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Calcineurin inhibitor therapy in combination with *Tripterygium wilfordii* polyglycoside tablets for idiopathic membranous nephropathy

A retrospective clinical observation

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Abstract

To compare the efficacy and safety of calcineurin inhibitor (CNI) and *Tripterygium wilfordii* polyglycoside tablets (TWPs) in treating idiopathic membranous nephropathy (IMN) with CNI and glucocorticoids (GCs).

Data of patients with IMN who were treated with CNI+TWPs (TWP group) or CNI+GCs (GC group) and followed up for more than 12 months at the Affiliated Hospital of Shandong University of Traditional Chinese Medicine from 2017 to 2020 were retrospectively analyzed. The 24-h urine protein (24hUP), serum albumin (ALB), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), serum creatinine, alanine aminotransferase, and aspartate transaminase levels on the third, sixth, ninth, and twelfth months of treatment and phospholipase A2 receptor (PLA2R) level before and after treatment were compared in both groups.

We recruited 64 patients who were assigned to either the GC group (n = 31) or TWP group (n = 33). No difference in baseline indicators between the two groups were observed ($P > .05$). After 12 months, the 24hUP levels of both groups significantly decreased compared with that at baseline ($P < .01$). At the end of the sixth month, 24hUP of the TWP group were less and reduced more quickly than those in the GC group ($P < .05$), but there is no difference at the other time point ($P > .05$). After treatment, the number of patients who up to the standard of TG and the ALB levels in both groups increased ($P < .05$), the LDL-C levels and the number of patients positive for PLA2R in both groups were reduced ($P < .05$), and no significant difference was observed in the overall changes of 24hUP, ALB and LDL-C levels, TG compliance rate, and PLA2R positive rate between both groups ($P > .05$). During treatment, no patient in either group had hepatorenal dysfunction, one case in the TWP group and two cases in the GC group experienced side effects, but no apparent difference in the side effects were observed between both groups ($P > .05$).

Two therapeutic schemes have the advantage of reducing urinary protein excretion in patients with IMN. Compared with CNI +GCs, CNI+TWPs have high efficiency and is widely applied, which might be considered as an optimum therapy in the future.

Abbreviations: 24hUP = 24-h urine protein, ALB = serum albumin, ALT = alanine aminotransferase, AST = aspartate transaminase, CNI = calcineurin inhibitor, CR = complete remission, CsA = cyclosporine A, GCs = glucocorticoids, IMN = idiopathic membranous nephropathy, KDIGO = Kidney Disease: Improving Global Outcomes, LDL-C = low-density lipoprotein cholesterol, MN = membranous nephropathy, NS = nephrotic syndrome, PLA2R = phospholipase A2 receptor, Scr = serum creatinine, SMN = secondary membranous nephropathy, TAC = tacrolimus, TG = triglyceride, TWPs = *Tripterygium wilfordii* polyglycoside tablets.

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1. Introduction

Membranous nephropathy (MN) is a common case of nephrotic syndrome. According to etiology, MN can be divided into idiopathic membranous nephropathy (IMN) and secondary membranous nephropathy (SMN). IMN accounts for 70% to 80% of MN,[1] including uncertain causes. The disease is characterized by an apparent thickening of glomerular capillary walls, which is derived from the subepithelial deposition or in situ formation of immune complexes[2]; therefore, immunosuppressive agents are considered the best choice. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline[3] recommends low-dose glucocorticoids (GCs) combined with cytotoxic drugs or novel immunesuppressants to treat IMN. A calcineurin inhibitor (CNI) combined with GC is regularly used in clinical treatment. In practical terms, GC should be forbidden or used with caution in patients with an underlying disease, such as osteonecrosis of the femoral head and diabetes mellitus, and in several patients sensitive to GC because of the influences of metabolism. Due to prolonged therapy and chronic efficacy, some patients easily lose hope and have low compliance. Therefore, it is necessary to develop a rapid, effective, and widely used therapy in patients with IMN to increase their enthusiasm to treatment. *Tripterygium wilfordii* polyglycoside tablets (TWPs) are extracted from *Tripterygium wilfordii* Hook, mainly composed of *Tripterygium* diterpenoids and *Tripterygium wilfordii* alkaloids. TWP could cure IMN through the direct action of anti-inflammatory, immunosuppressive, and protective podocytes. It is reported that tacrolimus (TAC) combined with TWP is effective in treating patients with IMN[4]; however, only a small number of clinical observations about CNI and TWP for IMN treatment are available. This study aimed to compare the efficacy and safety of CNI and TWP in patients with IMN with CNI and GC treatment. As mentioned earlier, CNI in combination with TWP may be considered an optimum therapy.

