A meta-analysis of integration of Traditional and Western Medicine treatment versus Western treatment in patients with lupus nephritis

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Abstract

Objective: To systematically evaluate the clinical effect of integrated traditional Chinese medicine and Western Medicine (TCM-WM) and to investigate effective therapy of traditional Chinese medicine (TCM) for lupus nephritis (LN).

Methods: A meta-analysis was performed of all the literatures germane to estimate the patients treated with TCM-WM and Western Medicine (WM) alone from published randomized controlled trials (RCTs) from 1990 to February 2013. Relative risk (RR) and 95% confidence intervals (CIs) were calculated and the meta-analysis was conducted with Revman 5.2 software. GRADE Profile 3.6 was used to evaluate the quality of the evidence.

Results: 12 RCTs were included. The complete remission rate (RR = 1.58, 95% CI 1.4-1.78, P < 0.00001) and the total remission rate (RR = 1.18, 95% CI 1.13-1.24, P < 0.00001) of TCM-WM were higher than that of WM. The relapse rate (RR = 0.32, 95% CI 0.22-0.44, P < 0.00001), incidence of adverse reactions (RR = 0.47, 95% CI 0.41-0.55, P < 0.00001) and mortality rate (RR = 0.38, 95% CI 0.23-0.63, P = 0.00002) of TCM-WM were much lower than WM.

Conclusion: Our results indicate that TCM-WM therapy may be superior to therapy with WM alone. However, due to the lower quality of the included studies, high quality of multicenter, large sample, randomized and double-blind controlled trials are needed to validate the result.

Keywords
Lupus nephritis, Traditional Chinese medicine, herbal medicine, meta-analysis

Introduction

Lupus nephritis (LN) is a frequent and severe organ involvement in patients with Systemic Lupus Erythematosus (SLE)[1]. As the most important complication of SLE, it is closely linked to morbidity and mortality and occurs in 25-75% of patients[2]. LN can be detected by finding abnormalities in blood tests, urinalysis, X-rays, ultrasound scans of the kidneys, and a kidney biopsy. It may cause acute or chronic renal failure, end-stage renal disease and nephrotic syndrome. Despite treatment, at least 10-15% of patients still progress to end-stage kidney disease requiring dialysis or kidney transplant[3].

The medical therapy for LN depends on the severity of the disease. For mild disease, corticosteroids are prescribed in general. While severe disease requires treatment with immunosuppressant agents. Intravenous cyclophosphamide (CTX) and mycophenolate mofetil are the two most commonly used agents in Western medicine[4]. However, mycophenolate mofetil may cause diarrhea, leukopenia and sepsis[5], while CTX may cause bone marrow suppression, hemorrhagic cystitis, myocardial necrosis and so on[6,7].

Traditional Chinese medicine (TCM) is a unique theoretical and methodological system incorporating concepts of causes, diagnosis and treatment[8]. Typical treatment in TCM is based on one or several herbs as the basic drug for a disease and all are combined by a distinctive method to form a prescription. Recently, some TCMs have been integrated with Western medicine to incorporate its etiological, diagnostic and therapeutic concepts.

Although the clinical manifestation of LN is variable and complicated, the basic pathogenesis is known in TCM. It was concluded that the etiology and pathogenesis of LN could be divided in two parts: 1) kidney-yin deficiency is the root cause of LN[9]; 2) retaining of stagnant toxin is the manifestation of LN[10]. TCM has
its own approach for preventing LN and has been used for long years. In clinical practice, TCM may be used alone or combined with conventional medicine.

A typical TCM prescription contains several herbs. In a special TCM prescription for LN, some herbs act on improving the blood flow in kidney, some reducing the relapse rate, some consolidating the therapeutic effect and so on [11]. However the chemical constituents, the quantities and the percentage of any impurities or contaminants in TCM are very precisely known. Incorrect use may lead to adverse events. Moreover, the number of patients was small and the therapy was different in most of those investigations. There is still no definite effective therapy of TCM-WM. Therefore, there is a need to systematically assess the effect and safety of TCM for treating LN.

