Systematic Review and Meta-Analysis

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Efficacy and safety of tacrolimus monotherapy versus tacrolimus-corticosteroid combination therapy for idiopathic membranous nephropathy

A meta-analysis

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Abstract

Objective: The objective of this meta-analysis was to compare the efficacy and safety of tacrolimus (TAC) monotherapy versus TAC-corticosteroid combination therapy in idiopathic membranous nephropathy (IMN) patients.

Methods: Databases including PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure, and Wanfang database were searched from inception to January 10, 2021. Eligible studies comparing TAC monotherapy and TAC-corticosteroid combination therapy in IMN patients were included. Data were analysed using Review Manager Version 5.3.

Results: Seven studies were included in the meta-analysis. One randomized controlled trial and six cohort studies involving 372 patients were identified. Compared with TAC monotherapy, TAC-corticosteroid had a higher total remission at the sixth month (odd ratio (OR) 0.49, 95% confidence interval (CI) 0.31–0.78, $P < .01$). The two therapy regimens had similar complete remission rates (OR 0.79, 95% CI 0.43–1.48, $P = .47$) at the sixth month and similar relapse rates (OR 1.44, 95% CI 0.70–2.92, $P = .32$). TAC-corticosteroid combination therapy had a higher incidence of infection (OR 0.38, 95% CI 0.18–0.81, $P = .01$). The two therapy regimens had similar incidences of gastrointestinal symptoms (OR 0.96, 95% CI 0.34–2.70, $P = .93$), abnormal aminotransferase (OR 0.90, 95% CI 0.34–2.38, $P = .84$), and glucose intolerance (OR 0.58, 95% CI 0.32–1.07, $P = .08$).

Conclusion: TAC-corticosteroid combination therapy had a higher total remission rate at the sixth month but had a higher incidence of infection than TAC monotherapy in the treatment of IMN. The two therapeutic regimens had similar relapse rates.

Abbreviations: CIs = confidence intervals, CNI = calcineurin inhibitors, CR = complete remission, CTX = cyclophosphamide, IMN = idiopathic membranous nephropathy, KDIGO = Kidney Disease Improving Global Outcomes, OR = odds ratios, PR = partial remission, RCTs = randomized controlled trials, TAC = tacrolimus, TR = total remission.

Keywords: corticosteroid, idiopathic membranous nephropathy, meta-analysis, tacrolimus

1. Introduction

Idiopathic membranous nephropathy (IMN) is one of the most common causes of nephrotic syndrome in adults.[1] Approximately 30% to 40% of IMN patients with persistent nephrotic syndrome will progress to end-stage renal disease within 10 years.[2–4] Cyclophosphamide (CTX) combined with corticosteroids has been recommended as an initial therapy for IMN according to Kidney Disease Improving Global Outcomes (KDIGO).[5] Among IMN patients with contraindications to CTX, cyclosporine and tacrolimus (TAC) were recommended as alternative therapy regimens for IMN.[6] Compared to cyclosporine, TAC showed a stronger immunosuppressive effect and fewer side effects.[7,8]

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LG and MX contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Some meta-analyses showed that TAC combined with corticosteroids also had a satisfactory effect on IMN compared with CTX combined with corticosteroids.[9,10] However, corticosteroids still exhibited adverse effects. In recent years, some studies have compared TAC monotherapy with TAC combined with corticosteroids for IMN concerning efficacy and safety, and the results were controversial. Our meta-analysis was conducted to compare the efficacy and drug safety between TAC monotherapy and TAC-corticosteroid combination therapy for IMN.

2. Materials and methods

2.1. Search strategy

Our meta-analysis has been reported in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Assessing the methodological quality of systematic review guidelines. Our meta-analysis was registered at the International Prospective Register of Systematic Reviews (Registration number: CRD42021231540). Ethical Approval is not applicable.

We searched PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure, and Wanfang database from inception to January 10, 2021. The combined text and MeSH terms included idiopathic membranous nephropathy, corticosteroid, and TAC. In addition, the cited papers and relevant references were searched manually to identify eligible studies. There was no language restrictions.

2.2. Inclusion and exclusion criteria

The inclusion criteria were defined as follows:

(i) randomized controlled trials (RCTs), cohort, or case-control studies;
(ii) studies of biopsy-confirmed IMN patients with nephrotic syndrome and serum creatinine level of <133 μmol/L; and
(iii) studies designed to compare TAC monotherapy with TAC-corticosteroid combination therapy.

The primary endpoint of this review was partial remission (PR), complete remission (CR), and total remission (TR). Secondary endpoints were relapse and drug-related adverse effects.

