Meta-Analysis of Tripterygium Wilfordii Hook F in the Immunosuppressive Treatment of IgA Nephropathy

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Abstract

Objective Numerous Chinese patients with IgA nephropathy (IgAN) have benefited from Tripterygium wilfordii Hook F (TwHF) from two decades ago. However, to date there is no systematic evaluation of this remedy for IgAN.

Methods We conducted a meta-analysis of all eligible randomized clinical trials (RCTs) to assess the effect of TwHF on IgAN for the first time. In August 2009 a systematic search was performed among eight electronic databases. Review Manager (RevMan) version 5.0 was used.

Results (i) Four eligible RCTs with 188 participants were included; (ii) The validities of included RCTs were generally acceptable; (iii) TwHF brought about a favorable increase in complete remission (CR) (RR 1.53, 95%CI 1.09 to 2.16, I²=12%) and total remission (TR) (RR 1.27, 95%CI 1.08 to 1.48, I²=0%) compared with non-TwHF treatment; and this result was further confirmed by intention-to-treat analysis; (iv) Exploiting subgroup meta-analysis, TwHF led to significantly greater improvements of IgAN with non-nephrotic proteinuria with regard to the increase of CR (RR 1.80, 95%CI 1.21 to 2.68, I²=0%) and TR (RR 1.32, 95% CI 1.11 to 1.57, I²=0%), and decrease of urinary proteinuria excretion (UPE) (MD -467.41 mg/24h, 95%CI -633.99 to -300.82, I²=0%). Meanwhile, the renal function was well preserved (MD -2.66 μmol/L, 95%CI -9.26 to 3.94, I²=0%).

Conclusion Although the results of this meta-analysis should be interpreted with caution and warrant further investigation, TwHF was certainly a valuable and promising immunosuppressive remedy for IgAN, which was in accordance with the accruing evidence from numerous large clinical and experimental studies.

Key words: glomerulonephritis, IGA, tripterygium, drug therapy, meta-analysis

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Introduction

IgA nephropathy (IgAN) is an immune complex-mediated glomerulonephritis defined immunohistologically by the presence of glomerular IgA deposits accompanied by a variety of lesions identified histopathologically in the absence of systemic disease (1). IgAN still represents the majority of primary glomerular disease ranging from 45.26% (2) to 54.3% (3), and is the most common cause of end-stage renal disease (ESRD) in China (2, 4). The increasing incidence and poor outcome of IgAN result in a large expenditure of healthcare resources and a significant burden for patients and society. In terms of immunosuppressive therapy, medications including glucocorticoids, cyclophosphamide (CTX), leflunomide (LEF), cyclosporine A (CsA), and mycophenolate mofetil (MMF), have been used in IgAN treatment (5-9). Despite the clinical efficacy of these therapies,
many patients do not acquire clinically meaningful remis-

sion or they discontinue treatment because of various adverse

events. Furthermore, the relatively high cost of certain

new immunosuppressive drugs has hampered the access to

to these therapies in many patients with IgAN in developing
countries. Therefore, searching for both efficient and afford-
able medications is a pivotal target with respect to the im-

munosuppressive treatment of IgAN.

Tripterygium wilfordii Hook F (TwHF) is a member of the

Celastraceae family of perennial vine-like plants. In Tra-
ditional Chinese Medicine (TCM) TwHF has been widely

used to treat autoimmune and inflammatory diseases such as

rheumatoid arthritis (RA) (10-13). Exciting results derived

from non-randomized controlled trials (nRCTs) in China ul-

timately promoted the performance of RCTs in Western
countries, which have already demonstrated the efficacy and

safety of TwHF in the treatment of RA (14, 15). The signifi-
cant immunosuppressive therapeutic benefit of TwHF in pa-

tients with primary glomerulonephritis (GN) and nephrotic

syndrome (NS) has also been widely reported based on find-
ings in clinical trials (16-18). Recently a meta-analysis of

TwHF for idiopathic refractory NS in adults has been ac-

complished (19). It was found that TwHF indeed resulted in

a significant increase of complete remission (CR) [odds ratio

(OR) 2.81, 95% CI 1.26 to 6.30] and total remission (TR)

(OR 3.25, 95% CI 1.20 to 8.76) compared with CTX or pla-

cbo.