Materials and methods

Publication selection

This review included RCTs (both individual and cluster randomisation). We were interested in comparisons of TCM-WM with WM in LN patients. The primary outcome of our meta-analysis were complete remission rate, total remission rate, relapse rate, the incidence of adverse reactions, mortality rate. While Serum creatinine (Scr) and urine protein before and after treatment were the second outcome of our meta-analysis.

Searches were applied to the following electronic databases: MEDLINE, EMBASE, the Cochrane Library, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), VIP, and WANFANG databases without language restrictions. The search strategy was based on combinations ‘Lupus nephritis or LN, Chinese medicine or Chinese herbs, Randomized’. We also modified the terms according to the different databases. Last query was updated on 28 February 2013. References of retrieved articles were cross-searched to identify any studies missed by the electronic search strategies.

Inclusion criteria for original studies were as follows: Firstly, only RCTs of TCM-WM comparing with WM for LN were included regardless of follow up, language or publication status. Secondly, the articles must be proven publication, sex, mean or median age, complete remission rate, total remission rate, relapse rate, the incidence of adverse reactions, mortality rate, average course of LN, treatment and control group interventions and assessment of outcomes. We manually searched the reference lists of the found articles. We also screened references from the relevant literature, including all of the identified studies, but no additional reviews and editorials. Disagreements were resolved by consensus between the two readers. In case of persistent disagreement, the final decision was made by our expert.

Statistical methods

All statistical analyses were performed using Statistical Analysis System software (Revman 5.2), and the P value for the overall effect <0.05 with two-tailed was considered statistically significant. The heterogeneity of all involved studies was assessed by I2. When it was lower than 50%, the studies with an acceptable heterogeneity were considered, and then the fixed-effects model with Mantel-Haenszel method was used; otherwise, a random effect model with the Der Simonian and Laird (DL) method was adopted. The combined RR were initially estimated using Forrest plots raphically. For each trial, the RR was estimated from the original article. If not available, we found the total numbers of events and the numbers of patients at risk in each group to determine the RR estimate.

Assessment of publication bias was investigated for each of the pooled study groups mainly by the Egger’s linear regression test. As supplement approach, the Begg’s rank correlation also was applied to assess the potential publication bias, when P <0.05 was considered that there was no publication bias in the study.

Results

A total of 614 references were retrieved for initial review using search strategies as described. 286 citations were excluded from analysis after the first screening based on abstracts or titles. After exclusion of the articles that were out of the scope of our meta-analysis, we identified 59 potential studies for detail evaluation. Upon further review, 2 studies of clinical report on the suspected LN patients was excluded upon further scrutiny and the other 17 case reports and 14 case-control studies were identified. There were 25 RCTs identified. Further exclusion included 7 studies identified as randomized sample, but not real randomized, 4 studies compared WM versus WM for LN and the other 3 studies which were duplicate publication. Finally, 12 studies were performed on the integration of TCM-WM versus WM in patients with LN. Selection process for the studies included in the meta-analysis are summarized in Figure 1. The main features of eligible studies in our meta-analysis are summarized in Tables 1.

Risk of bias in included studies
Most of the included studies were of poor methodological quality and at high risk of bias (Table 2). “randomization” was mentioned by all 12 studies, but none of them described the methods in details. After telephoning the study authors, it was determined that four studies used a random-number table, and one used computer software. All 12 studies did not used allocation concealment. After telephoning the study authors, it was established that none of the studies adopted an adequate allocation concealment method. Blinding of key study personnel (patients, investigators, assessors) was not used in any study. Withdrawals and loss of follow-up were only reported in 3 studies, and no trial reported an intention-to-treat analysis. Because we are unable to check the protocols, it was not possible to determine whether the primary and secondary outcomes of the studies were reported in a prespecified way, so there is a potential risk of selective reporting.

