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Efficacy and safety of tacrolimus combined with glucocorticoid treatment for IgA nephropathy: a meta-analysis

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Abstract

Objective: As a classical immunosuppressant, tacrolimus (TAC) has been widely used in organ transplantation therapy, but the general benefits of TAC for the treatment of IgA nephropathy (IgAN) remain uncertain. We conducted a meta-analysis to examine the effects of TAC combined with glucocorticoid on IgAN.

Methods: We searched the information databases PubMed/Medline, Embase, Science Citation Index, Chinese Biomedical Literature and the Chinese databases VIP, CNKI and Wan Fang for randomized controlled trials of TAC combined with glucocorticoid as a therapy for IgAN.

Results: Ten relevant studies involving 472 patients were included in a meta-analysis. Overall, the TAC group showed a significant decrease in proteinuria compared with the control group (MD: −0.18 g/d, 95% CI: −0.32 to −0.04). No increased risk of adverse events was observed (OR: 0.93, 95% CI: 0.65 to 1.33). In general, the TAC group showed good tolerance.

Conclusion: Evidence to date clearly indicates that TAC combined with glucocorticoid is quite effective in reducing proteinuria and albuminuria in patients with IgAN. Moreover, we found that patients receiving TAC therapy did not show an increased risk of side effects compared with control group patients. TAC combined with glucocorticoid is a promising medication and merits further research.

Keywords

Tacrolimus, glucocorticoid, IgA nephropathy, meta-analysis, immunosuppressant, proteinuria

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Introduction

Immunoglobulin A nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide, and its underlying mechanism is attributed to immune complex reactions.[1] Many patients develop end-stage renal disease (ESRD) after 20–30 years and require continuous renal-replacement therapy.[2] A wide variety of therapies have been developed to reduce the likelihood of kidney failure in IgAN patients. IgAN can occur at any age and is more prevalent in males; individuals from Caucasia and Asia are more susceptible to IgAN than are individuals from South Africa and the United States.[3,4] The renal prognosis following IgAN depends on the presence of proteinuria, impaired renal function, hypertension and further histological lesions.[5] The immunologic mechanism underlying IgAN was first proposed by Suzuki et al.[6] in 2011 and was based on the four-hits model. Suzuki et al.[6] noted that immune complexes activate mesangial cells, which results in renal injury. This may constitute a potential mechanism of immunosuppressive therapy for IgAN.[7,8]

Tacrolimus (TAC), a powerful calcineurin inhibitor (CNI), can inhibit the immune response by altering transcription of various genes in T cells and is effective in treating patients with nephritic syndrome.[9,10] As an immunosuppressive agent, TAC was first used for transplant patients, with successful applications in kidney, heart, pancreas and liver transplantation and is associated with impressive short-term prognosis.[11–13] Indeed, TAC has no adverse effects on lipid metabolism or antioxidant status, and it can protect neuronal tissue from hypoxic lesions.[14] TAC exerts its immunemodulatory action by disrupting the expression of cytokines and T cell activation.[15] Most researchers believe that TAC reduces proteinuria by affecting podocyte cytoskeleton stability.[16,17] Although TAC can relieve symptoms of proteinuria in patients with refractory IgAN, the efficacy and tolerability of TAC plus glucocorticoid treatment in IgAN patients remain unclear.[18]

There are few randomized control trials (RCTs) of TAC plus glucocorticoid for the treatment of IgAN. Owing to the shortage of such clinical trials, we were unable to locate a relevant meta-analysis on this topic. Nonetheless, as several recent studies have used TAC plus glucocorticoid for IgAN patients, the current meta-analysis was conducted to ascertain the benefits and risks of TAC combined with glucocorticoid in these patients.

Methods

The data analysed were derived from previously published studies. Therefore, no ethical approval or patient consent was required.

Search strategy

Two researchers (YZ and JL) performed a comprehensive literature search, which produced 11 relevant studies that met all the eligibility criteria. To identify all relevant randomized placebo-controlled trials regardless of publication status, we searched the electronic databases PubMed/Medline, Embase, Science Citation Index (SCI), Chinese Biomedical Literature (CBM), Chinese Science and Technology Journal Database (VIP), China National Knowledge Infrastructure (CNKI) and Wan Fang Data Knowledge Service Platform up to February 24, 2017. The following keywords were used: 'IgA nephropathy', 'IgA nephritis', 'IgAN', 'Bergers disease', 'immunoglobulin A nephropathy', 'tacrolimus', 'TAC', 'FK506' and 'prograf'. Reference lists from the identified studies were also consulted to extend the search.