During the past two decades hundreds of thousands of

Chinese patients with IgAN have been successfully treated

with TwHF which were mainly reported by clinical retro-
spective or uncontrolled studies, just like the primitive situa-
tion of TwHF in RA treatment. In recent years a few RCTs

concerning the effect of TwHF on IgAN have been de-
dsigned (20-23), however, there is no systematic evaluation of

this remedy for IgAN. Thus, in this study we carried out a

meta-analysis of RCTs to assess the efficacy and safety of

TwHF in the treatment of IgAN. We expected that the re-

sults could expedite worldwide utilization of TwHF not only

for IgAN but also for other primary GN and even secondary

GN.

Materials and Methods

Inclusion and exclusion criteria

RCTs that evaluated the efficacy and safety of a special

preparation of TwHF on IgAN were included. Secondary

IgAN was excluded. The “special preparation” is defined as

ethyl acetate (EA) extract of peeled roots of TwHF or

chloroform-methanol extract of woody portion of roots of

TwHF which is also designated as TwHF multiglycoside

(TWG). Any other preparations of TwHF such as decoction

and formula were excluded. Meanwhile any other forms of

Chinese herbal medicine other than TwHF were excluded.

Studies were also excluded if any immunosuppressive drugs

other than glucocorticoids were investigated or served as

comparisons. We also excluded nRCTs, for example con-

trolled clinical trials (CCTs).

Search strategy

PubMed/MEDLINE, EMBASE, Cochrane Central Regis-
ter of Controlled Trials (CENTRAL), Science Citation Index

(SCI), Chinese Biomedical Literature Database (CBM), Chi-

nese science and technology periodicals databases (CNKI,
VIP, and Wan Fang) were searched (August 2009). The fol-

lowing medical subject heading items and free-text words

were used: glomerulonephritis, IgA, IgA glomerulonephritis,

and IgA nephropathy, Tripterygium, Tripterygium wilfordii,
Tripterygium wilfordii multiglycoside, and Tripterygium wil-
fordii Hook F, randomized controlled trial, controlled clin-
cial trial, randomized, randomly, placebo, and trial. The ele-

tronic search strategy described was performed to obtain the

titles and abstracts of studies that may be relevant to the re-

view. Two reviewers independently assessed retrieved ab-

stracts and, if necessary the full text, of these studies to de-
termine which studies satisfied the inclusion criteria. Data

extraction was also carried out by the same reviewers inde-

pendently using standard data extraction forms. Disagree-

ments were resolved in consultation with a third reviewer.

Study validity assessment

The commonly-used Jadad scale for assessing quality or

risk of bias for RCTs has been discouraged by the Cochrane

Collaboration (24). Thus, we evaluated the validity of stud-

ies using a specific tool which has recently been recom-

mended by the Cochrane Collaboration (24). This tool for

assessing risk of bias addresses such specific domains as se-
quence generation, blinding, incomplete outcome data, and

selective outcome reporting. Each domain comprises a de-

scription and judgement for each included study. The de-

scription provides a succinct summary from which judge-

dment of risk of bias can be made, whereas the judgement in-
volves answering a specific question for each domain. In all
cases, an answer “Yes” indicates low risk of bias, “No” indi-
cates high risk of bias, and “Unclear” indicates either lack of
information or uncertainty over the potential for bias.

