Rheumatol Int (2014) 34:1647–1655
DOI 10.1007/s00296-014-3010-6

ORIGINAL ARTICLE

Traditional Chinese medicine versus western medicine as used in China in the management of rheumatoid arthritis: a randomized, single-blind, 24-week study

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Received: 18 December 2013 / Accepted: 28 March 2014 / Published online: 24 April 2014

Abstract This study is designed to compare the efficacy and safety of traditional Chinese medicine (TCM) with western medicine (WM) in the management of rheumatoid arthritis (RA). This is a 24-week, randomized, multicenter, single-blind study comparing TCM with WM (as used in China) carried out between June 2002 and December 2004 in nine research centers in China, involving 489 patients. Patients were randomized to receive TCM ($n = 247$), MTX and SSZ ($n = 242$). MTX was started at a dose of 5 mg to a final dose of 7.5–15 mg weekly. The maintenance dose was 2.5–7.5 mg weekly. The starting dose of SSZ was 0.25 g bid, increasing by 0.25 g a day once a week to a final dose of 0.5–1 g qid. The maintenance dose was 0.5 g tid to qid. Primary end point was the proportion of patients with response according to the American College of Rheumatology 20 % improvement criteria (ACR20) at weeks 24. At 24 weeks, ACR20 responses were 53.0 % in TCM group and 66.5 % in WM group, ($P < 0.001$) at 24 weeks. ACR 50 responses were 31.6 % of TCM group and 42.6 % in WM group, ($P = 0.01$). ACR70 responses were 12.6 % in TCM group and 17.4 % in WM group, ($P = 0.14$). Side effects were observed more frequently in WM group. In this study, ACR20, ACR50 responses at 24 weeks were significantly better in the WM treated group, by intention to treat (ITT) and per protocol analysis. The ACR 70 response showed no significant difference between the two groups. TCM, while effective in treating RA, appears to be less effective than WM in controlling symptoms, but TCM is associated with fewer side effects.

Keywords Rheumatoid arthritis · Therapy · Traditional Chinese Medicine · Western medicine · Randomized · Single-blind

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Introduction

Rheumatoid arthritis (RA) affects 1–2 % of the population worldwide. It is associated with significant mortality and morbidity [1]. Disease-modifying antirheumatic drugs (DMARDs) are effective in controlling symptoms and decreasing radiologic progression. However, these drugs are associated with potentially serious toxicities [2, 3]. RA is one of the rheumatic diseases under the broad category of Bi syndrome (痹病) in traditional Chinese medicine (TCM). Bi syndrome in TCM concept includes a group of disorders with the clinical manifestations similar to arthritis and rheumatism in western medicine (WM) (see Appendix 3) [4, 5]. In the opinion of TCM practitioners, TCM has been a safe and effective treatment of RA for over 2000 years [6, 7]. Due to the lack of blinded and placebo controlled trials, the real efficacy and safety of TCM in RA has always been questioned. To our knowledge, the efficacy and safety of TCM in RA treatment has not been compared with well-established western RA treatment. The purpose of this study is to compare the efficacy and safety between RA patients treated over 24 weeks with TCM or WM (as used in China) using a randomized, single-blind approach. The endpoints include clinical and safety parameters.

Materials and methods

Patients

Four hundred and nine patients between the ages of 18 and 70, all fulfilling both the American College of Rheumatology (ACR) and TCM criteria for RA [8–12] for at least 1 year, with a DAS 28–3 > 2.6, and in ACR functional classes I, II or III participated in this study. Informed consents were obtained from all participants. Patients with the following major diseases or conditions were excluded: cardiovascular, pulmonary, hepatic, renal, hematologic, psychological, gastrointestinal; history of sensitivity to any of the study medications; potential of becoming pregnant or breast feeding; use of corticosteroid or immunosuppressive within 1 month, or use of TCM for RA within 2 weeks of study entrance; current enrollment in any other clinical research.

Protocol

This is a 24-week, single-blind, parallel group, multicenter study conducted at nine sites in China. As it was not practical to conduct clinical TCM studies using a double-blind design [13], this study was carried out using a single-blind design. The safety and efficacy were evaluated by a blinded, independent assessor. Patients were randomly assigned using the SZS-12 PRCO PLAN system (Windows Version 6.12) to receive TCM or WM treatment. The study was approved by the Ethical Research Committee, Guangdong Provincial Hospital of TCM. Informed consent was obtained from each patient.