Selection criteria

Two authors (YZ and BH) independently carried out the primary review to search for

trials that met the inclusion criteria. Any discrepancy was resolved by discussion and consensus (Figure 1). The following criteria were included: 1) the study design was an RCT; 2) the study focused on patients with biopsy-proven IgAN; 3) the study compared TAC plus steroids versus steroids/placebo in induction therapy for IgAN; and 4) one of the following outcomes must have been included: partial remission (PR), complete remission (CR) or total remission (TR, including CR and PR) of proteinuria, changes in clinical outcomes (including proteinuria, serum creatinine (SCr) or estimated glomerular filtration rate (eGFR)) and adverse events.

Risk of bias assessment

The quality of all trials was assessed independently by two authors (YZ and BH)

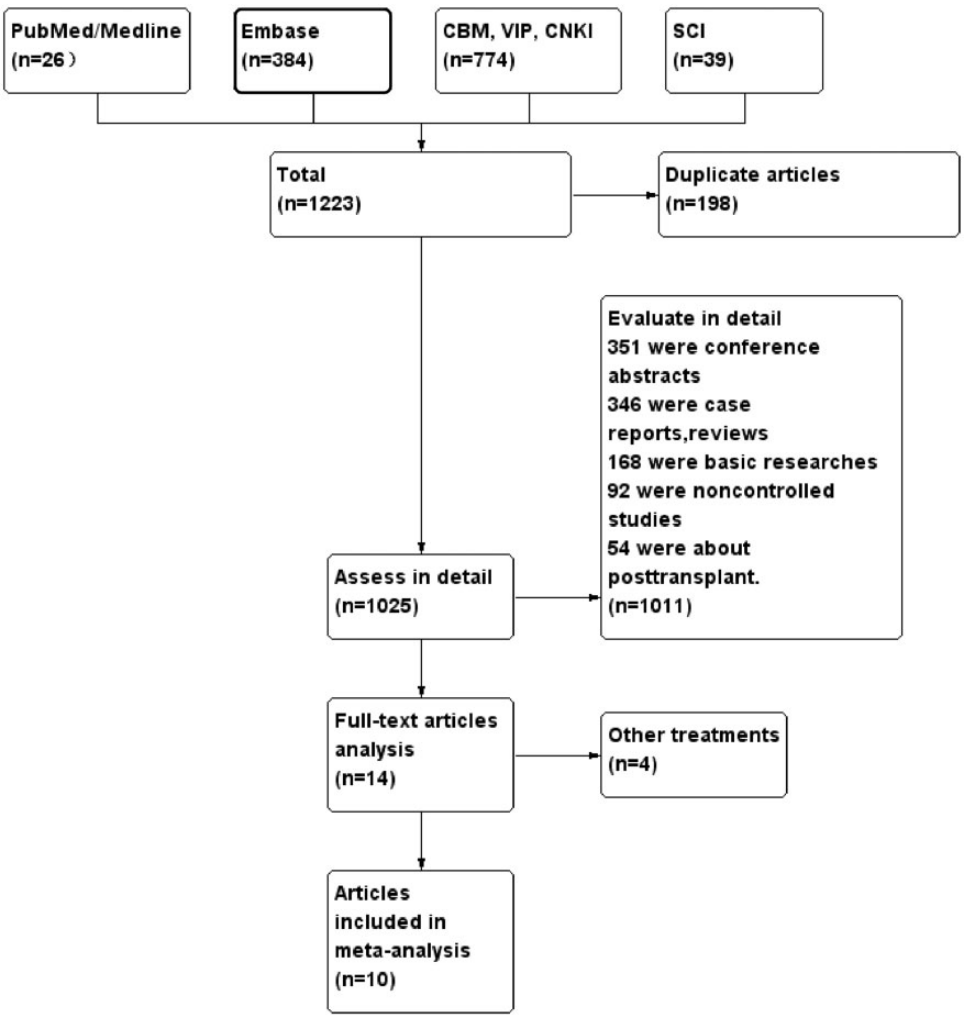

Figure 1. Flowchart of the process for selecting studies for the systematic review.
SCI: Science Citation Index; CBM: Chinese Biomedical Literature; VIP: Chinese Science and Technology Journal Database; CNKI: China National Knowledge Infrastructure.

according to the Cochrane quality criteria (Figure 2). Any disagreement between the two authors was resolved by discussion with a third author (JL) until a consensus was reached.

Statistical analysis

Cochrane RevMan 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) was used to perform statistical analyses. The odds ratio (OR) was used as the effect size. The weighted fixed-effect model was used with the Mantel–Haenszel statistical test, followed by a test of homogeneity. Heterogeneity was analysed statistically using the heterogeneity I^2 statistic and visually using scatter plots. The critical value for homogeneity was a P value less than 0.05. The random effect model was used when the hypothesis of homogeneity was rejected ($P > 0.05$). To explore sources of heterogeneity, meta-regression analyses were used. Sensitivity analysis was performed by omitting each study in turn to assess the quality and consistency of the results using STATA 12.0 (StataCorp LP, College Station, TX, USA). Funnel plots were used to detect publication biases. Additionally, we performed subgroup analysis to assess adverse reactions and remission ratios for all outcomes based on TAC treatment and control groups.