The exclusion criteria were:

(i) case series, comments, reviews;
(ii) lack of relevant outcomes data;
(iii) secondary membranous nephropathy, malignant tumor, infection (hepatitis B or C virus infection, tuberculosis, and syphilis), diabetes mellitus, pregnancy or lactating, and active gastrointestinal bleeding.

2.3. Data extraction and quality assessment

Data were extracted independently by two investigators using standard data extraction forms. In the case of disagreement, a third investigator was consulted. We extracted characteristics including first author, year of publication, location, study design, follow-up period, age, sex, sample size, specific drug treatment program, and all the outcomes (definitions of CR, PR, and relapse are shown in Table 1). TR is defined as either CR or PR. Relapse was defined as proteinuria >3.5 g/d in patients who had achieved CR or PR. The Cochrane assessment tool was used to evaluate the quality of RCTs.[11] The Newcastle–Ottawa scale (NOS) was used to evaluate the quality of nonrandomized studies.[12]

2.4. Statistical analysis

We performed the data analysis by using Review Manager Version 5.3 (Cochrane Collaboration). Heterogeneity between studies was assessed by using I^2 statistics. We considered $I^2 > 50\%$ and $P < .10$ to imply significant heterogeneity. Homogeneous data were analyzed using the fixed-effects model. Heterogeneous data were analyzed using the random-effects model. We presented categorical variables as odds ratios (ORs). Summary estimates and 95% confidence intervals (CIs) were calculated. Overall effects were determined by the using *Z*-test. A

Table 1

Definition of complete remission, partial remission, and relapse.

Study	Complete remission	Partial remission	Relapse
Liang Ludan[13]	Proteinuria <0.3 g/d with normal serum ALB and SCr	Proteinuria <3.5 g/d, which had declined to ≤50% of the baseline value with serum ALB elevated and stable SCr	Proteinuria >3.5 g/d after remission
Lin Jiaqun[14]	Proteinuria <0.3 g/d with normal serum ALB (≥35 g/L) and SCr	Proteinuria 0.3–3.5 g/d, which had declined to ≤50% of the baseline value with serum ALB ≥30 g/L and stable SCr	–
Shang Shunlai[15]	Proteinuria <0.3 g/d at least twice per week with normal serum ALB and SCr	Proteinuria 0.3–3.5 g/d, which had declined to ≤50% of the baseline value with normal or improved serum albumin and stable SCr	Proteinuria >3.5 g/d and more than 50% higher than the lowest urinary protein level after remission
Yao Zhuane[16]	Proteinuria <0.3 g/d with normal serum ALB and SCr	Proteinuria <3.5 g/d, which had declined to≤50% of the baseline value with serum ALB elevated and stable SCr	Proteinuria >3.5/d g/d in patients who had achieved CR or PR
Zhu Aimin[17]	Proteinuria <0.3 g/d with normal serum ALB (≥35 g/L) and SCr	Proteinuria had declined to ≤30% of the baseline value with stable renal function	–
Zhang Xiaojuan[18]	Proteinuria <0.3 g/d, confirmed by two values at least one week apart, with normal serum ALB and renal function	Proteinuria <3.5 g/d, which had declined to≤50% of the baseline value, confirmed by two values at least one week apart, with serum ALB elevated and stable SCr	Proteinuria >3.5 g/d in patients who had achieved CR or PR
Zhang Xiaoxiao[19]	Proteinuria <0.3 g/d with stable renal function	Proteinuria 0.5–3.0 g/d, which had declined to ≤50% of the baseline value with stable renal function	Proteinuria >3.0 g/d in patients who had achieved CR or PR

ALB = serum albumin, CR = complete remission, PR = partial remission, SCr = serum creatinine.

P value <.05 was considered significant. Publication bias was assessed using sensitivity analysis.

3. Results

3.1. Study selection and characteristics

A flow diagram of the selection process is shown in Figure 1. Finally, seven studies from China were included in this analysis.[13–19] Of the seven studies, one was an RCT, and six were cohort studies. Five studies were published in Chinese journal. Overall, 177 patients were included in the TAC monotherapy group, and 195 patients were included in the TAC-corticosteroid combination therapy group. The follow-up period was from 6 to 12 months. The risk of bias in the included RCTs was moderate. The cohort studies achieved scores of ≥6 points, which were considered to be of high quality. The baseline characteristics of these studies are listed in Table 2. Specific drug treatment programs are listed in Table 3. The Cochrane assessment is listed in Table 4, and the NOS assessment is listed in Table 5.