Those RA subjects randomized to the TCM treatment groups are further subdivided into the four TCM syndromes (see Appendix 3) [4, 5]. These subjects are then treated accordingly based on the TCM theory of treating these syndromes. All patients in the TCM groups were treated with Tripterygii totorum (雷公藤多甙片), 10 mg, tid (dosage adjusted as shown in Appendix 2), and Yishen Juanbi tablet (益肾蠲痹丸) 8 g tid. After further grouping into Cold Damp (Hanshibi 寒湿阻络型), Damp Heat (Shirebi 湿热阻络型), Cold Heat (Hanrebi 寒热错杂型), Liver and Kidney Deficiency and Meridian-Phlegm Stagnancy (肝肾亏损兼痰瘀阻络型) arthralgia syndromes according to TCM theory, one of the following preparations, Hanshibi granule (寒湿痹颗粒) for the Hanshibi syndrome, Shirebi granule (湿热痹颗粒) for the Shirebi syndrome, Hanrebi granule (寒热痹颗粒) for Hanrebi syndrome or Granule for Arthralgia (尪痹颗粒) for arthralgia syndrome was added as follows: Hanshibi granule (寒湿痹颗粒) 5 g tid in Hanshibi syndrome (Hanshibi 寒湿阻络型); Shirebi granule (湿热痹颗粒) 5 g tid, in Shirebi syndrome (Shirebi 湿热阻络型); Hanrebi granule (寒热痹颗粒) 10 g tid, in Hanrebi syndrome (Hanrebi 寒热错杂型); Granule for Arthralgia (尪痹颗粒) 6 g tid, in arthralgia syndrome (肝肾亏损兼痰瘀阻络型) (see Appendix 4).

Patients in the WM group were treated with slow-release diclofenac tablet 75 mg once daily. This was discontinued when there was no longer any joint swelling or when the ESR had returned to normal. Patients in this group also received methotrexate (MTX) and sulfasalazine (SSZ) combination. MTX, was started at a dose of 5 mg weekly, with a weekly increment of 2.5 mg, to a final dose of 7.5–15 mg weekly. The dose was reduced to a maintenance of 2.5–7.5 mg a week when there was no longer any joint swelling or when the ESR had returned to normal. The starting dose of SSZ was 0.25 g bid, increasing by 0.25 g a day once a week to a final dose of 0.5–1 g qid. When there was no longer any joint swelling or when the ESR had returned to normal, the dose was reduced to 0.5 g tid to qid. The starting and maintenance doses of MTX and SSZ reflect the standard of practice in China at that time.

If clinically indicated, use of other medications such as liver-protective drugs: Glucurolactone (肝泰乐), Wu Zhi Capsule (五酯胶囊), Diammonium (甘力欣), Yiganling tablet (益肝宁片) and Jibuyin (鸡布茵); folic acid and other hematologic tonic: Inosine (肌苷片), Leucogen (利血生); and gastroprotective drugs: Famotidine, Sucralfate, Weinaian Capsules (胃乃安片),Metoclopramide (胃复安), Lijunsha tablets (利菌沙片), Hydrotalcite (胃达喜), fragrant sarcococca root (胃友), Sanjiuweitai

(三九胃泰) and Marzulene (麦滋林); and TCM agents for general well-being: Granules of Banlangen (板兰根颗粒), Huoxiang Zhengqi pills (藿香正气丸) or Zhibai dihuang pills (知柏地黄丸) were permitted. All these concomitant agents are used for side effects only. None of these agents have any effects on treatment efficacy. Steroid was not allowed in this study.

Clinical assessment

Blinded independent assessors were TCM physicians experienced in clinical research and with special training in joint assessment. Patients were assessed at baseline, weeks 12 and 24. Clinical responses were defined by ACR criteria for 20, 50 and 70 % improvements [14, 15]. Physical function was assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI) [16] at baseline and at each visit.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 17.0. Baseline comparability between the treatments was evaluated by summarizing. Continuous variables analyzed by t test or Mann–Whitney U test for non-normally distributed data. Categorical variables analyzed by chi-square test (Fisher's exact test), were used to assess duration of RA in baseline characteristics. Analyses were based on intention to treat (ITT) and per protocol (PP) analysis. Sample size 241 for each treatment group was calculated by a projection of 91.11 % efficacy for TCM, and a 79 % efficacy for WM; and a 20 % dropout rate, with $\alpha = 0.05$, $\beta = 0.10$.