Heterogeneity was categorized as follows: light when the I^2 statistic was 0% to 25%; medium: 25% to 50%; heavy: 50% to 75%; and powerful heterogeneity: 75% to 100%.[19] The P value was determined using the χ^2 test; P values < 0.05 were considered statistically significant for all included studies.

Results

Study selection

We identified 1223 articles in the initial retrieval. Of these, 198 duplicate articles were excluded after carefully examining the title and abstract. After detailed evaluation, 1011 articles were excluded because 351 were conference abstracts, 346 were case reports or reviews, 168 were basic research, 92 were non-controlled studies and 54 were on post-transplant IgAN. The remaining 14 articles were reviewed for further selection. An additional four articles were excluded because of insufficient data. Eventually, 10 studies (n = 472) were included in this meta-analysis, as listed in Table 1.[20–29] Our search strategy is described in the flow diagram (Figure 1).

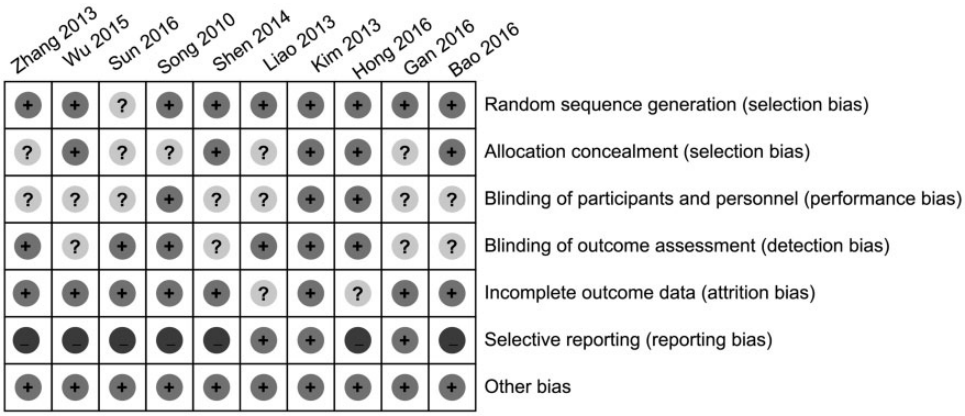

Figure 2. Assessment of risk of bias in included studies.

Table 1. Main characteristics of the included studies

Study	Year	Sample size		Age		TAC group	Control group	Follow-up (months)	Pathology
		T(F/M)	C(F/M)	T	C				
Hong[20]	2016	12/10	4/15	32.9 ± 10. 5	32.7 ± 8. 5	TAC 0.05 mg/kg/d. PDN 0.5 mg/kg/d, then tapered.	PDN 0.5 mg/kg/day, then tapered.	24	Lee Grade II–IV
Gan[21]	2016	6/14	7/13	36.4 ± 10.3	35.8 ± 11.0	TAC 0.05–0.08 mg/kg/d. PDN 0.5–0.8 mg/kg/d, then tapered.	PDN 0.5 mg/kg/day, then tapered.	6	Unclear
Liao[22]	2013	20	14	35.2 (18–54)		TAC 1 mg/d, then tapered. PDN 30 mg/d, then tapered.	PDN 30 mg/d, then tapered.	6	Lee Grade III–V
Song[23]	2010	6/8	13/4	37.7 ± 21.3		TAC 0.075–0.1 mg/kg/d. PDN 30 mg/d, then tapered.	PDN 1 mg/kg/day, then tapered.	6	Unclear
Kim[24]	2013	14/6	14/6	36.9 ± 11.4	40.1 ± 12.8	TAC 0.1 mg/kg/day, then tapered.	Placebo	4	Oxford classification
Zhang[25]	2013	14	11	36.3 (16–57)		TAC 0.075 mg/kg/d. PDN 30 mg/day, then tapered	PDN 0.5 mg/kg/day (max 60 mg/day)	6	Lee Grade II–IV
Shen[26]	2014	2/10	1/11	32.8 ± 8.3	37.2 ± 8.6	TAC 0.05–0.08 mg/kg/d. PDN 10–15 mg/d, then tapered.	PDN 0.5–0.8 mg/kg/d, then tapered.	6	Unclear
Sun[27]	2016	20/14	15/15	30.7 ± 10.5	34.0 ± 11.4	TAC 0.02–0.05 mg/kg/d, PDN 0.5 mg/kg/d, then tapered.	PDN 1.0 mg/kg/day, then tapered.	6	Lee Grade III–V
Bao[28]	2016	25/22	23/20	28.2 ± 2.7	27.3 ± 2.8	TAC 0.05–0.08 mg/kg/d, PDN 0.5 mg/kg/d, then tapered.	PDN 0.5 mg/kg/day, then tapered.	6	Unclear
Wu[29]	2015	13/29	11/31	38.8 ± 12.1	36.5 ± 10.2	TAC 0.075 mg/kg/d. PDN 30 mg/d, then tapered.	PDN 30 mg/d, then tapered.	6	Lee Grade II–IV

TAC: tacrolimus; PDN: prednisolone.