3.2. Meta-analysis results

3.2.1. CR at the sixth month. Data about CR at the sixth month were reported in all articles: 23/175 (13.1%) for the TAC group and 28/190 (14.7%) for the TAC-corticosteroid group. The heterogeneity between the two studies was not substantial ($P=.40$, $I^2=3\%$), so finally, the fixed-effects model was used for the meta-analysis. There was no significant difference between the two groups concerning CR at the sixth month (OR 0.79, 95% CI 0.43–1.48, $P=.47$) (Fig. 2).

3.2.2. TR at the sixth month. Data about TR at the sixth month were reported in all articles: 104/175 (59.4%) for the TAC group and 140/190 (73.7%) for the TAC-corticosteroid group. The heterogeneity between the two studies was not substantial ($P=.97$, $I^2=0\%$), so finally, the fixed-effects model was used for the meta-analysis. TR at the sixth month of TAC-corticosteroid group was higher than TAC group, but the difference was statistically significant (OR 0.49, 95% CI 0.31–0.78, $P<.01$) (Fig. 3).

3.2.3. Relapse rate. Data on the relapse rate were reported in five articles: 25/103 (24.2%) for the TAC group and 12/78 (20.5%) for the TAC-corticosteroid group. The heterogeneity between the two studies was not substantial ($P=.82$, $I^2=0\%$), so finally, the fixed-effects model was used for the meta-analysis. The relapse rate of the TAC-corticosteroid group was lower than that of the TAC group, but the difference was not statistically significant (OR 1.44, 95% CI 0.70–2.92, $P=.32$) (Fig. 4).

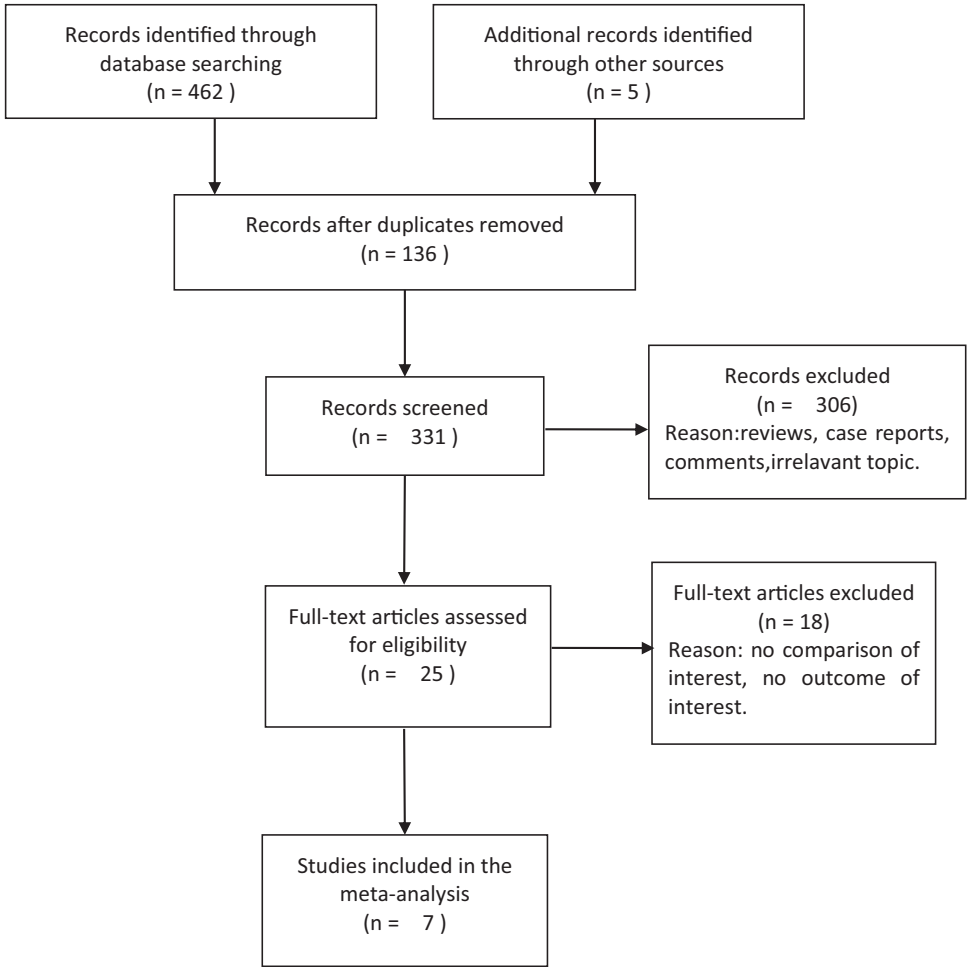

Figure 1. Flow diagram of the literature search.