Results

Patient disposition

As described in detail in Fig. 1, 522 patients were screened. Of these, 489 were randomized: 247 into TCM group, and 242 into WM group. Fifty-two patients withdrew during the study due to patient dissatisfaction with his/her therapeutic benefit, side effects or other reasons: 29 from the TCM group, and 23 from the WM group. One patient in the WM group discontinued treatment due to a GI bleed. Nineteen patients and 22 patients were excluded from the per protocol (PP) analysis in the TCM and WM groups, respectively, due to protocol violation.

Patient characteristics

Patients in the TCM and WM treatment groups were as described in Tables 1 and 2. WM treated patients were significantly younger and have shorter disease duration.

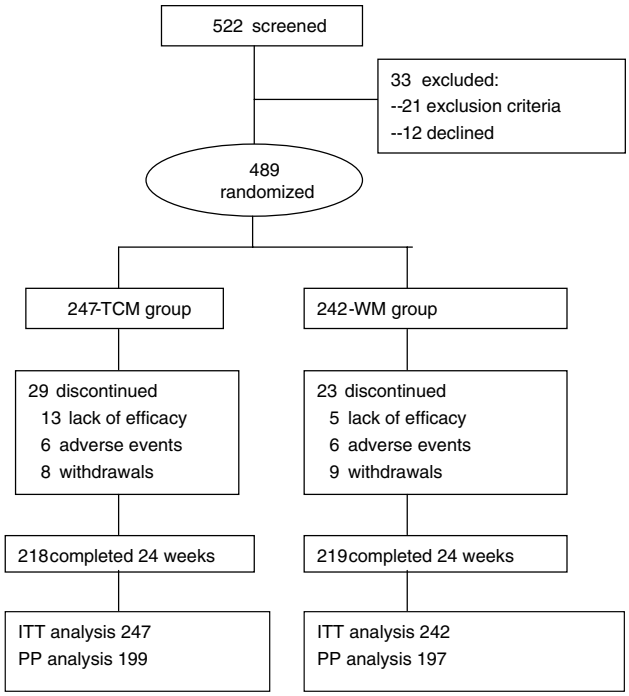

Fig. 1 Patient disposition

Signs and symptoms

ACR20, ACR50 responses at 24 weeks are significantly better in the WM treated groups, as compared with the TCM treated groups by ITT and PP analysis as indicated in Tables 3 and 4. The ACR 70 response shows no significant difference between the two groups.

Safety

Safety analysis was carried out in 510 patients, including 21 patients who were not randomized into ITT groups, but who had been administered at least one dose of the study medication. One single SAE (GI bleed) was observed in the WM group. Other adverse events (AE) are summarized in Tables 5 and 6. TCM appears to cause less gastrointestinal, hematological and hepatic AE.

Concomitant medications

NSAID: Seventeen patients in the TCM group and two patients in the WM group took concomitant NSAID. These patients were removed from the statistical analysis of the results. Of the 17 patients in the TCM group, three used NSAID continuously for 25, 15 and 10 days. The other 14 patients used NSAID very irregularly. Of the two patients in the WM group, one used concomitant NSAID continuously for 30 days, while the other used NSAID very infrequently.