The characteristics, drug dosages, period of treatment, interventions and pathological grade of the patients are summarized in Table 1. Forest plots (Figures 3–7) show the number of patients in the TAC treatment and control groups who exhibited an alteration in proteinuria, SCr, eGFR or adverse events.

Effect on clinical remission rate

The definitions of PR and CR are shown in Table 2. A measure of CR, PR or TR was reported in 9 of the 10 trials, including 432 patients. CR (OR: 2.22, 95% CI: 1.16 to 4.26, $I^2 = 55\%$, $P = 0.02$) and TR (OR: 3.01, 95% CI: 1.21 to 7.50, $I^2 = 35\%$, $P = 0.02$) occurred more frequently in

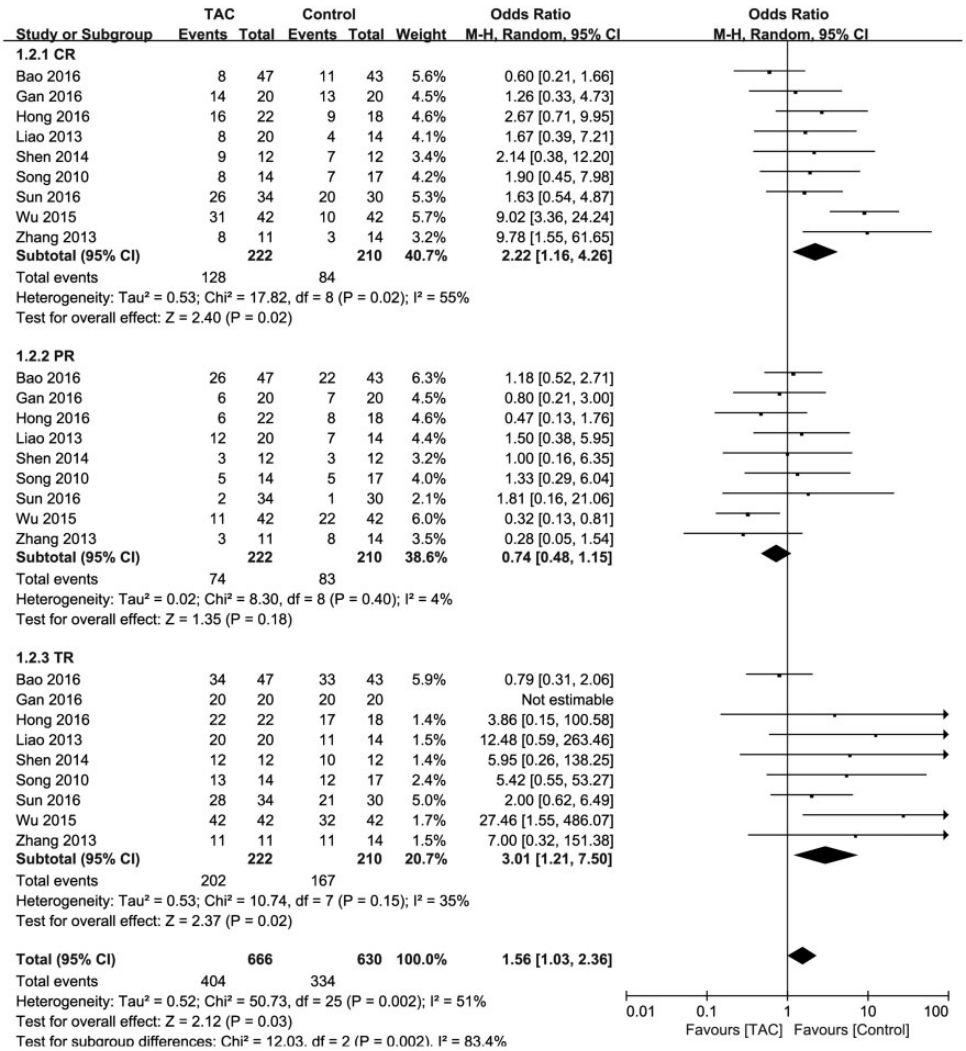

Figure 3. Forest plot of the relative risks for CR, PR and TR for TAC group versus control group in the treatment of IgAN.
TAC: tacrolimus; PR: partial remission; CR: complete remission; TR: total remission.