Table 2

Characteristics of the included studies.

Study (year)	Country	Study design	Follow-up period (mo)	Sample size	Mean age (years)	Male/ Female	SCr (μmol/L)	Proteinuria (g/d)	ACEI and/or ARB treatment
Liang Ludan 2014[13]	China	Cohort study	6	TAC: 7 TAC+corticosteroid: 19	58.4±6.0 57.8±2.6	3/4 11/8	68.4±9.1 72.4±4.9	-	+
Lin Jiaqun 2015[14]	China	Cohort study	6	TAC: 12 TAC+corticosteroid: 14	54.2±9.4 45.8±11.6	11/1 11/3	81.8±14.7 78.6±16.8	5.3±0.9 5.0±1.2	+
Shang Shunlai 2018[15]	China	Cohort study	10	TAC: 33 TAC+corticosteroid: 24	42.0±15.3 43.3±14.6	13/20 14/10	72.4±19.8 77.3±23.8	–	?
Yao Zhuane 2017[16]	China	Cohort study	6	TAC: 18 TAC+corticosteroid: 13	48.3±13.2 42.2±11.4	8/10 8/5	54.2±14.9 79.4±31.0	4.9±1.0 9.2±4.9	+
Zhu Aimin 2020[17]	China	RCT	6	TAC: 22 TAC+corticosteroid: 25	52.8±9.7 53.2±11.6	16/6 18/7	87.2±10.2 87.0±11.2	7.2±0.7 7.2±0.8	?
Zhang Xiaojuan 2019[18]	China	Cohort study	12	TAC: 40 TAC+corticosteroid: 46	32.9±6.4 33.5±6.1	25/15 27/19	69.9±12.2 68.9±13.4	5.56 6.54	+
Zhang Xiaoxiao 2019[19]	China	Cohort study	6	TAC: 45 TAC+corticosteroid: 54	55.1±11.1 51.9±13.0	27/18 17/37	68.9±16.8 74.4±18.5	5.3±2.8 6.5±3.2	+

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II subtype 1 receptor blocker, RCT = randomized controlled trials, SCr = serum creatinine, TAC = tacrolimus.
+: patient was treated by ACEI and/or ARB; ?: no description.

Table 3

Specific drug treatment program.

Study	TAC monotherapy regimens	TAC-corticosteroid combination therapy regimens
Liang Ludan[13]	Oral TAC 0.05 mg/kg/d (the trough blood concentration of 4–10 ng/mL for 6 mo)	Oral TAC regimen was the same as TAC monotherapy regimen; oral prednisone initial dose of 0.5 mg/kg/d
Lin Jiaqun[14]	Oral TAC 0.05 mg/kg/d (the trough blood concentration of 4–8 ng/mL) with gradual tapering after remission (the trough blood concentration was maintained at 2–5 ng/mL)	Oral TAC regimen was the same as TAC monotherapy regimen; oral prednisone initial dose of 0.5–1 mg/kg/d for 2 mo with gradual tapering
Shang Shunlai[15]	Oral TAC 0.045 to 0.06 mg/kg (the trough blood concentration of 4–8 ng/mL for 6 mo) with gradual tapering	Oral TAC regimen was the same as TAC monotherapy regimen; oral methylprednisolone initial dose of 0.5 mg/kg/d for 2 mo with gradual tapering
Yao Zhuane[16]	Oral TAC 0.05 mg/kg/d (the trough blood concentration of 4–10 ng/mL for 6 mo)	Oral TAC regimen was the same as TAC monotherapy regimen; oral prednisone 0.8–1 mg/kg/d with gradual tapering
Zhu Aimin[17]	Oral TAC 0.05 mg/kg/d (the trough blood concentration of 5–10 ng/mL)	Oral TAC regimen was the same as TAC monotherapy regimen; oral prednisone 30–40 mg with gradual tapering
Zhang Xiaojuan[18]	Oral TAC 0.05–0.1 mg/kg/d (the trough blood concentration of 5–10 ng/mL for 6 mo) with gradual tapering	Oral TAC regimen was the same as TAC monotherapy regimen; oral prednisone initial dose of 0.5 mg/kg/d for 2–3 mo with gradual tapering
Zhang Xiaoxiao[19]	Oral TAC 0.1 mg/kg/d (the trough blood concentration of 5–10 ng/mL for 6 mo)	Oral TAC regimen was the same as TAC monotherapy regimen; oral prednisone initial dose of 1 mg/kg/d with gradual tapering

TAC = tacrolimus.