2. Materials and methods

2.1. Patients

This retrospective clinical study was conducted at the Affiliated Hospital of Shandong University of Traditional Chinese Medicine. Patients with IMN hospitalized from March 2017 to March 2020 were recruited.

Inclusive criteria were as follows:

(1) patients aged 18 to 70 years,
(2) a biopsy-proven IMN (stage I–IV),
(3) 24hUP level >3.5 g/24 h accompanied by serum albumin (ALB) <30 g/L,
(4) estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2,
(5) followed up more than 12 months,
(6) treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for more than 3 months before or after renal needle biopsy, which failed to improve condition.

Exclusive criteria were as follows:

(1) patients unsigned informed consent or nonadherence to the therapy,
(2) patients with secondary nephrotic syndrome (malignancy, drug use, etc) and/or pathological manifestation of kidney disease (renal interstitial fibrosis >50%),
(3) patients with SMN due to hepatitis, malignancy, systemic lupus erythematosus, autoimmune diseases, chronic inflammatory disease, diabetes mellitus, etc;
(4) patients with other serious mental or physical problems.

3. Methods

3.1. Medication regimens

Two groups of patients were given Chinese medicine and basic treatment according to their condition, such as lowering blood pressure, adjusting lipid levels, preventing blood clots, and protecting hepatic function. Simultaneously, all patients were given TAC or cyclosporine A (CsA) orally. The specific way of taking this medication was as follows: Patients who take TAC start with a dose of 0.03 to 0.05 mg/kg/day, divided into two doses at 12-h intervals, taken 1 hour before meals. The blood TAC concentration is monitored 2 weeks later, and the dosage adjusted according to the whole blood concentration, with a target of 5 to 10 ng/mL throughout the first 6-month therapy period. As for CsA, the starting dose is 2.5 to 6 mg/kg/day, with a blood CsA concentration of 125 to 175 ng/mL throughout the first 6-month therapy period. The remaining method of taking CsA are essentially the same with that for TAC. After gradual alleviation of the illness for maintenance, TAC/CsA treatment was reduced. TAC/CsA was tapered by 1/3 to 1/4 every 6–8 weeks. Beyond that, patients in the TWP group were given TWPs (Jiangsu MEITONG Pharmaceutical Co., Ltd.) 40 mg each time, three times a day, after meals, for 4 weeks initially, then 2 weeks, and finally every other 2 weeks. As for GCs, prednisone was initially given orally at 0.5 mg/kg/day, 2 weeks after the clinical remission and was tapered to 5 mg every 2 weeks to 10 mg/day and to a maintenance dose of 10 mg/day. Methylprednisolone was given orally at 0.4 mg/kg/day initially, 2 weeks after the clinical remission and was tapered to 4 mg every 2 weeks to 8 mg/day and to a maintenance dose of 8 mg/day.

3.2. Outcome measures

Patients were scheduled for an initial visit and follow-up visits before treatment and at the third, sixth, ninth, and twelfth months of treatment. At each visit, the 24hUP level was measured through the biuret assay; the ALB, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), serum creatinine (Scr), alanine aminotransferase, and aspartate aminotransferase levels were measured using an automatic biochemical analyzer, and the phospholipase A2 receptor level was measured through immunofluorescence detection before and after treatment. All indicators were recorded at each visit. In addition, patients were asked to report any symptoms and side effects during the follow-up visit or immediately when they occur, such as irregular

menstruation, liver function injury, and gingival hyperplasia. In the first 6 months, the levels of TAC or CsA were examined.