Data collection and analysis

Data were extracted from all included studies in terms of

participant characteristics of the study sample, baseline of

study, and intervention characteristics for each group. Pri-

mary outcomes were remission rates of proteinuria, such as

complete remission (CR), partial remission (PR), and total

remission (TR). TR=CR+PR. CR was defined as proteinuria
<0.15-0.30 g/day with normal serum creatinine. PR was de-

fined as proteinuria <0.15-0.30 g/day and <1.0-2.0 g/day and

the decrease of protein excretion >50% accompanied by

stable serum creatinine (increase of serum creatinine <25%

of baseline). Secondary outcomes included the level of uri-
nary protein excretion (UPE), serum albumin, and serum

creatinine.
Statistics analysis

All statistics analyses were performed using Review Manager (RevMan) [Computer program] (Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). The results were expressed as risk ratio (RR) for dichotomous data, and mean difference (MD) for continuous data, with 95% confidence intervals (95% CI). Heterogeneity among included trials was analyzed using chi-squared (χ²) or Chi² test. If a p value of >0.10 indicated no heterogeneity across included trials, the Mantel-Haenszel (M-H) method in fixed-effect model was carried out for meta-analyses of dichotomous data and Inverse variance (IV) method in fixed-effect model for continuous data. Otherwise, M-H and IV methods in random-effect model were used for dichotomous and continuous data, respectively. The potential publication bias was examined by the funnel plot method.

Results

The details of characteristics of the four included studies are summarized in Table 1. We identified 11 RCTs involving TwHF in the treatment of IgAN. We excluded six studies in which other preparations of TwHF such as decoction and formula or other forms of Chinese herbal medicine were administered. One study comparing TwHF with LEF was also excluded. Thus, only four RCTs fulfilled the inclusion criteria of this meta-analysis (20-23). Three trials compared TwHF with non-TwHF in the treatment of IgAN with non-nephrotic proteinuria (20-22), and one trial compared TwHF with prednisone in the treatment of IgAN with NS (23).

Risk of bias of inclusion studies is summarized in Table 2. Adequate methods of allocation sequence generation were described in three studies where random number tables were used (21-23). Blinding was not confirmed, however, the outcome and outcome measurement were not likely to be influenced by lack of blinding. All four studies have low risk of bias concerning “incomplete outcome data”: no missing outcome data existed in two studies (20, 23), and missing outcome data were balanced in numbers and had similar reasons across the two intervention arms in other two studies (21, 22). Main outcomes (both primary and secondary outcomes) were all reported in three studies (20-22), whereas only primary outcomes were reported in one study (23). In a word, the overall level of included studies validity was acceptable.

Data for primary outcomes of CR, PR and TR at the end of studies were available in four trials (20-23) with a total
sample size of 188 participants (94 were assigned to the TwHF groups and 94 in non-TwHF groups) (Fig. 1). TwHF resulted in an increased CR and TR rate compared with controls (RR 1.53, 95%CI 1.09 to 2.16, $I^2$=12% for CR, and RR 1.27, 95%CI 1.08 to 1.48, $I^2$=0% for TR, respectively), but had no significant increase of PR (RR 1.01, 95%CI 0.69 to 1.49, $I^2$=0%) (Fig. 1). The result of an intention-to-treat analysis further confirmed this favorable effect of TwHF on TR (RR 1.23, 95%CI 1.06 to 1.48, $I^2$=0%) (Fig. 1). Subgroup analysis was also performed among three RCTs (20-22) which compared TwHF with non-TwHF in the treatment of IgAN with non-nephrotic proteinuria. There was still a significant increase in CR and TR (RR 1.80, 95%CI 1.21 to 2.68, $I^2$=0% for CR, RR 1.32, 95%CI 1.11 to 1.57, $I^2$=0% for TR, respectively) but no significant increase in PR (RR 0.94, 95%CI 0.62 to 1.42, $I^2$=0%). These results indicated that the direction of effect of subgroup analysis was the same as that of total analysis, with the effect size being greater than that of total analysis.