Table 4

Quality assessment of randomized control trial.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Selective reporting	Other bias
Zhu Aimin	?	?	?	+	+	?

The randomized control trial was evaluated using the Cochrane assessment tool. +, low risk of bias; ?, unclear risk of bias; -, high risk of bias.

Table 5

Quality assessment of cohort studies.

Studies	Selection	Comparability	Outcome	Score
Liang Ludan	****	*	***	8
Lin Jiaqun	****	*	***	8
Shang Shunlai	****	*	***	8
Yao Zhuane	****	*	***	8
Zhang Xiaojuan	****	*	***	8
Zhang Xiaoxiao	***	*	**	6

The cohort studies were evaluated using the Newcastle–Ottawa scale, which are comprised of the study of selection (representativeness of the exposed group, representativeness of the nonexposed group, ascertainment of exposure, demonstration that outcome of interest was not present at start of study), group comparability(controls for the most important factor, controls for any additional factor), outcome measures (assessment of outcome, was follow-up long enough for outcomes to occur, adequacy of follow up of cohorts), a total of nine points. *, 1 point.

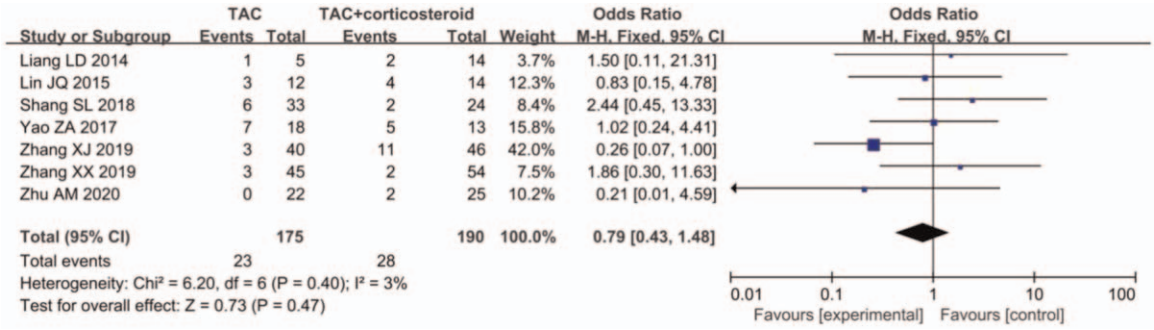

Figure 2. Forest plot of CR at the sixth month between TAC group and TAC-corticosteroid group. CR = complete remission, TAC = tacrolimus.

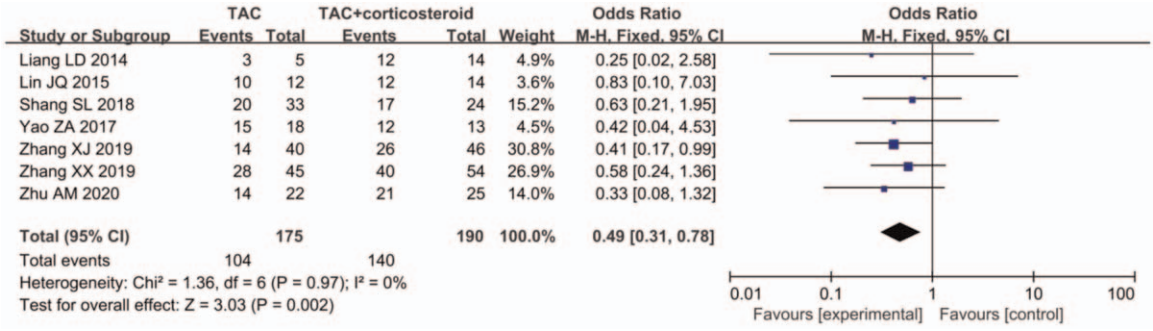

Figure 3. Forest plot of TR at the sixth month between TAC group and TAC-corticosteroid group. TAC = tacrolimus, TR = total remission.