3.3. Clinical curative effect evaluation

Complete remission (CR) was achieved when the 24hUP level was <0.3 g/24 h and the ALB level was ≥40 g/L with stable renal function. Partial remission (PR) was achieved when the 24hUP level was <3.5 g/24 h and 50% lower than baseline indicator and ALB level was ≥30 g/L with stable renal function. Non-responders (NRs) had a 24hUP level ≥3.5 g/24 h or more than half of the baseline indicator and an ALB level <30 g/L. The overall effective rate = (CR + PR)/(CR + PR + NR) × 100%.

3.4. Statistical analysis

Analyses were performed using SPSS Statistics, version 25.0 (IBM). Quantitative data, fitted by normal function, were presented in $\overline{x} \pm S$. Differences of quantitative parameters between the two groups were assessed using the *t*-test, as appropriate. Moreover, qualitative results were compared using chi-square test. $P < .05$ was considered statistically significant.

4. Results

4.1. Comparison of baseline indicators

A total of 64 patients with biopsy-proven IMN were included, with 31 patients in the GC group, including 24 males and 7 females, and 33 in the TWP group, including 23 males and 10 females. The patients' average age in the GC group was 45.32 ± 8.80 years and those in the TWP group was 47.61 ± 10.17 years. The patients' baseline indicators were compared, and no significant difference was found between the two groups ($P > .05$) (Table 1).

4.2. Comparison of 24hUP levels

During treatment, the 24hUP levels of the two groups were significantly decreased compared with that at baseline. From baseline to the end of the twelfth month, the 24hUP levels decreased from 6.16 ± 2.32 g/24 h to 0.72 ± 0.92 g/24 h ($P < .01$) in the GC group and from 6.85 ± 1.79 g/24 h to 0.75 ± 1.00 g/24 h ($P < .01$) in the TWP group. At the end of third, ninth, and twelfth months, the rate of change and the 24hUP levels were all comparable between the two groups ($P > .05$). At the end of the sixth month, the 24hUP levels of the TWP group were less and reduced more quickly than those of the GC group ($P < .05$), showing that the level of 24hUP in the TWP group decreased faster and earlier than that in the GC group. The 24hUP levels during the 12-month treatment period are shown in Table 2 and Figure 1.

Table 1

Comparison of baseline indicators.

Baseline indicators	GC group	TWP group	*P*
Gender (male/female)	24/7	23/10	.485
Age (years)	45.32 ± 8.80	47.61 ± 10.17	.342
24hUP (g/24 h)	6.16 ± 2.32	6.85 ± 1.79	.190
ALB (g/L)	27.56 ± 1.69	26.83 ± 1.84	.106
TG (mmol/L)	2.20 ± 0.66	2.06 ± 0.53	.359
LDL-C (mmol/L)	4.08 ± 0.86	4.11 ± 0.69	.878
Scr (μmol/L)	64.61 ± 11.04	61.09 ± 12.51	.239
AST (U/L)	20.92 ± 7.71	18.42 ± 4.60	.119
ALT (U/L)	22.07 ± 11.33	18.91 ± 6.37	.170
PLA2R (+/−)	29/2	28/5	.265

There were no significant differences between the GC group and the TWP group ($P > .05$).
24hUP = 24-h urine protein, ALB = serum albumin, ALT = aspartate aminotransferase, AST = alanine aminotransferase, GC = glucocorticoid, LDL-C = low-density lipoprotein cholesterol, PLA2R = phospholipase A2 receptor, Scr = serum creatinine, TG = triglyceride, TWP = *Tripterygium wilfordii* polyglycoside tablet.

Table 2

Comparison of 24hUP.