Secondary outcomes of UPE, serum albumin, and serum creatinine were reported in three RCTs which all compared the effects of TwHF with non-TwHF for IgAN with non-nephrotic proteinuria (Fig. 2) (20-22). UPE decreased with the treatment of IgAN with non-nephrotic proteinuria. There were no significant differences in serum albumin and creatinine (MD -2.66 μmol/L, 95%CI -9.26 to 3.94, $I^2$=0% for creatinine, respectively) (Fig. 2).

Adverse events and withdrawal were recorded in three trials. No severe adverse events except for one withdrawal due to a serious adverse event (severe diarrhea) in the TwHF group. There were no significant differences in adverse events and withdrawal between the groups (RR 0.97, 95%CI 0.64 to 1.48, $I^2$=88% for withdrawal, $I^2$=88% for adverse events).
(A) Urinary protein excretion

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Tripterygium wilfordii</th>
<th>Non-tripterygium wilfordii</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Chen 2009</td>
<td>925.2</td>
<td>341</td>
<td>8</td>
<td>1,429.4</td>
</tr>
<tr>
<td>Shen 2009</td>
<td>680</td>
<td>440</td>
<td>26</td>
<td>1,110</td>
</tr>
<tr>
<td>Yang 2008</td>
<td>800</td>
<td>500</td>
<td>38</td>
<td>1,300</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>72</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.17, df = 2 (P = 0.92); I² = 0%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 5.50 (P &lt; 0.00001)</td>
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</table>

(B) Serum albumin

<table>
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<th>Study or Subgroup</th>
<th>Tripterygium wilfordii</th>
<th>Non-tripterygium wilfordii</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Chen 2009</td>
<td>45.5</td>
<td>8.2</td>
<td>8</td>
<td>39.4</td>
</tr>
<tr>
<td>Shen 2009</td>
<td>38.92</td>
<td>2.76</td>
<td>26</td>
<td>40.33</td>
</tr>
<tr>
<td>Yang 2008</td>
<td>45.8</td>
<td>6.4</td>
<td>38</td>
<td>41.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>72</strong></td>
<td></td>
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</tr>
<tr>
<td>Heterogeneity: Tau² = 16.03; Chi² = 17.28, df = 2 (P = 0.0002); I² = 88%</td>
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<tr>
<td>Test for overall effect: Z = 0.91 (P = 0.36)</td>
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</table>

(C) Serum creatinine

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Tripterygium wilfordii</th>
<th>Non-tripterygium wilfordii</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Chen 2009</td>
<td>96.5</td>
<td>21.6</td>
<td>8</td>
<td>93</td>
</tr>
<tr>
<td>Yang 2008</td>
<td>88.5</td>
<td>48.5</td>
<td>38</td>
<td>87.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>72</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.54, df = 2 (P = 0.76); I² = 0%</td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.79 (P = 0.43)</td>
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</table>

Table 3. Number of Adverse Events and Withdrawal

<table>
<thead>
<tr>
<th>Items</th>
<th>TwHF (n=76)</th>
<th>Non-TwHF (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry cough</td>
<td>9 (12%)</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Elevated transaminase</td>
<td>7 (9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>4 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>4 (5%)</td>
<td>3 (4%)</td>
</tr>
</tbody>
</table>

Discussion

To our best knowledge, this is the first meta-analysis to appraise the efficacy and safety of TwHF in the treatment of IgAN. Our assessment was based on four included RCTs that were all conducted within the past two years. All of the nRCTs including CCTs were excluded, and thus the strength of this meta-analysis implicated acceptable standards and methodology. In this analysis, about 84% (79/94) of patients with IgAN could acquire significant therapeutic benefits (total remission rate of proteinuria) from TwHF.
The results of this meta-analysis indicated that patients with IgAN could benefit from TwHF, especially for those with non-nephrotic proteinuria (20-22). Compared with non-TwHF treatment, TwHF led to significantly greater improvement in terms of increase of CR and TR, and decrease of UPE. Meanwhile, the renal function was well preserved. Moreover, the directions of effects of TwHF on IgAN with non-nephrotic proteinuria were consistent among these three included studies.