**WM treatment analysis**

All of the patients in the two groups received identical WM therapy using CTX and prednisone (PSN). The CTX therapy: 200 mg CTX was taken orally or injected every other day. The patients were given pulse CTX therapy (8-12 mg/kg/d for 2 days, repeated every 2 weeks to an accumulated dose which no more than 150 m/kg if they were complicated with distinctly active chronic glomerulonephritis, rapidly progressive glomerulonephritis or nephritic syndrome. After that, it was repeated every 3 months till the condition was stable for 1 year. The PSN therapy: latent nephritis, 30-40 mg/d; rapidly progressive glomerulonephritis patients was treated by pulse methylprednisolone(MP); chronic nephritis and nephritic syndrome, 1 mg/kg/d for 8weeks, then reduced it to maintenance dose 10 mg/d.

**TCM-MW treatment analysis**

The TCM-MW group were treated using different prescription according to their TCM diagnosis. 90.2% patients were treated using “langchuang prescription” including mikvetch, tangshen, polygonum muliflorum, Chinese angelica, suberect spatholobus stemetal, morus alba fructus et al. The herbs nourishing kidney yin (herb of yerbadetajo, rhizome of rehmannia,
fruit of glossy privet, fruit of barberry wolfberry, root of common anemarrhena, bark of boxthorn root et al) were used when pulse MP therapy were performed or high doses PSN initially administrated. The herbs benefiting vital energy and warming yang (dodderseed, leaf of epimedium, fruit of malyleu scufpea, root of milkvetch, tangshen, et al) were administrated when PSN reduced. The following is the rank of main herbs by administration frequency: herb of spreading hediyotis 86.2%, root of dan-shen 85.8%, radix arnebiae 80.6%, motherwort herb 80.2%, herbe of barbedskullicap 77.2%, radixpaeniae rubra 72.4%, centipede 72.1%, Szechwan lovge rhizome 67.5%, safflower64.6%, semen persicae61.3%.

**Complete remission rate**

12 studies reported the effect of TCM-WM comparing with WM on the complete remission rate (770 patients and 671 controls) 9 of the studies used "langchuang prescription" in their TCM-WM group while the left 3 were not. According to it, we divided them to two subgroups. There was no statistical heterogeneity among the studies. Thus, the fixed-effect model was used for statistical analysis. In “langchuang prescription” subgroup, the complete remission rate of TCM-WM group was higher than that of WM group (RR =1.61, 95%CI 1.38-1.88, P<0.00001). In “non-langchuang prescription” subgroup, the complete remission rate of TCM-WM group was higher than that of WM group (RR =1.56, 95%CI 1.02-2.39, P=0.004). The complete remission rate of TCM-WM group was higher than that of WM group (RR =1.58, 95%CI 1.4-1.78, P<0.00001) (Fig.2a).

**Total remission rate**

The total remission rate was reported in 12 studies. There was no statistical heterogeneity among the studies. In “langchuang prescription” subgroup and “non-langchuang prescription”, the total remission rate of TCM-WM group were higher than that of WM group (RR =1.18, 95%CI 1.13-1.24, P<0.00001), (RR =1.16, 95%CI 1.02-1.33, P=0.03) respectively. The total remission rate of TCM-WM group was higher than that of WM group (RR =1.18, 95%CI 1.13-1.24, P<0.00001) (Fig.2b).

**Relapse rate**

The relapse rate was reported in 8 studies. There was no statistical heterogeneity among the studies. Thus, the fixed-effect model was used for statistical analysis. In “langchuang prescription” subgroup and “non-langchuang prescription”, the relapse rate of TCM-WM group were lower than that of WM group (RR =0.31, 95%CI 0.22-0.45, P<0.00001), (RR =0.32, 95%CI 0.11-0.92, P=0.03) respectively. The total relapse rate of TCM-WM group was lower than that of WM group (RR =0.32, 95%CI 0.22-0.44, P<0.00001) (Fig.3a).

