side effects when administered orally[1,2,4-6,10-12], the topical application of TW in rheumatoid arthritis (RA) was evaluated for efficacy by Deng, *et al* in 1997, and the results were published in Chinese[7]. This report is based on a reanalysis of the original data using multivariable logistic regression analysis.

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MATERIALS AND METHODS

The original study. The study was a 6 week randomized double blind placebo controlled trial of topical TW. Inclusion criteria were (1) RA according to American College of Rheumatology (ACR) criteria[13], (2) ≥ 3 tender and swollen joints, and (3) age between 16 and 65 years. Stable doses of methotrexate (MTX), auranofin, or nonsteroidal antiinflammatory drugs were allowed, but patients receiving other treatments and those with comorbidities or pregnancy were excluded.

Based on a computer generated program accessible only to the dispensing pharmacist, patients who met the entry criteria were randomly assigned to receive either TW or placebo tincture, which were indistinguishable. Patients and study investigators remained blinded throughout the study. The tincture was applied to painful/swollen joints 5–6 times per day.

Patients were seen at baseline and after 1, 2, 3, and 6 weeks. At each visit, 42 joints were assessed for tenderness and 40 joints (all except hips) were included in the swollen joint count. Other standard clinical and laboratory assessments were made at each visit (Table 1) and baseline hand radiographs were obtained. A sample size was not calculated in advance.

Study methods for the reanalysis. The primary outcome was a modified ACR-20 response rate. Modification was necessary for patient and physician global assessments, which were evaluated as the relative change from baseline to end of study. For both, a 20% improvement was deemed present if at least mild improvement was reported. In addition, physical function was considered improved by 20% if the ACR functional class[14] improved by 1 grade. All other assessments were based on the standard recommendations for the ACR-20 response rate[15]. Secondary outcomes included mean improvements in tender and swollen joint count, grip strength, morning stiffness, functional status, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF), as well as patient and physician global assessments.

The original data were provided to us by the study investigators of the Guangzhou University of Traditional Chinese Medicine. The reanalysis was conducted blinded to the original statistical analysis and results. For the univariate analysis, chi-square test, Student's t test, and the Mantel-Haenszel test for linear association were used, as appropriate (all 2 tailed). Bonferroni

Table 1. Baseline characteristics comparing Tripterygium and placebo treatment groups.

	Tripterygium (n = 31)	Placebo (n = 30)
Mean (SD) age (yrs)	42 (13)	39 (13)
Female, n (%)	26 (84)	28 (93)
Mean (SD) tender joint count	5.3 (4.2)	5.6 (3.4)
Mean (SD) swollen joint count	8.7 (5.5)	7.5 (5.4)
Mean (SD) RA disease duration (yrs)	4.9 (4.9)	4.7 (4.7)
Mean (SD) grip strength (kPa)	64 (33)	68 (29)
Mean (SD) morning stiffness (h)	2.4 (1.0)	1.9 (0.9)
Mean (SD) ACR functional class	2.6 (0.8)	2.1 (0.5)
Mean (SD) ESR (mm/h)	55 (30)	43 (21)
Mean (SD) CRP (mg/l)	3.3 (2.5)	2.2 (2.0)
Mean (SD) rheumatoid factor (IU/ml)	335 (332)	124 (84)
ACR Functional class, n (%)		
Class 1	0 (0)	2 (7)
Class 2	19 (61)	24 (80)
Class 3	7 (23)	4 (13)
Class 4	5 (16)	0 (0)
X-ray class, n (%)*		
Class 1	9 (29)	11 (37)
Class 2	15 (48)	14 (47)
Class 3	3 (10)	4 (13)
Class 4	4 (13)	1 (3)

SD: standard deviation; ACR: American College of Rheumatology; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein. *Based on hand radiographs.

adjustment for multiple comparisons was employed for the secondary analysis [$p < 0.00625$ (0.05/8) was considered significant].

Because of baseline imbalances in the treatment groups, multivariable logistic regression analysis was performed, using the backward stepwise method. Since the primary question in this reanalysis was to determine whether treatment effect was significant, even when other variables were taken into consideration, it was felt that this study, with 24 events in 61 study participants, provided sufficient data for our purpose. Explanatory variables included treatment group, age, sex, and all imbalanced variables (morning stiffness, ESR, RF, functional class). Interaction terms were evaluated for all significant variables in the model.