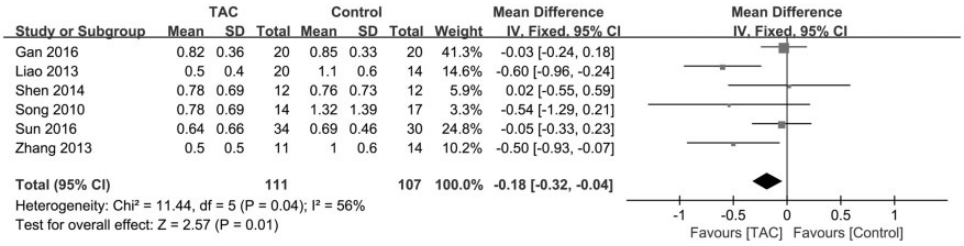

Figure 4. Forest plot of the effect on proteinuria (g/d) for TAC group versus control group at the end of treatment or during follow-up.
TAC: tacrolimus; SD: standard deviation; CI: confidence interval.

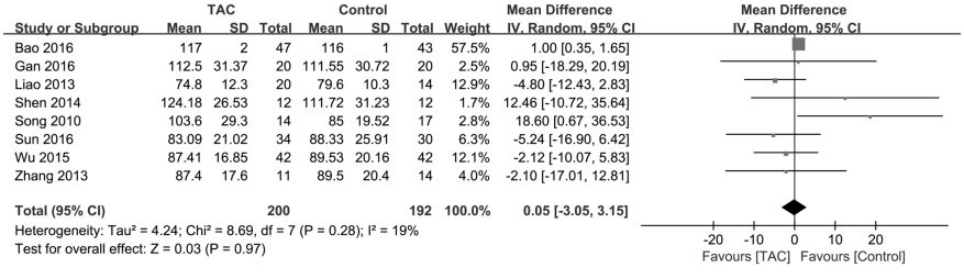

Figure 5. Forest plot of the effect on SCr for TAC group versus control group at the end of treatment or during follow-up.
TAC: tacrolimus; SD: standard deviation; CI: confidence interval.

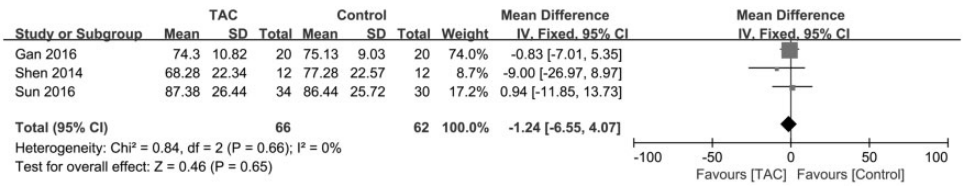

Figure 6. Forest plot of the effect on eGFR for TAC group versus control group at the end of treatment or during follow-up.
TAC: tacrolimus; SD: standard deviation; CI: confidence interval.

patients in the TAC group than in those in the control group. However, there was no significant difference in PR between the TAC group and the control group (OR: 0.74, 95% CI: 0.48 to 1.15) (Figure 3).

Effect on proteinuria

Six studies reported the outcome of 24-hour proteinuria in a total of 218 patients, of whom 111 were assigned to treatment groups and 107 to control groups. Compared with controls, patients receiving TAC plus glucocorticoid treatment showed a statistically significant reduction in proteinuria (MD: –0.18, 95% CI: –0.32 to –0.04, $I^2 = 56\%$, $P = 0.01$) (Figure 4). As there was substantial heterogeneity, meta-regression analyses were used to explore possible sources of heterogeneity among studies. The results suggested that publication year was a potential major source of