The incidence of adverse reactions

The incidence of adverse reactions was reported in 8 studies. There was no statistical heterogeneity among the studies. In “langchuang prescription” and “non-langchuang prescription subgroup”, the incidence of adverse reactions of TCM-WM group were lower than that of WM group (RR =0.47, 95%CI 0.40-0.55, P<0.00001), (RR =0.52, 95%CI 0.27-0.97, P=0.04) respectively. The total incidence of adverse reactions of TCM group was lower than that of WM group (RR =0.47, 95%CI 0.41-0.55, P<0.00001) (Fig.3b).

**Mortality rate**

The mortality rate was reported in 5 studies. There was no statistical heterogeneity among the studies. The fixed-effect model was used for statistical analysis. The total mortality rate of TCM group were lower than that of WM group (RR =0.38, 95%CI 0.23-0.63, P=0.00002).

**Scr and urine protein before and after treatment**

The Scr and urine protein before and after treatment was reported in 3 studies. We calculated the D-value about Mean and SD of Scr and urine protein before and after treatment. There was no statistical heterogeneity among the studies. The total descend range of Scr and urine protein of TCM group were higher than that of WM group (RR =2.46, 95%CI 1.80-3.54, P<0.00001), (RR =1.46, 95%CI 0.40-2.34, P<0.00001) respectively.

**Sensitivity analysis and publication bias**

The influence analyses revealed that none of the studies significantly affected the pooled RRs and CIs. When each study is sequentially removed and meta-analysis is repeated with the remaining studies, the pooled RR remain almost the same. Egger’s linear regression test and Begg’s test were used to examine publication bias. There was no evidence of publication bias for the analyses of complete remission rate, total remission rate, relapse rate (e.g. Funnel plot for the total remission rate about TCM-WM group and WM group treated LN, Fig.4).

Results of the level of evidence by GRADE system

We use GRADE profile 3.6 to assess the quality of design, risk of bias, inconsistency, indirectness, imprecision and other considerations of the main outcomes. The quality of the evidence for complete remission rate, complete remission rate-langchuang prescription, complete remission rate-non-langchuang prescription, total remission rate, total remission rate-langchuang prescription, total remission rate - langchuang prescription are all “LOW”(⊕⊕⊕). While, the quality of the evidence for relapse rate, relapse rate - langchuang prescription, relapse rate - non-langchuang prescription, the incidence of adverse reactions, the incidence of adverse reactions-langchuang prescription, the incidence of adverse reactions-non-langchuang prescription and mortality rate are all “MODERATE”(⊕⊕⊕⊕).
Figure 2. Meta-analysis of complete remission rate about TCM-WM group and WM group treated LN (2a)

Figure 3. Meta-analysis of total remission rate about TCM-WM group and WM group treated LN (2b)
Figure 4. Meta-analysis of relapse rate about TCM-WM group and WM group treated LN (3a)

Figure 5. Meta-analysis of the incidence of adverse reactions about TCM-WM group and WM group treated LN (3b)
Discussion

To assess accurately any potential benefits and risks in the treatment of LN, treatment of TCM must be scientifically evaluated. Our meta-analysis indicates that the complete remission rate and the total complete remission rate in TCM-WM group were higher than that in WM group, while relapse rate, the incidence of adverse reactions and mortality rate were lower than that in WM control group. We also find that after treatment, Scr and urine protein in TCM-WM group had a more significant decrease than that of WM group.

As for TCM is concerned, the pathogen of LN are yang evil, heat-evil and virulent fire-evil, which lead to the disorder of yin-yang balance, incoordination between vital energy and blood, obstruction of collaterals by blood stasis, virulent heat-evil hyperactivity. If heat-evil and virulent fire-evil stay long, they impair yin and involve viscera and tendon, then gradually cause branch asthenia and root asthenia. As for LN is concerned, kidney asthenia is root and virulent heat-evil is branch. Obstruction of collaterals by blood stasis is the pivotal of pathogenesis. Although virulent heat-evil and blood stasis is branch, they play quite an important role in the progression of LN. Both therapies of clearing away the heart, toxic materials and activating blood circulation to dissipate are aims of the special pathogenesis.