Table 1 Baseline characteristics

Items	TCM group		WM group		*P*
	n	$\bar{x} \pm s$	*n*	$\bar{x} \pm s$	
Age (years)	247	49.83 ± 11.49	242	47.10 ± 12.11	0.01**
Disease duration (months)	247	73.99 ± 74.44	242	60.69 ± 62.801	0.03*
SBP (mmHg)	247	120.67 ± 15.06	242	120.62 ± 14.35	0.97
DBP (mmHg)	247	77.39 ± 8.09	242	78.17 ± 8.295	0.29
HR (bpm)	247	77.12 ± 8.27	242	77.45 ± 8.82	0.68
Pulse Rate (bpm)	247	77.08 ± 8.11	242	77.23 ± 8.49	0.84
Respiration (times/m)	247	19.26 ± 1.77	242	19.43 ± 1.86	0.30
Resting pain (mm)	247	52.98 ± 30.11	242	55.47 ± 28.00	0.35
Tender joint count	247	12.09 ± 7.49	242	11.80 ± 7.52	0.67
Tender joint score	247	17.08 ± 12.14	242	15.81 ± 11.37	0.23
Swollen joint count	247	8.36 ± 7.30	242	8.12 ± 7.02	0.72
Swollen joint score	247	8.82 ± 7.54	242	8.65 ± 7.60	0.81
Morning stiffness (min)	247	81.83 ± 73.70	242	89.61 ± 79.99	0.26
Patient's global assessment (mm)	247	63.89 ± 19.16	242	62.70 ± 19.42	0.68
Physician's global assessment (mm)	247	63.12 ± 18.36	242	61.79 ± 18.84	0.11
Total Sharp score	245	16.56 ± 6.19	240	15.68 ± 5.94	0.49
HAQ-DI	243	1.00 ± 0. 69	242	0.91 ± 0.71	0.43
Grip strength (mmHg)	247	66.72 ± 42.39	242	65.17 ± 41.22	0.11
20-m walk time (S)	246	28.81 ± 43.02	242	23.97 ± 20.36	0.19
ESR (mm/h)	247	45.13 ± 31.54	242	43.19 ± 28.57	0.48
CRP (mg/l)	214	18.44 ± 20.90	210	16.76 ± 19.44	0.39
IgA (g/l)	238	3.06 ± 1.38	236	3.13 ± 1.35	0.55
IgG (g/l)	238	17.26 ± 6.77	236	17.07 ± 5.43	0.75
IgM (g/l)	238	1.89 ± 0.88	236	2.01 ± 0.98	0.14

$\bar{x} \pm s$ mean ± standard deviation

*P-value <0.05 between the two groups, **P-value <0.01 between the two groups

DMARD: one patient in the TCM group took methotrexate 10 mg weekly for 2 weeks.

Hepatoprotective drugs: These agents were prescribed for those who have abnormal AST and/or ALT. Four patients in the TCM group took hepatoprotective drugs, 1 for 2 months, 1 for 2 weeks and 2 for 1 week. 23 patients in the WM group took these agents, 13 for 1 month, 4 for 1.5 months, 1 for 2 months, 2 for 3 months, 2 for 4 months and 1 for 1 month.

Gastroprotective drugs (GPA): These agents were used for those who have dyspepsia, diarrhea, nausea, anorexia, mouth ulcer, stool positive for occult blood, frank GI bleeds. Eight patients in the TCM group took GPA, one for 2 months, the other seven from 1 week to 1 month. In the WM group, nine patients took GPA, one for 3 months, one for 2 months, three from 1 to 1.5 months and the other four for less than 1 month.

Hematologic tonics

These agents were given for those with any abnormalities in the complete blood count. Eight patients in the WM but no patient in the TCM group took these agents. Of these eight in the WM treated group, four use the agent for 1.5 months, two for 0.5 months and the other two for less than 2 weeks.

TCM

Six patients each in each group took TCM concomitant agents. Granules of Banlangen, Huoxiang Zhengqi pills or Zhibai dihuang pills were added in 12 cases (six in TCM group, six in western group).

After eliminating subjects who used additional medications, the observed therapeutic effect at 24 week (Table 7) was the same as observed for the entire groups.

Discussion

The exact pathophysiology of RA remains unknown. Current treatment is directed toward decreasing pain, decreasing inflammation and preventing joint damage. The treatment algorithm stresses the importance of the early use of disease-modifying antirheumatic drugs (DMARD), often in combination [17]. In our study, subjects in the