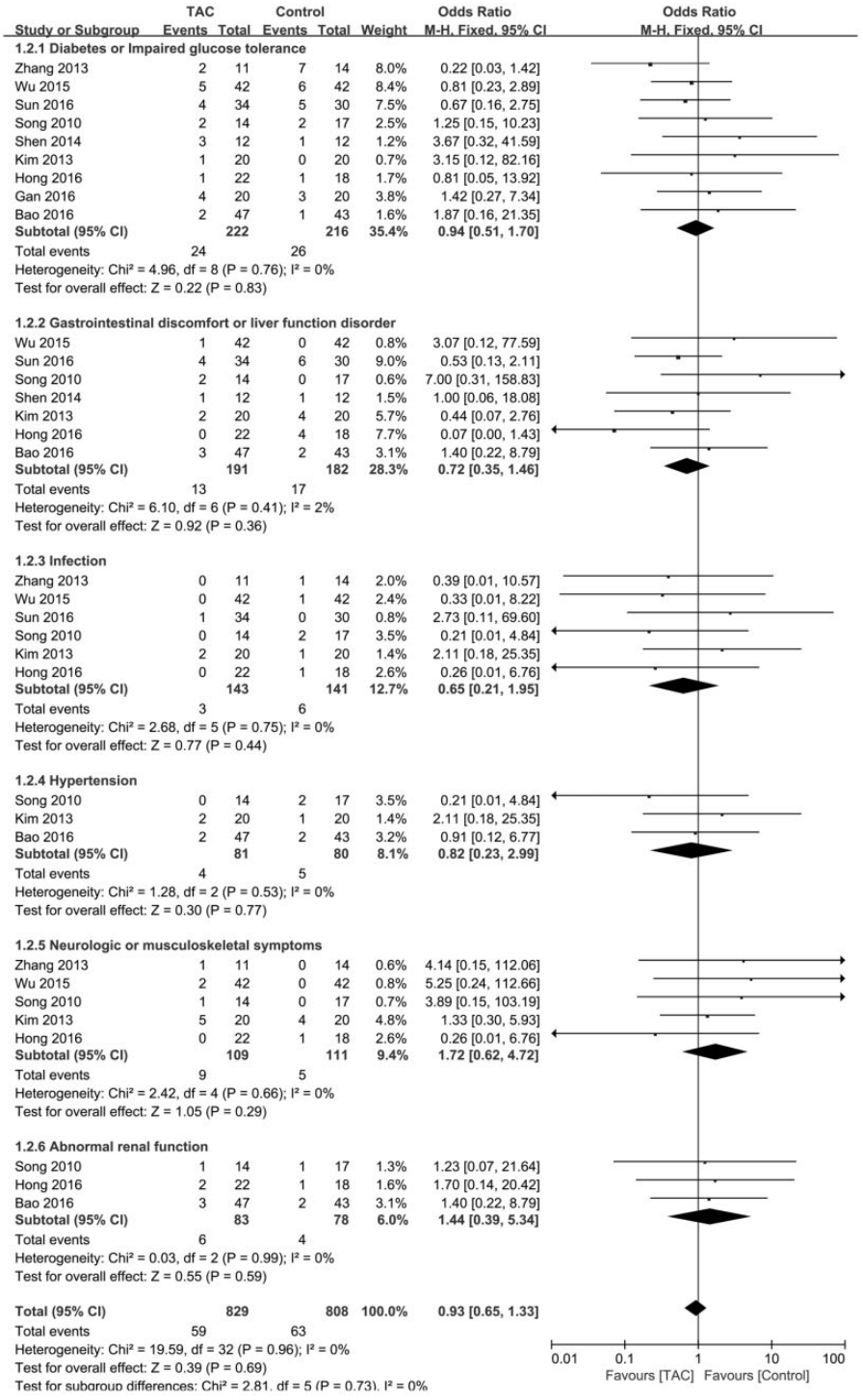

Figure 7. Forest plot of the relative risk of adverse events at the end of treatment or during follow-up. TAC: tacrolimus; CI: confidence interval M–H: Mantel–Haenszel test.

Table 2. Definitions of partial remission (PR) and complete remission (CR)

Study	Year	Definitions of PR and CR
Hong[20]	2016	CR: Normal SCr, serum albumin >35g/L, and proteinuria less than 0.5g/day. PR: Normal SCr, serum albumin >30g/L, and proteinuria reduced to at least half the baseline measurement and an absolute value of >0.5g/day.
Gan[21]	2016	CR: Stable SCr, and proteinuria less than 0.3g/day. PR: Stable SCr, and proteinuria higher than 0.3g/day, but reduced by >50%.
Liao[22]	2013	CR: No reactive urinary sediment, and proteinuria less than 0.5g/day. PR: Normal SCr (range less than 30%), and proteinuria reduced to at least half the baseline measurement and an absolute value of <3.5g/day.
Song[23]	2010	CR: Normal SCr, serum albumin >35g/L, and proteinuria less than 0.5g/day. PR: Normal SCr, serum albumin >30g/L, and proteinuria reduced to at least half the baseline measurement and an absolute value of 0.5–3.0g/day.
Kim[24]	2013	Not described in detail.
Zhang[25]	2013	CR: Normal SCr (range less than 20%), and proteinuria less than 0.3g/day. PR: Normal SCr (range less than 20%), and proteinuria higher than 0.3g/day, but reduced by >30%.
Shen[26]	2014	CR: Stable SCr (range less than 15%), and proteinuria less than 0.3g/day. PR: Stable SCr (range less than 15%), and proteinuria higher than 0.3g/day, but reduced by >50%.
Sun[27]	2016	CR: Normal SCr and BUN (range less than 15%), and proteinuria less than 0.3g/day. PR: Normal SCr and BUN (range less than 15%), and proteinuria higher than 0.3g/day, but reduced by >50%.
Bao[28]	2016	CR: Normal SCr and BUN (range less than 15%), and proteinuria less than 0.3g/day. PR: Normal SCr and BUN (range less than 15%), and proteinuria higher than 0.3g/day, but reduced by >50%.
Wu[29]	2015	CR: Stable SCr (range less than 15%), and proteinuria less than 0.3g/day. PR: Stable SCr (range less than 15%), and proteinuria higher than 0.3g/day, but reduced by >50%.