Time	GC group (g/24 h)	TWP group (g/24 h)	P1	P2
Third month	2.97 ± 1.20	3.28 ± 1.01	0.268	0.385
Sixth month	2.09 ± 1.52	1.45 ± 0.92	0.043*	0.003**
Ninth month	1.18 ± 1.74	1.12 ± 1.05	0.873	0.121
Twelfth month	0.72 ± 0.92	0.75 ± 1.00	0.908	0.165

P1: comparison of 24hUP between the two groups at each time point.
P2: comparison of the differences of all 24hUP levels at each time point from their baseline between the two groups.
* A significant difference in 24hUP levels between the two groups at sixth month of therapy, $P < .05$.
** The amount of 24hUP reduction in TWP group is larger than that in GC group at sixth month of therapy, $P < .05$.
24hUP = 24-h urine protein, GC = glucocorticoid, TWP = *Tripterygium wilfordii* polyglycoside tablet.

4.3. Comparison of ALB levels

During treatment, the ALB levels of the two groups were significantly increased compared with that at baseline. During 12 months of therapy, the ALB levels increased from 27.56 ± 1.69 g/L to 39.52 ± 3.92 g/L in the GC group and from 26.83 ± 1.84 g/L to 40.01 ± 3.63 g/L in the TWP group. A significant difference in the ALB levels before and after treatment in each group was observed ($P < .05$). The increases of ALB levels in the GC group continued throughout the treatment and that in the TWP group focused on the first 9 months. The total increase of ALB levels in the TWP group was larger than that in the GC group, but no significant difference was observed between the two groups in all time points ($P > .05$). The ALB levels during the 12-month treatment period are shown in Table 3.

4.4. Comparison of LDL, TG, and Scr levels

After treatment, the LDL-C levels decreased in both the GC and TWP groups, and a statistically significant difference was observed ($P < .05$). As TG level, the number of people who up to the standard from 7 to 26 in the GC group, and 7 to 27 in the TWP group, no difference was found in two groups ($P > .05$). No significant fluctuations in the Scr level were observed ($P > .05$). The LDL-L, TG, and Scr levels during the 12-month treatment period are shown in Table 4.

4.5. Comparison of phospholipase A2 receptor levels

After the 12-month treatment, 28 patients had a negative result and 3 patients a positive result in the GC group, with a positive rate change of 93.5% to 9.7%. As for the TWP group, 31 patients had a negative result and 2 patients a positive result, with positive rate change of 84.8% to 6.1%. The positive rate in the TWP group changed less frequently compared with that in the GC group, but the difference was not statistically significant ($P > .05$) (Table 5).