Table 2 Baseline characteristics

Items	Classification	TCM group $n = 247$ (x, %)	WM group $n = 242$ (x, %)	Total	*P*
Marital status	Single	10 (4.1)	17 (7.0)	27 (5.5)	0.15
	Married	236 (95.9)	225 (93.0)	461 (94.5)	
Gender	Male	42 (17.0)	38 (15.7)	80 (16.4)	0.70
	Female	205 (83.0)	204 (84.3)	409 (83.6)	
Rheumatoid factor	Positive	189 (76.5)	195 (80.6)	384 (78.5)	0.27
	Negative	58 (23.5)	47 (19.4)	105 (21.5)	
Outpatient or inpatient	Outpatient	226 (91.5)	223 (92.1)	449 (91.8)	0.79
	Inpatient	21 (8.5)	19 (7.9)	40 (8.2)	
Previous treatment	Yes	198 (80.2)	194 (80.2)	392 (80.2)	1.00
	No	49 (19.8)	48 (19.8)	97 (19.8)	
Previous drugs use	Chinese herbal	133 (53.8)	129 (53.3)	262 (53.6)	0.91
	DMARDS	45 (18.2)	41 (16.9)	86 (17.6)	0.71
	NSAIDs	93 (37.7)	91 (37.6)	184 (37.6)	1.00
	Corticosteroid	26 (10.5)	19 (7.9)	45 (9.2)	0.31
TCM syndrome diagnosis	Cold damp syndrome	60 (24.3)	71 (29.3)	131 (26.8)	0.41
	Damp heat syndrome	54 (21.9)	59 (24.4)	113 (23.1)	
	Cold and heat syndrome	56 (22.7)	48 (19.8)	104 (21.3)	
	Liver and kidney deficiency and meridian-phlegm stagnancy syndrome	77 (31.2)	64 (26.4)	141 (28.8)	
ACR functional class	1	21 (8.5)	34 (14.0)	55 (11.2)	0.14
	2	175 (70.9)	158 (65.3)	333 (68.1)	
	3	51 (20.6)	50 (20.7)	101 (20.7)	

n the number of cases in each group, *x* the proportion of the total cases, *P* the *P* values

Table 3 ACR responses at 24 weeks by ITT analysis

Time	Improve rate (ACR) (%)	TCM group		WM group		*P*
		n	Effective rate (x, %)	*n*	Effective rate (x, %)	
24 week	≥20	247	131 (53.0)	242	161 (66.5)	0.01
	≥50	247	78 (31.6)	242	103 (42.6)	0.01
	≥70	247	31 (12.6)	242	42 (17.4)	0.14

At 24 weeks, ACR20 responses were 53.0 % in TCM group and 66.5 % in WM group ($P < 0.01$). ACR 50 responses were 31.6 % in TCM group and 42.6 % in WM group ($P = 0.01$). ACR70 responses were 12.6 % in TCM and 17.4 % in WM group ($P = 0.14$)

n the number of cases in each group, *P* the *P* values

Table 4 ACR responses at 24 weeks by PP analysis

Time	Improve rate (ACR) (%)	TCM group		WM group		*P*
		n	Effective rate (x, %)	*n*	Effective rate (x, %)	
24 week	≥20	199	131 (65.8)	197	159 (80.7)	0.01
	≥50	199	78 (39.2)	197	102 (51.8)	0.01
	≥70	199	31 (15.6)	197	42 (21.3)	0.14

At 24 weeks, ACR20 responses were 65.8 % in TCM group and 80.7 % in WM group ($P < 0.01$). ACR 50 responses were 39.2 % in TCM group and 51.8 % in WM group ($P = 0.01$). ACR70 responses were 15.6 % in TCM and 21.3 % in WM group ($P = 0.14$)