3.2.4. Drug-related adverse effects. Data about drug-related adverse effects were reported in six articles. Incidences of infection (7.3%, 10/137), gastrointestinal symptoms (4.6%, 6/130), abnormal aminotransferase (3.9%, 6/155), and glucose intolerance (13.5%, 21/155) were in TAC group. Incidences of infection (17.8%, 28/157), gastrointestinal symptoms (5.1%, 7/138), abnormal aminotransferase (4.7%, 8/170), and glucose intolerance (22.4%, 38/170) were in TAC-corticosteroid group. There was no statistically significant difference between the two groups concerning gastrointestinal symptoms (OR 0.96, 95% CI 0.34–2.70, $P = .93$), abnormal aminotransferase (OR 0.90, 95% CI 0.34–2.38, $P = .84$), and glucose intolerance (OR 0.58, 95%CI 0.32–1.07, $P = .08$). The incidences of infection in the TAC-corticosteroid group were all higher than those in the TAC group (OR 0.38, 95% CI 0.18–0.81, $P = .01$). All forest plots of drug-related adverse effects are listed in Figs. 5–8.

3.3. Sensitivity analyses

Sensitivity analyses for all outcomes after the two therapy regimens were used to judge the dependability of the results. Deleting the study of Yao Zhuane or Zhang Xiaojuan at a time, the results of meta-analysis showed glucose intolerance of TAC-corticosteroid group was higher than TAC group. Deleting the study of Zhang Xiaoxiao, the results of the meta-analysis showed no significant difference between the two groups concerning infection.

4. Discussion

IMN is the most common nephritic syndrome in adults and causes antibody-mediated damage to glomerular podocytes.[20] TAC, a calcineurin inhibitor, mainly binds to a particular intracellular receptor called FK-506-binding protein 12 to inhibit

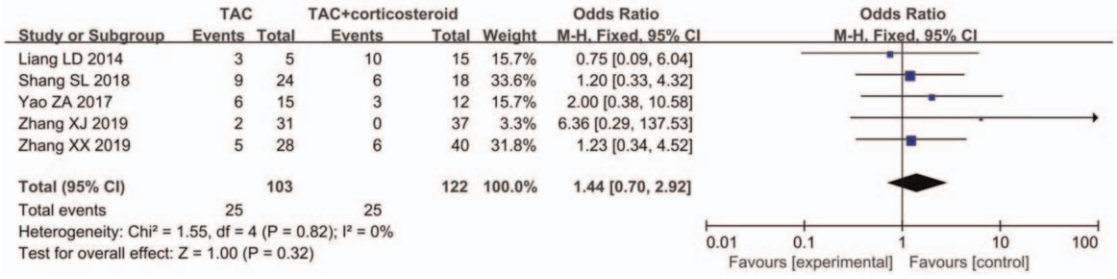

Figure 4. Forest plot of relapse rate between TAC group and TAC-corticosteroid group. TAC = tacrolimus.

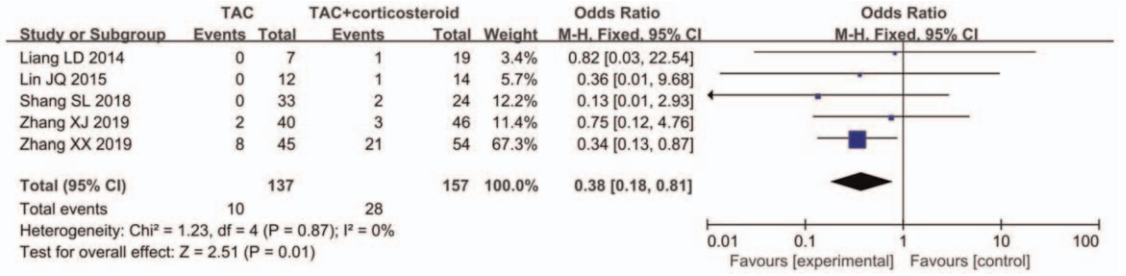

Figure 5. Forest plot of infection between TAC group and TAC-corticosteroid group. TAC = tacrolimus.

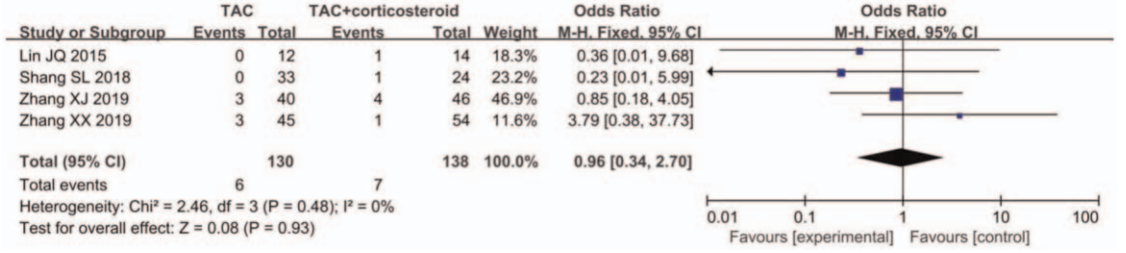

Figure 6. Forest plot of gastrointestinal symptoms between TAC group and TAC-corticosteroid group. TAC = tacrolimus.