In our studies, 90.2% patients were treated using “langchuang prescription”. While the complete remission rate and total remission rate were higher, relapse rate and the incidence of adverse reactions were lower in “langchuang prescription” than in other prescriptions. It was more effective than that of other therapies and it had been widely accepted in China[12]. The medicine of invigorating vital energy, nourishing kidney-yin, benefiting vital energy can modulate immunity, stimulate hematopoiesis in bone marrow, reduce inhibitive effect of PSN to pituitary-adrenal axis and accelerate the release of cortex hormone. According to different TCM diagnosis, the treatment combined TCM can relieve side effects caused by PSN and CTX. Moreover, Dan-shen and Szechwan lovge rhizome in “langchuang prescription” can promote the product of metal proteinase and inhibit the expression of metal proteinase inhibitor and collagen. Therefore, the medicine of activating blood circulation to dissipate might improve hemodynamic status of the kidney, inhibit renal fibrosis and relieve immune inflammation.

In our meta-analysis, the side effects incidence in TCM-WM group (30.5%) was lower than that of WM group (65.8%). In summary, the TCM-WM treatment might have superiority compared with other therapies. In the published literature selected to our analysis, 91.3% patients in TCM-WM group were administrated medicine of activating blood circulation to dissipate, which suggested that these medicine are very important for LN treatment.

However, most of the studies are of poor methodological quality, there was no concealment and blinding of key personnel was not adopted. The quality of the evidence for complete remission rate, total remission rate, total remission rate are all “LOW”. While the quality of the evidence for relapse rate, relapse rate, the incidence of adverse reactions and mortality rate are all “MODERATE”.

In conclusion, TCM-WM therapy using medicine of clearing away heat and toxic materials and activating blood
circulation to dissipate can enhance complete remission rate and reduce recurrence rate and side effects might have superior to WM therapy. “langchuang prescription” in TCM might have superior to other prescriptions. Several limitations of the current studies could not be ignored. First, although we did not detect significant publication bias between studies, it is uncertain whether the cases are comparably representative. We attempted to minimise publication bias by making our literature search as complete as possible, however we could not account for unpublished studies, and missing information may reflect “negative” or more conservative outcomes, which represented potential selection bias. Second, most of the included studies were small and without formal sample size calculation. The results were likely to be underpowered. Third, LN has different stages or classes of severity, however most of the included studies don’t taken them into consideration, we can only get a comprehensive effect of TCM-WM on treating different stages of LN. Fourth, In some cases, different TCM interventions were grouped together for analysis. The results might have been compromised by the heterogeneity within each TCM intervention and by the study design. Fifth, the concept of TCM syndrome was not considered when analyzing the data, as some studies only targeted LN in a particular type of TCM symptom. Finally, the complete remission rate, total remission rate, relapse rate were all composite indexes in our meta-analysis. Although the judgement of the indexes are all based on similar laboratory and clinical signs, there may be some bias in the study. Therefore, the actual therapeutic effect might not have been fully captured. However, this conclusion should be interpreted cautiously since this analysis was ideally be performed on individual patient data. Further investigation into this subset of patients from other RCTs should pay more attention to blinding and allocation concealment. The results should be in accordance with international requirements of the CONSORT statement to conduct a comprehensive specification of the report. In the similar circumstances of safety and efficacy, the economic evaluation is an important indicator to determine the selection of the scheme in order to provide more evidence for the clinical decision. We are looking forward to more high quality researches in this field, the clinical effect of TCM-WM will be more clear.

Conclusions

Our meta-analysis shows that TCM-WM therapy may be superior to therapy with WM alone. High quality of multicenter, large sample, randomized and double-blind controlled trials are needed to validate the result.

Competing interests

The authors have no proprietary interest in any aspect of the study.

Authors’ contributions

Fangxiang Mu and Yi Jiang carried out the literature search and wrote the manuscript. Ronghua Zhang and Xiaochuan Hu reviewed titles, abstracts and papers for inclusion in the review. Dejun Jiang and Qinghua Zou assessed the quality of paper, Yang Meng and Feige Ao did the statistical analysis. All authors read and approved the final manuscript.

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