n The number of cases in each group, *P* the *P* values

Table 5 Adverse events

Adverse event *n* (%)	Symptoms	TCM group $n = 259$	WM group $n = 251$	*P*
Deaths		0	0	
SAEs		0	1	1.00
Discontinuation due to AE		6	5	0.80
Discontinuation due to SAEs		0	1	1.00*
Gastrointestinal		25	31	0.40
	Diarrhea	3 (1.16)	0	0.25*
	Dyspepsia	9 (3.47)	13 (5.18)	0.34
	Nausea	7 (2.70)	9 (3.59)	0.57
	Anorexia	2 (0.77)	8 (3.19)	0.06*
	Oral ulcer	3 (1.16)	0	0.25*
	Stool positive for occult blood	1 (0.39)	0	1.00*
	GI bleed	0	1 (0.40)	1.00*
Other		5	21	0.01
	Skin rash	0	1 (0.40)	1.00*
	Chest discomfort and/or shortness of breath	0	2 (0.80)	0.24*
	Blurred vision	0	4 (1.59)	0.06*
	Excessive or decreased perspiration	1 (0.39)	2 (0.80)	0.62*
	Sleep disturbance	2 (0.77)	0	0.50*
	Flu-like symptoms	1 (0.39)	1 (0.40)	1.00*
	Dizziness	0	4 (1.59)	0.06*
	Anxiety	0	2 (0.80)	0.24*
	Dry mouth	1 (0.39)	3 (1.20)	0.37*
	Backache	0	0	–
	Facial flushing	0	1 (0.40)	1.00*
	Tinnitus	0	1 (0.40)	1.00*

Table 6 Laboratory parameters

Category adverse event	Items abnormality	TCM group		WM group		*P*
		Total	Cases incidence *n* (*x*, %)	Total	Cases incidence *n* (*x*, %)	
Hematological abnormalities			97		143	0.01
	Abnormal WBC count	235	33 (14.04)	235	41 (17.45)	0.79
	Abnormal HGB level	202	27 (13.37)	201	34 (16.92)	0.28
	Abnormal RBC count	228	18 (7.90)	217	39 (17.97)	0.01
	Abnormal platelet count	242	19 (7.85	242	29 (11.98)	0.10
Routine urinalysis			31		31	1.00*
	Hematuria	229	20 (8.73)	232	17 (7.32)	0.68
	Proteinuria	249	11 (4.42)	245	14 (5.71)	0.49
Stool examination	Positive OB test	259	1 (0.39)	251	0	1.00*
Liver function	Abnormal ALT (>40 U/l)	252	25 (9.92)	231	50 (21.65)	0.01
Abnormal renal functions	Creatinine (>84 μmol/l)	257	3 (1.17)	250	4 (1.60)	1.00*
Abnormal ECG		194	11 (5.7)	185	7 (3.8)	0.37

* Fisher's exact test

n the number of cases in each group, *x* the proportion of the total cases, *P* the *P* values

WM treatment arm received diclofenac and combination DMARD therapy of methotrexate and sulfasalazine, a frequently used combination DMARD [18–20]. Using this combination, subjects in the WM arm reached ACR-20 of 80.7, 66.5; ACR 50 of 51.8, 42.6 % by ITT and PP analysis, respectively. These results are arguably similar or better

Table 7 Therapeutic Effect after eliminating subjects who took additional medications not allowed in the study

Time	Improve rate (ACR) (%)	TCM group		Western group		*P*
		n	Effective rate *n* (*x*, %)	*n*	Effective rate *n* (*x*, %)	
24 week	≥20	187	125 (66.8)	196	158 (80.6)	0.002
	≥50	187	76 (40.6)	196	101 (51.5)	0.033
	≥70	187	30 (16.0)	196	42 (21.4)	0.177

n the number of cases in each group, *x* the proportion of the total cases, *P* the *P* values

than those reported in the literature [21–23]. We have no explanation why our results are so favorable.

In TCM, RA falls into the category of Bi syndrome (痹病) and is believed to be caused by "attacks of wind, cold, damp humor causing dysfunction of the TCM liver and kidney". (It should be noted that the evil humors such as cold and damp are conceptual thinking in TCM, and not to be interpreted literally. It should also be noted that in TCM, organs such as kidney, liver and spleen are conceptual descriptions and not an anatomical description as understood in WM.) This, in turn, results in bone and tendon damage [24, 25], Subjects in the TCM treatment arm are classified into the different TCM syndromes, and given treatment to restore "kidney" and "liver" function, as well as treatment for inflammation using Tripterygii tororum, with Yishen Juanbi (益肾蠲痹丸), supplemented with Hanshibi granule (寒湿痹颗粒), Shirebi granule (湿热痹颗粒), Hanrebi granule (,寒热痹颗粒) and Granule for Arthralgia (尪痹颗粒), according to the different TCM syndrome classifications. In TCM treatment arm at 24 weeks, ACR-20 reached 65.8, 53 %; ACR-50 reached 39.2, 31.6 % by ITT and PP analysis, respectively, demonstrating beneficial effect of TCM treatment.