calcineurin phosphatase, thereby inhibiting cytokines such as IL-2. Consequently, TAC can inhibit the growth and differentiation of T cells, thereby reducing the immune damage of podocytes.[21] TAC monotherapy or TAC combined with corticosteroids was effective in treating IMN patients. Clinicians need a therapeutic regimen with a stronger effect and fewer side effects. Our meta-analysis revealed that TAC-corticosteroid combination therapy had a higher TR at the sixth month than TAC monotherapy for IMN. The two therapy regimens had similar relapse rates. TAC-corticosteroid combination therapy had a higher incidence of infection.

Sustained remission of nephrotic syndrome is very important for patients with IMN and can reduce complications and prevent progression to end-stage renal disease. In previous

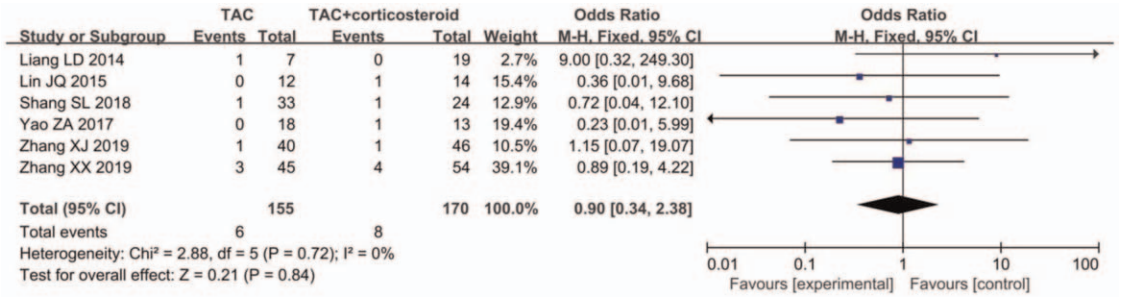

Figure 7. Forest plot of abnormal aminotransferase between TAC group and TAC-corticosteroid group. TAC = tacrolimus.

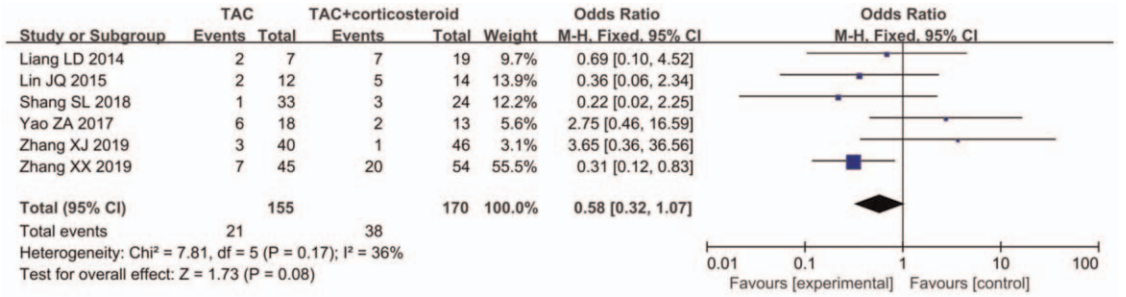

Figure 8. Forest plot of glucose intolerance between TAC group and TAC-corticosteroid group. TAC = tacrolimus.

studies, CTX-corticosteroid combination therapy had a TR of nearly 70% for IMN at the sixth month.[22] Our study found that TAC-corticosteroid combination therapy had a TR of 73.7% at the sixth month, which was similar to CTX-corticosteroid combination therapy. TAC monotherapy had a lower TR of 59.4% at the sixth month. However, in previous studies concerning TAC monotherapy versus CTX-corticosteroid combination therapy for IMN, TAC monotherapy had an average TR of nearly 70%.[23–25] The follow-up time was short, with most studies limited to only 6 months, which can influence the response rate. Some patients may have PR or CR after 6 months. In the included studies of Shang Shunlai and Zhang Xiaojuan, after TAC monotherapy or combination therapy, the TR at the tenth to twelfth month was higher than the TR at the sixth month.[15,17] However, TAC monotherapy had similar TR compared with TAC-corticosteroid combination therapy at the tenth to twelfth month.[15,17] More studies are needed to prove that TAC-corticosteroid combination therapy may have stronger immunosuppressive effects than TAC monotherapy for IMN.