SCr: serum creatinine; BUN: blood urea nitrogen.

heterogeneity ($P = 0.04$). Sensitivity analysis was performed to assess the influence of each individual study on the pooled ORs by omitting individual studies. The analysis results suggested that no individual studies significantly affected the pooled OR, indicating that the results were statistically robust.

Effect on SCr

Seven studies assessed SCr in a total of 392 patients, 200 of whom were assigned to treatment groups and 192 to control groups. Because there was no significant heterogeneity, the fixed-effects model was used. The statistical analysis showed no significant difference (MD: 0.05, 95% CI: –3.05 to 3.15) (Figure 5).

Effect on eGFR

Only three studies assessed eGFR; 66 patients were assigned to treatment groups and 62 to control groups. The fixed-effects model was used for evaluation because there was no significant heterogeneity. There was no significant difference (MD: –1.24, 95%

CI: –6.55 to 4.07) between the TAC group and the control group (Figure 6).

Adverse effects of treatment

All adverse events mentioned in the included articles were recorded and the most prevalent events were analysed. The following outcomes were included: diabetes or impaired glucose tolerance; gastrointestinal discomfort or liver function disorder; infection; hypertension; neurologic or musculoskeletal symptoms; abnormal renal function and withdrawal (Figure 7).

The analysis showed that the TAC therapy group exhibited no significant difference (OR: 0.93, 95% CI: 0.65 to 1.33) from the control group. The fixed-effects model was used for evaluation because heterogeneity was extremely low. Significantly, patients receiving TAC therapy experienced no additional risk compared with control group patients.

Publication bias

A symmetrical funnel plot was constructed for adverse events, proteinuria, remission rate, eGFR and SCr. The plot indicated that there was no significant publication bias.

Discussion

Worldwide, IgAN is the most prevalent form of basic chronic glomerular disease. One Chinese study reported that IgAN accounts for 40–50% of primary glomerulonephritis cases.[30] Furthermore, IgAN is one of the most important pathogeneses that lead to ESRD. Studies with a long follow-up time show that approximately 25–30% of patients with IgAN will progress to ESRD within 20 to 25 years.[31,32] IgAN is considered an autoimmune disease with an aetiology and a pathogenesis that have yet to be fully elucidated.[33] A common pathological feature of primary IgAN is considered to be diffuse deposition of IgA in the glomerular mesangial area, though clinical manifestations and histology vary. One study reported that in patients with IgAN, deposited immune complexes induce proliferation of resident mesangial cells with an increased production of extracellular matrix proteins; the inflammatory cytokines produced by mesangial cells damage the filtration barrier, resulting in haematuria and proteinuria and ultimately leading to progressive renal damage.[34]

Recent histological, serological, epidemiological and clinical evidence indicates that the risk factors for progressive IgAN are mainly related to proteinuria or chronic renal insufficiency.[35]

Proteinuria is one of the strongest independent prognostic factors of IgAN.[36,37] IgAN with severe proteinuria is conventionally treated with various immunosuppressive regimens, with conflicting results,[38,39] and studies have suggested that TAC is effective at decreasing proteinuria in a variety of glomerular diseases, including IgAN.[40,41]

TAC (also known as FK506 or fujimycin) is a new type of immunosuppressant that was previously used mostly in the early stage of organ transplantation rejection. Recently, TAC has been used in therapy for certain autoimmune diseases, such as primary and secondary glomerular diseases. TAC inhibits activation of nuclear factor T (nuclear factor of activated T cells), which is essential for transcription of cytokine genes in T cells, thereby blocking transcription of IL-2 and IFN-γ and ultimately exerting a strong effect on immune suppression.[42]

However, no studies have specifically analysed the effect of TAC in patients with IgAN. The present meta-analysis of 11 trials involving 540 patients with IgAN showed that TAC combined with glucocorticoid is effective at reducing proteinuria when compared with control conditions. The findings reveal that TAC plus glucocorticoid has

a significant synergistic effect on reducing proteinuria in patients with IgAN.