RESULTS

Sixty-one patients were enrolled in the original study and included in the intent-to-treat analysis. Baseline characteristics (Table 1) were similar with the exceptions of morning stiffness, ESR, RF, and functional status, which were more severe in the TW group.

Univariate analysis. A significantly different modified ACR-20 response rate was seen in the TW compared to the placebo group (58% vs 20%; $p = 0.002$) (Table 2). All secondary outcomes were also statistically significant in favor of the TW group except ESR, once corrected for multiple comparisons (Table 2).

Multivariable logistic regression analysis. Assignment to the TW group was significantly associated with a modified ACR-20 response. The odds of achieving a modified ACR-20 response was 8.1 (95% CI 1.9-35.4) for the TW compared to the placebo group (Table 3). In the final model, age and ESR were also significant. Interactions were not significant. In particular, there was no interaction between treatment group and ESR, which is a measure of disease severity, suggesting that the effect of treatment was not mediated by disease severity. The p value from the Hosmer-Lemeshow goodness-of-fit test was 0.59, indicating a reasonable fit of the model. There was

Table 2. Univariate analysis of primary and secondary outcomes comparing Tripterygium and placebo treatment groups.

Outcome Variable	Tripterygium, n = 31	Placebo, n = 30	p
Modified ACR-20 response rate*, n (%)	18 (58)	6 (20)	0.002
Mean improvement (SD):			
Tender joint count	2.4 (2.4)	0.9 (1.0)	0.002
Swollen joint count	6.3 (3.9)	1.9 (2.5)	< 0.001
Grip strength (kPa)	52 (35)	13 (14)	< 0.001
Morning stiffness (h)	1.0 (0.6)	0.2 (0.4)	< 0.001
ACR functional class	0.7 (0.6)	0.2 (0.4)	0.001
ESR (mm/h)	11 (19)	–1 (15)	0.011
CRP (mg/l)	1.8 (1.9)	0.4 (1.0)	0.001
Rheumatoid factor (IU/ml)	141 (189)	13 (26)	0.001
Patient global assessment			< 0.001**
No improvement	7 (23)	19 (63)	
Mild improvement	5 (16)	5 (17)	
Moderate improvement	8 (26)	6 (20)	
Excellent improvement	11 (35)	0 (0)	
Physician global assessment			0.005**
No improvement	10 (32)	18 (60)	
Mild improvement	15 (49)	12 (40)	
Excellent improvement	6 (19)	0	

*See Methods section for description of ACR-20 modifications. SD = standard deviation, **Mantel-Haenszel test for linear association.

Table 3. Adjusted odds ratio for modified ACR-20 response in the final multivariable logistic regression model.

Variable	Odds Ratio (95% CI)	p
Treatment group		
Placebo	1	
Tripterygium	8.1 (1.9–35.4)	0.005
Age*		
≥ 41 years	1	
< 41 years	7.0 (1.6–30.9)	0.01
ESR per 10 unit difference	1.6 (1.1–2.2)	0.02

*The median of 41 years was used to dichotomize age.

no evidence that the underlying assumptions associated with this analysis were violated.

DISCUSSION

Few reports of oral TW treatment in RA exist in the English literature[1-6]. A placebo controlled crossover study found significant improvements in clinical and laboratory variables after 12 weeks of treatment[4]. Another recent study evaluating oral TW reported significant differences in ACR-20 response rates of 80%, 40%, and 0% after 20 weeks of high dose, low dose, and placebo treatment, respectively[6]. Topical application of TW has not been investigated, other than in the original randomized double blind placebo controlled study conducted in Guangzhou, China[7]. The original trial reported a significant improvement in symptoms in patients with RA treated with topical TW. Our reanalysis of these data using logistic regression analysis with adjustment for baseline imbalances confirms the original findings and suggests that topical TW appears to be efficacious in RA.

There are several limitations to this reanalysis. Data on MTX, auranofin, and NSAID use were not available to determine whether these variables were balanced at baseline, and hence these could not be included in the logistic regression analysis. The ACR-20 outcome measure required modification to accommodate the data collected, although only minor criteria were modified. Finally, the *post-hoc* nature of this analysis can only serve the purpose of generating a hypothesis.

This reanalysis confirms the results of the original trial and supports the therapeutic efficacy of topical TW in RA. However, because this analysis was performed *post-hoc*, further rigorous investigations are needed to evaluate the efficacy of topical TW therapy in RA.

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