A low relapse rate is beneficial for IMN patients. Relevant literature has reported that TAC treatment for IMN has a higher relapse rate after drug withdrawal than CTX.[26,27] In our meta-analysis, compared with TAC-corticosteroid combination therapy for IMN patients, TAC monotherapy did not significantly increase the relapse rate. For patients with recurrence, the use of TAC is still effective. However, the follow-up time of most studies is short. We do not know about the recurrence rate of these included patients after longer follow-up, especially after drug withdrawal. There are low levels of evidence that prolonged TAC treatment with a low blood concentration is beneficial to sustained remission and reducing the relapse rate.[28]

Long-term use of immunosuppressive therapy can increase the incidence of drug-related adverse effects, so clinicians should evaluate the beneficial and adverse effects when prescribing treatment regimens for IMN patients. Infection, gastrointestinal symptoms, abnormal aminotransferase, and glucose intolerance were the main drug-related adverse effects of TAC monotherapy and TAC-corticosteroid combination therapy. Our meta-analysis revealed that TAC-corticosteroid combination therapy had a higher incidence of infection than TAC monotherapy. Additional use of corticosteroids enhances the anti-inflammatory effect and increases the risk of infection. Most types of infection are respiratory infections, which are all controllable. There were 2 cases of severe pneumonia in the TAC combined corticosteroid treatment group and no severe pneumonia in the TAC monotherapy group. The dose of corticosteroids was reduced in one patient due to severe pneumonia, which did not lead to recurrence. A previous meta-analysis showed that TAC-corticosteroid combination therapy was associated with a significantly lower risk of infection than intravenous CTX combined with corticosteroid therapy.[29] Our study found that TAC-corticosteroid combination therapy did not increase the risk of gastrointestinal symptoms, abnormal aminotransferase, and glucose intolerance. However, after the sensitivity analyses deleted the individual study, the results showed that TAC-corticosteroid combination therapy might increase the risk of glucose intolerance and might not increase the risk of infection. The reason may be related to the dose size of TAC and corticosteroids in the individual study.

According to KDIGO guidelines, TAC monotherapy is recommended as an alternative therapy regimen for IMN, and CTX combined with corticosteroids has been recommended as an initial therapy. There are no guidelines to determine whether TAC monotherapy or TAC-corticosteroid combination therapy is better. In our meta-analysis, compared with TAC monotherapy, TAC-corticosteroid combination therapy may have stronger immunosuppressive effects and at the same time increase the risk of complications of immunosuppressive treatment. For young patients with severe IMN, CTX contraindications, and low risk of potential complications from the use of TAC and corticosteroids, TAC-corticosteroid combination therapy may be attempted to help improve TR, which is very helpful for long-term prognosis. Clinicians need to prescribe individualized treatment regimens for patients with IMN. More studies are needed to verify this hypothesis further, especially with regard to the recurrence rate.

There were some limitations in our meta-analysis. First, IMN has the possibility of spontaneous remission. KDIGO guidelines suggested that immunosuppressive therapy can be given to IMN patients with urine protein >4 g/24 h and no decrease in urine protein after 6 months of conservative treatment.[6] However, in the majority of studies, immunosuppressants were used as soon as IMN was detected without six months of conservative treatment. Second, in some included studies, IMN patients were treated with angiotensin-converting enzyme inhibitor or angiotensin II subtype 1 receptor blocker antihypertensive drugs. Since angiotensin-converting enzyme inhibitor and angiotensin II subtype 1 receptor blocker drugs have the effect of reducing proteinuria, they will affect the interference results. Third, in the included studies, there were some differences concerning the specific drug regimen and definition of outcomes, which may cause a risk of bias. Moreover, it may also increase the risk of bias because only studies from China were included and only one RCT was included.

5. Conclusions

Our meta-analysis revealed that TAC-corticosteroid combination therapy had a higher TR at the sixth month but had a higher incidence of infection than TAC monotherapy for IMN. The two therapy regimens had similar relapse rates. To further confirm this conclusion, additional large multicenter randomized controlled trials are necessary.

Author contributions

Data curation: Wei Xu, Weigang Tang, Wei Jiang, Fengyan Xie, Liping Ding, Xiaoli Qian.
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Methodology: Lifeng Gong, Min Xu, Wei Xu.
Software: Wei Xu, Weigang Tang, Jingkui Lu.
Supervision: Lifeng Gong, Min Xu, Wei Xu.
Writing – original draft: Wei Xu, Wei Jiang, Fengyan Xie, Liping Ding, Xiaoli Qian.
Writing – review & editing: Wei Xu, Wei Jiang, Fengyan Xie, Liping Ding, Xiaoli Qian.

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