In the trial which compared TwHF with prednisone in the treatment of IgAN with NS (23), there was no significant difference in terms of CR (44.4% of TwHF group, 50% of prednisone) and TR (77.8% of TwHF group, 72.2% of prednisone). The result indicated that the efficacy of TwHF on IgAN with NS was comparable with that of prednisone. However, more and larger RCTs should be encouraged and further meta-analyses are warrant to confirm these results.

It is noteworthy that the results of large amounts of excluded nRCTs and other observational clinical studies were generally concordant with that of the included RCTs with respect to the total number of IgAN patients whose clinical conditions were significantly improved after TwHF treatment. In the field of medical practice hundreds of thousands of Chinese patients with IgAN have benefited from TwHF, which manifested high efficacy and low toxicity. More important, TwHF have indeed decreased medical burden due to the suppression of cytoskeleton disruption, and nephrin and podocyte abnormal expression (25). These effects were associated with suppression of reactive oxygen species (ROS) generation and restoration of RhoA signaling activity (25). It has been demonstrated that ROS activation can stimulate the renin-angiotensin system (RAS) and play a pivotal role in the development of IgAN (26). It is conceivable that TwHF with the capacity of ROS inhibition and subsequently RAS blockage could retard the development and progression of IgAN. Mattii et al (27) demonstrated that RhoA activity represented a key molecule in the cellular pathogenetic dynamics of renal fibrosis in IgAN. TwHF may also exert anti-proteinuric and antifibrotic potential on IgAN via restoring the normal RhoA signaling pathway.

In previous studies, the release of inflammatory and fibrogenic factors in glomerular mesangial cells, such as monocyte chemotactic peptide-1 (MCP-1), interleukin-6 (IL-6) and transforming growth factor-beta (TGF-beta), has proved a critical downstream event in the pathogenesis and progression of IgAN (28, 29). Recently, the effects and mechanisms of TWG on both experimental acute GN and chronic phase of progressive GN have been investigated (30, 31). TWG could ameliorate proteinuria, lessen mesangial injury and improve renal function in both acute and chronic GN. TWG significantly attenuated the glomerular expression of platelet-derived growth factor (PDGF), MCP-1, and IL-6 in experimental acute GN. In addition, the mechanisms underlying the effect of TWG on experimental chronic progressive GN involved suppression of TGF-beta, IL-2, and Interferon-gamma (IFN-gamma), as well as inhibition of glomerular infiltration of inflammatory cells. These findings suggested that TwHF was a potential immunosuppressive agent for various injurious factors observed in human IgAN.

While the results of this meta-analysis are promising, it should be interpreted with caution and warrants further investigation for several reasons. First, the relatively small sample size (188 participants) may influence the extent of the effect of TwHF. But it could have no power to impact the direction of effect of TwHF on IgAN because the accruing clinical trials data and experimental studies data generally endorse the effectiveness of TwHF on IgAN. Secondly, the follow-up periods (6 months) were relatively short and thus inadequately powered to detect the long-term outcomes of renal function deterioration and more serious adverse events of reversible amenorrhea in women and infertility in men. However, this issue was attributed to the fact that all of the included RCTs with high standards and acceptable methodology were conducted within the most recent two years.

Taken together, TwHF may be efficient and safe for the clinical treatment of IgAN with either non-nephrotic proteinuria or NS, and the mechanisms underlying the dramatic antiproteinuric and immunosuppressive effects of TwHF could be multiple. To further verify the current results from this meta-analysis, well-designed RCTs with high-quality study design are still warrant. A long-term study data from clinical trials will need to be systematically assessed to ascertain the long-term efficacy and toxicity of TwHF on IgAN.

References