Symptom-modifying anti-rheumatic drugs (SMARD's) in WM, such as non-steroidal anti-inflammatory drugs (NSAID), work rapidly by targeting directly the inflammatory pathway [26, 27]. In contrast, TCM treatment works slowly by "invigorating the kidney and liver; restoring circulation in the blood and meridian, expelling wind and damp evil, thus alleviating the 'bi' syndrome" [28, 29].

While our study showed that WM is superior to TCM in achieving ACR 20 and 50, the duration of this study is only 24 weeks. Whether a longer follow-up might show further benefit for TCM treatment can only be answered with such a longer study. Furthermore, the WM treated patients were statistically younger and had shorter disease duration. This could be a potential confounding factor in the ACR outcomes. The longer disease duration in the TCM group make it less likely that they would respond to treatment compared with the WM group [30]. The superiority of WM may be balanced by the TCM safety. WM is numerically more likely to be associated with GI, hematological, hepatic and renal adverse event. There were no differences in the observed GU, menstrual AE between the two groups. We recognize that with the single-blind design of this study, bias could be introduced by the treating physicians.

The ultimate goals in managing RA are to decrease pain, prevent or decrease joint damage and to maintain function [19]. The use of traditional DMARD therapy in WM has not been universally successful in achieving these goals [31]. Newer biologic agents have provided significant additional improvement in controlling symptoms and decreasing joint damage in RA. However, due to cost and long-term safety concerns, biologic treatment is not easily accessible for many RA patients [32, 33].

We also recognize that in our study, in the WM treatment arm, we did not use the higher dose of methotrexate which is more commonly used currently. However, the dosages used in our study reflected the standard of practice in China at that time. It should be noted that in Japan, the maximum dose of methotrexate permitted at that time was <10 mg weekly. In our protocol, we adjusted the methotrexate and sulfasalazine dosage once the patient has achieved clinical and laboratory control. While this is not the usual practice for many clinical trials, this was done in our protocol. In China, there is a perception that WM is toxic. In order to achieve target enrollment, we had built this into the protocol. As the patient has already achieved clinical and laboratory control, the analysis of efficacy should not be affected by such dosage adjustment. If anything, this would lower the adverse event profile of the WM treatment group.

Two questions remain unexplored. While we have demonstrated the comparability of TCM and WM in symptom-modifying effects, due to the small number of patients in each TCM subgroups, we decided not to analysis the efficacy and safety between TCM and WM in each TCM RA subgroups. We plan to do such a study in the future. Secondly, the potential benefit of combining WM and TCM for RA patients remain unexplored.

Finally, this is a large scale long-term multicenter study comparing TCM with WM in managing patients with RA, using standardized western treatment outcome instruments. This study utilized a single-blind randomized control design practical for the study of TCM. It is impossible to blind the treating physician, as the physician has to identify the specific TCM syndrome in order to prescribe the

appropriate treatment for the subject. However, the assessor is blinded, which should minimize assessment bias. It also adheres to TCM principles. Instead of one single TCM treatment for all patients 14 with RA, this study subdivides the RA patients into different TCM syndromes. The patients in each TCM syndrome within the western classification of RA were treated differently according to these TCM syndromes.

Acknowledgments The authors gratefully acknowledge Prof. LAI Shi-long (Center for DME; Guangzhou University of Traditional Chinese Medicine), Prof. John Esdaile, Prof. Ian Tsang, Prof. Simon Huang and Prof. Barry Koehler (Arthritis Research Centre of Canada and University of British Columbia) for their assistance in developing the concept of this study.

Conflict of interest The authors declare that they have no conflict of interest.

Appendix 1: The clinical trial centers in the trial

Guangdong Provincial Hospital of Traditional Chinese Medicine, China-Japan Friendship Hospital, Guang An Men hospital of China academy of Traditional Chinese Medicine, Long Hua Hospital affiliated to Shanghai University of Traditional Chinese Medicine, Institute of Traditional Chinese Medicine of Hubei Province, Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, First Affiliated Hospital, Tianjin College of Traditional Chinese Medicine, Jiangsu Provincial Hospital of Traditional Chinese Medicine and Nantong Liangchun Clinical Research Institute of Traditional Chinese Medicine.