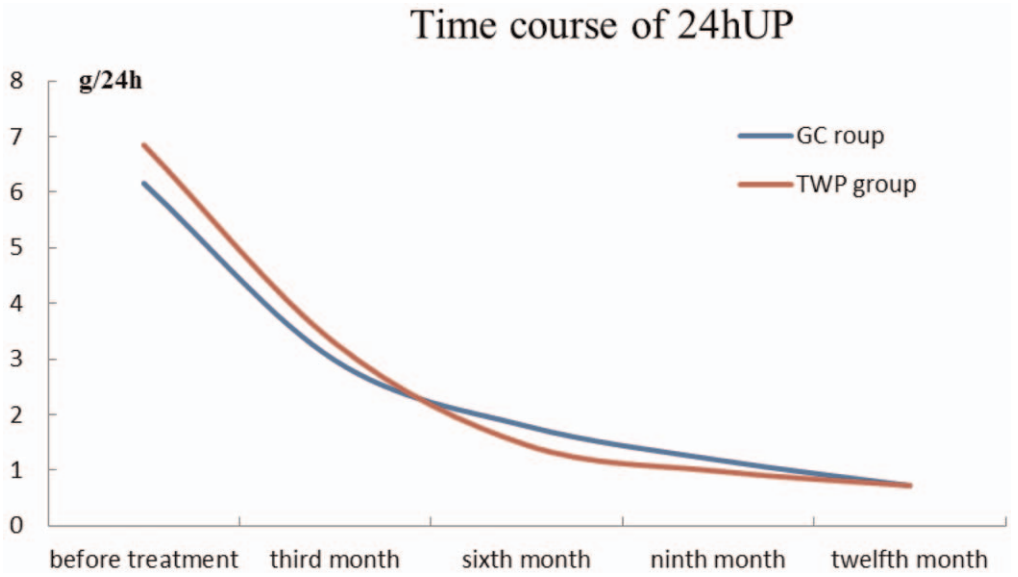

Figure 1. Estimated marginal means of time course of 24hUP. This graph indicates the 24hUP trend of the patients in the two groups worked out by curve estimation of regression. The most suitable equation of the GC group is Compound, Growth, and Exponential, and the R^2 are 0.636. The most suitable equation of the TWP group is Cubic, and the R^2 is 0.784. And there is a statistically significant difference in the trend of these two folds ($P < .05$), which work out by Repeated Measures.

Table 3

Comparison of ALB.

Time	GC group (g/L)	TWP group (g/L)	*P*
Third month	33.17 ± 3.05*	32.25 ± 2.22*	.167
Sixth month	36.68 ± 2.73*	36.77 ± 3.10*	.904
Ninth month	38.24 ± 2.99*	39.38 ± 3.21*	.147
Twelfth month	39.52 ± 3.92*,**	40.01 ± 3.63**	.608

P: Comparison of the ALB levels between the two groups at each time point.
* Compared with the ALB levels at last time in the same group, $P < .05$.
** Compared with baseline indicators, $P < .05$.
ALB = serum albumin, GC = glucocorticoid, TWP = *Tripterygium wilfordii* polyglycoside tablet.

4.6. Comparison of clinical curative effect evaluation

After the 12-month treatment, treatment in 29 patients was effective and 2 patients were nonresponders in the GC group, with overall effectivity rate of 93.55%. As for the TWP group, the treatment in 31 patients were effective, and 2 patients were nonresponders, with an overall effectivity rate of 93.94%. The TWP group had a higher overall effectivity rate compared with that in the GC group, but the difference was not statistically significant ($P > .05$) (Table 6).

4.7. Comparison of side effects

Severe infections in 1 patient were observed in the GC group, with the patient's condition improving after Western medicine conventional symptomatic treatment. In addition, loose teeth in 1 patient were observed in the GC group, and exacerbation of the patient's condition was not observed upon increasing the calcium dosage, supplementation with vitamin D, and treatment in the department of stomatology. Irregular menstruation was observed in 1 patient in the TWP group, with the patient's condition improving after administration of Chinese medicine. The patients in the two groups were not found to have abnormal liver function and serious life-threatening complications during treatment. No significant difference in the side effects between the two groups were observed ($P > .05$).

5. Discussion

Based on the pathogenesis of IMN, immunosuppressants are critical in therapy. It would be better to take immunosuppressants early if patients with IMN were characterized with NS.[5] At present, clinical practice guidelines recommend low-dose GC combined with cytotoxic drugs or novel immunosuppressants to

Table 4

Comparison of LDL, TG, and Scr.

	LDL-C (mmol/L)		TG (mmol/L)		Scr (μmol/L)	
	GC group	TWP group	GC group	TWP group	GC group	TWP group
Third month	3.39 ± 0.78	3.46 ± 0.81	1.92 ± 0.89	1.84 ± 0.52	65.08 ± 12.08	61.97 ± 8.26
Sixth month	2.99 ± 0.85	2.97 ± 0.89	2.04 ± 1.50	1.69 ± 0.60	64.98 ± 9.96	63.82 ± 7.69
Ninth month	2.79 ± 0.95	2.70 ± 0.93	1.79 ± 0.83	1.51 ± 0.48	63.25 ± 11.93	61.79 ± 6.58
Twelfth month	2.62 ± 1.36*	2.44 ± 0.90*	1.53 ± 0.75*	1.34 ± 0.47*	63.10 ± 11.24	62.59 ± 6.72

* Compared with baseline indicators, the difference had statistical sense ($P < .05$).
GC = glucocorticoid, LDL-C = low-density lipoprotein cholesterol, Scr = serum creatinine, TG = triglyceride, TWP = *Tripterygium wilfordii* polyglycoside tablet.

Table 5

Comparison of PLA2R.