Our results are similar to those of a previous study showing that patients with IgAN may experience significant improvement in proteinuria and hypoalbuminemia during TAC treatment.[43] Moreover, this meta-analysis concluded that there is no significant difference in the relative risk of adverse events at the end of treatment or during follow-up. IgAN patients who achieved remission had far better outcomes than those who did not.[44,45] These findings suggest that achieving remission, regardless of the glomerular disease type or CR or PR, is important for improving renal survival in IgAN patients. In the current meta-analysis, the TAC group showed increased rates of CR ($P = 0.02$) and TR ($P = 0.02$) compared with the control group.

A recent meta-analysis by Song et al.[46] reported that CNI drugs significantly reduced proteinuria in IgAN patients. However, the safety of CNIs was found to be inadequate; for example, the incidence of liver function disorder or neurologic and musculoskeletal symptoms increased in the TAC group, and the incidence of adverse reactions was significantly higher than in the control group. However, in our study, there was no significant difference in incidence of adverse reactions between the TAC and control groups. Song et al. included seven studies in their meta-analysis, only two of which ($n = 65$) involved TAC. Therefore, the high incidence of adverse reactions they found may be associated with the use of cyclosporin A (CsA). Both TAC and CsA are CNIs, but the immunosuppressive effect of TAC is approximately 50–100 times stronger than that of CsA;[47] therefore, a much smaller dose of TAC is needed compared with CsA to achieve the same level of immunity. Ren[48] has shown that adverse reactions to TAC are related to different dosages; therefore, small doses of TAC may reduce the incidence of adverse reactions.

Thus far, the safety of TAC has been poorly understood, particularly in the treatment of proteinuria in IgAN. The main reported adverse reactions to TAC are gastrointestinal symptoms, (such as gastrointestinal discomfort), liver function disorder, increased SCr and hypertension.[18]

In a previous study by our group,[26] two patients developed elevated blood sugar and one patient developed liver function disorder about 6 months after initiation of treatment with TAC combined with low-dose methylprednisolone. The three patients fully recovered after receiving appropriate therapy. Another study reported that TAC was effective in a patient who had experienced no therapeutic effect when using cyclophosphamide and CsA.[49]

The results of one study showed that TAC combined with glucocorticoid therapy significantly improved renal function in patients with IgAN. Significant reductions in proteinuria after 3 months of treatment have been reported.[26,49] These findings are consistent with our results.

Weng et al. have proposed that the concentration of TAC should be regularly measured during the treatment period to ascertain the therapeutic window for personalized drug regimens (to determine a reasonable dose).[50] Detection of the blood concentration of TAC can reduce the incidence of adverse reactions.[50,51]

Overall, the side effects of TAC are tolerable. The current meta-analysis showed no significant difference in the risk of SCr increase between patients in the TAC and control groups.

There are five limitations to our meta-analysis. First, several studies contained incomplete information and the protein level before treatment was not clearly marked. Second, evaluation indicators in several studies were lacking or incomplete (e.g., lack of data on blood Cr or Cr

clearance, or no provision of initial data). Third, this meta-analysis did not include a particularly large number of RCTs, and the quality of the included trials was poor. Fourth, proteinuria outcomes were measured while the patients were on TAC; therefore, it is unclear whether the TAC-associated reduction in proteinuria was sustained or whether proteinuria rebounded after treatment was stopped. The limitation of using proteinuria as a surrogate outcome measure, and the implication of rebounding proteinuria after stopping TAC, should also be considered. Fifth, most of the RCTs included adult patients, so the results cannot be used to evaluate the efficacy and safety of TAC plus glucocorticoid in paediatric patients with IgAN. Finally, there is a lack of published small studies with negative outcomes. The risk of publication bias against studies with negative results is also a limitation.

Based on the above issues, we suggest that the following measures would improve future research: i) complete information for the TAC and control groups should be recorded; ii) high-quality RTCs with large numbers of participants are needed to assess TAC plus glucocorticoid therapy in IgAN patients, and the dose of TAC should be strictly monitored; iii) owing to the characteristics of IgAN, the follow-up time should be extended to ESRD, or dialysis or renal transplantation. The present results may be helpful in mitigating the reluctance to use TAC plus glucocorticoid for patients with IgAN. Indeed, the fear of an increase in SCr appears to have prevented researchers from designing clinical trials to study the use of this valuable immunosuppressive agent to treat IgAN, and we suggest that such trials may offer better long-term assessment of its effects.

In conclusion, TAC combined with glucocorticoid therapy for IgAN is both efficacious and safe. The anti-proteinuria effect of TAC plus glucocorticoid therapy is significant, though there was no statistically significant difference between the two groups in SCr or eGFR after treatment. The adverse events directly related to TAC plus glucocorticoid therapy are tolerable, but this conclusion needs confirmation by more carefully designed clinical trials.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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