Appendix 2: The Tripterygium wilfordii multiglycoside tablet was administrated in the following way

1. Starting dose: 10 mg tid;
2. When mild adverse reactions such as slight gastrointestinal side reaction, menstrual disorder, facial flush and skin itching occurred, the dose is reduced to 10 mg bid;
3. When clinical evidence of progressive injuries of the liver, gastrointestinal tract, amenorrhea occurred, the dose is reduced to 5 mg bid;
4. When serious toxicity such as severe gastrointestinal side reaction, amenorrhea, serious hepatic dysfunction occurred, the drug is discontinued.

Appendix 3 [4, 5]

Bi syndrome (痹病) is a disorder resulting from the obstruction of meridians, sluggishness of qi and blood circulation after the invasion of exterior/interior pathogenic wind, cold, dampness or heat. It manifests as pain, soreness, aches, numbness or heaviness of muscles, sinews, and joints, and/or swelling and burning pain.

RA subjects randomized to the TCM treatment groups are further subdivided into the four syndromes of Bi syndrome (痹病) as listed below.

1. Cold Damp (Hanshibi 寒湿阻络型): A syndrome that arises when the movement of qi and blood is impeded by cold and dampness in combination. It is marked by cold pains with inconvenient flexion in joint and muscle and intolerance of cold. The pain improves with warmth. The tongue may be enlarged and have white slimy or white greasy coat. The pulse may be wiry slippery or tense pulse.
2. Damp Heat (Shirebi 湿热阻络型): A syndrome caused by a combination of dampness and heat, with manifestations of inflamed hot pain or swollen and stiff in joint and muscle. The tongue may be red and have off-white or yellow greasy coat. The pulse may be rapid and soft or rapid and slippery or wiry.
3. Cold Heat (Hanrebi 寒热错杂型): A syndrome that local symptoms characterized by cold 15 syndrome, and general symptoms by heat syndromes or local symptoms characterized by heat syndrome, and general symptoms by cold syndromes. The tongue coat may be white or yellow. The pulse may be string-like and/or rapid.
4. Liver and Kidney Deficiency and Meridian-Phlegm Stagnancy (肝肾亏损兼痰瘀阻络型): A syndrome that characterized by a long-term course with distortion and stabbing pain or numbness/ache in joint, muscle and bone. It may be purple tongue or purple spots on the tongue. The pulse may be weak (deep, fine, soft, thready) or hidden (not obvious, very deep).

Appendix 4

Drug name	Manufacturer	Main components
Tripterygii totorum (雷公藤多甙片)	WuHan pharmaceutical factory	Triptolide (50 μg in one tablet)
Yishen juanbi tablet (益肾蠲痹丸)	Qingjiang Pharmaceutical Factory of Jiangsu Province	*Davallia, Radix Rehmanniae Preparata., Cynanchi Paniculati Radix Et R., Eupolyphaga seu Steleophaga, Nidus Vespae Honeysuckle Flower, Pheretima, Epimedium brevicornu Maxim, Kadsura interior,* et al.

Drug name	Manufacturer	Main components
Hanshibi granule (寒湿痹颗粒)	Dalian Changbaishan Pharmaceutical Co., Ltd.	*Radix Aconiti Lateralis Preparata, Radix Aconiti, Astragalus membranaceus, CassiaTwig, Atractylodes macrocephala Koidz., Radix Angelica Sinensis, Chaenomeles sinensis (Thouin) Koehne, Ephedra minuta Florin,* et al.
Hanrebi granule (寒热痹颗粒)	Dalian Changbaishan Pharmaceutical Co., Ltd.	*CassiaTwig, Radix Paeoniae Alba*, Anemarrhena asphodeloides Bung, *Ephedra minuta Florin*, et al.
Granule for Arthralgia (尪痹颗粒)	Dalian Changbaishan Pharmaceutical Co., Ltd.	*Radix Rehmanniae Preparata, Radix Dipsaci, RadixAconitiLateralisPreparata, Araliafargesii Franch, Davallia, CassiaTwig, Divaricate Saposhnikovia Root, Epimedium brevicornu Maxim, Rhizoma Cibotii, Lycopodii Herba,* et al.

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