	GC group	TWP group	*P*
Before treatment (+/−)	29/2	28/5	.265
After treatment (+/−)	3/28	2/31	.590

*There was no difference between the two groups, $P > .05$.
GC = glucocorticoid, PLA2R = phospholipase A2 receptor, TWP = *Tripterygium wilfordii* polyglycoside tablet.

Table 6

Comparison of clinical curative effect evaluation.

Group	Total	CR	PR	NRs	Overall effective rate
GC group	31	12	17	2	93.55%*
TWP group	33	19	12	2	93.94%

* There was no difference between the two groups, $P > .05$.
CR = complete remission, GC = glucocorticoid, NRs = nonresponders, PR = partial remission, TWP = *Tripterygium wilfordii* polyglycoside tablet.

cure IMN. *Tripterygium* diterpenoids and *Tripterygium wilfordii* alkaloids are the main active constituents of *Tripterygium wilfordii* Hook. A meta-analysis that included 716 patients confirms the clinical effects of TWP combined with conventional medical therapy or immunosuppressants in curing IMN.[6]

This study is a retrospective study comparing the combined application of TWP and CNI in treating IMN with those of GC and CNI. Sixty-four patients were enrolled, the observation period was 12 months. At the end of the treatment, the 24hUP levels were comparable between the two groups ($P > .05$). However, the 24hUP levels of the TWP group were less than those of the GC group ($P < .05$) at the end of the sixth month, showing that the levels of 24hUP in the TWP group decreased faster and earlier than that in the GC group. During the entire observation period, the liver and kidney functions of the patients in the TWP group and the GC group were relatively stable, conditions of hypoproteinemia and hyperlipidemia improved, and adverse effects occasionally occurred, which can improve after treatment. Compared with the GC group, no more adverse effects were found in the TWP group, indicating that the overall safety of TWP is not worse than that of GC.

The mechanism of treating IMN with TWP mainly consider the following aspects:

(1) *Tripterygium* diterpenoids have a direct protective effect on podocytes, maintain and repair the integrity of the glomerular basement membrane charge barrier[7,8] and block the apoptotic effect of podocytes,[9] decreasing glomerular permeability and reducing urinary protein excretion.
(2) *Tripterygium* diterpenoids could suppress the immune system by inhibiting the p38MAPK pathway.[10]
(3) *Tripterygium* diterpenoids could prevent the epithelial immune complex from depositing.[7]
(4) *Tripterygium* diterpenoids and *Tripterygium wilfordii* alkaloids could enhance the effects of endogenous GC.[11]

Compared with GC, the broader range of targets for the action of TWPs may account for their rapid onset of action. And according to the literature, though *Tripterygium wilfordii* Hook can inhibit T cell proliferation, it does not influence thymocytes. *Tripterygium wilfordii* Hook could inhibit a part of immunoreaction, which was the causation of illness, but not inhibit the immunoreaction excessively, so it could not decrease the resistance of patients who took TWP.[12]

In summary, the combination of TWPs with CNI for IMN has the advantages of rapid onset of action, definite efficacy, safety, and broad applicability. And it is a new treatment choice for patients with IMN who are unwilling or unable to take GC and have lost hope. Moreover, we hope for its widespread applications, to boost patients' confidence, improve patients' compliance, and avoid the side effects of GC, such as disruption of glucose and lipid metabolism and low resistance. However, TWPs have gonadal suppressive effects and should prescribe with caution in patients with fertility needs. Its overall effectivity rate in this study is higher than that in some studies. As reported previously, it may be due to the administration of traditional Chinese medicine. The study has a small sample, which may have caused a sampling bias. Moreover, this study is a retrospective clinical observation, which may not be thoroughly randomized and may restrict the reliability of the conclusion.

Author contributions

YG designed the study; YL, ZG, and LZ performed the research, analyzed data, and wrote the paper.
Conceptualization: Ying Gao.
Data curation: Yingying Liu.
Formal analysis: Zhaoan Guo, Lei Zhang.
Writing – original draft: Zhaoan Guo.

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