Immunosuppressants or corticosteroids compared with supportive therapy: a systematic review and meta-analysis on the efficacy and safety for IgA nephropathy treatment

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Background: Corticosteroids or immunosuppressants and supportive treatment in reducing the risk of proteinuria and end-stage kidney disease (ESKD) in immunoglobulin A (IgA) nephropathy (IgAN) patients were still controversial. The purpose of this meta-analysis was to evaluate the efficacy and safety of immunosuppressants or corticosteroids compared with supportive therapy for treatment of IgAN in order to provide guidance for clinical practice.

Methods: We conducted an online search in PubMed, Embase, Cochrane Library, and Web of Science databases to collect randomized control trials (RCTs) about the efficacy and safety of immunosuppressants or corticosteroids compared with supportive therapy for treatment of IgA for relevant literature published from the databases' inception to August 21, 2021. The Cochrane risk assessment tool was used to assess the risk of bias in the included studies and analyzed by Revman 5.4 software, and Stata 15.0 statistical software was adopted for meta-analysis.

Results: A total of 10,622 related studies were retrieved, and 11 RCTs were finally included in the meta-analysis, with a total sample size of 809 cases. The primary outcome measures for immunosuppressants or corticosteroids were better than those for supportive therapy: proteinuria [weighted mean difference (WMD) =−0.54, 95% confidence interval (CI): −0.63, −0.44, Z =10.79, P<0.001] and ESKD [relative risk (RR) =0.189, 95% CI: 0.059, 0.605, Z =2.81, P=0.005]. The secondary outcome measures were also better than that for supportive treatment: glomerular filtration rate [standardized mean difference (SMD) =0.32, 95% CI: 0.09, 0.54, Z =2.48, P=0.013]. The incidence of adverse reactions was consistent with that of supportive treatment, and the difference was not statistically significant (RR =1.06, 95% CI: 0.71, 1.59, Z =0.28, P=0.777).

Discussion: Current evidence shows that immunosuppressants and corticosteroids can significantly reduce the risk of proteinuria and ESKD in IgAN patients. Due to limited quality and quantity of the included studies, more high-quality studies are need to verify above conclusion. In addition, we hope that more rationally designed multicenter RCTs that are not limited to short-term treatment outcomes will be conducted in the future.

Keywords: Immunoglobulin A nephropathy (IgAN); steroids; immunosuppressants; supportive therapy; meta-analysis

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Introduction

Immunoglobulin A (IgA) nephropathy (IgAN) is the most common primary glomerulonephritis and main cause of chronic kidney disease (CKD) in children and young adults. The prevalence of IgAN varies by region, with a higher incidence in the Asia-Pacific region. A global cross-sectional study from 1980 to 2010 showed that the overall population incidence of IgAN was at least 25 cases per million people (pmp) per year (1). Another recent epidemiological study showed that globally, Australia has the highest incidence of IgAN (105 pmp), followed by Asia (45 pmp) (2). IgAN is diagnosed by renal biopsy and immunofluorescence microscopy, and in most cases, it is only accompanied by mild symptoms. As a result, IgAN may go undetected in many people for a long time, which may delay treatment (3). Meanwhile, IgAN has a wide risk interval for progressive renal function decline, with the 10-year risk interval for end-stage kidney disease (ESKD) ranging from 5–60% (4). A cohort study involving the Swedish national population showed that the mortality rate of IgAN increased compared with a matched control group, with an increase of 1 death for every 310 cases of IgAN each year and a 6-year reduction in life expectancy (5).

At present, supportive therapy continues to be an approved conservative treatment strategy for IgAN, mainly involving angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) with fish oil to maintain appropriate blood pressure (6). While supportive therapy can help some IgAN patients reduce proteinuria and alleviate the rate of renal decline to a certain extent, a large number of patients do not benefit from it and have a high risk of renal failure over time (7), and thus there is need to explore other effective and active treatments. The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines recommend stratified management of IgAN patients, with the application of immunosuppressant/corticosteroid therapy restricted to high-risk patients, although the risks and benefits of systemic corticosteroids should be weighed due to the increased risk of adverse events (8). Controversy over the effect of immunosuppressants/corticosteroids in IgAN patients persists, and usage and results vary widely around the world (9). A STOP-IgAN trial study showed that immunosuppressants did not significantly improve prognosis compared with supportive treatment and increased more adverse reactions (10). Further, a 10-year follow-up study showed that compared to supportive therapy alone, the addition of immunosuppressants to supportive therapy did not significantly benefit ESKD and death outcomes (11). Meanwhile, a recent review suggested that although the use of corticosteroids may reduce proteinuria, their long-term benefits are questionable and corticosteroid use is associated with serious adverse effects, particularly infections (12).

Randomized controlled trials (RCTs) are considered to provide the highest level of evidence for establishing causality in clinical studies. Although similar systematic reviews have been previously published, this study attempted to conduct a meta-analysis of high quality RCTs exploring the efficacy and safety of immunosuppressants/corticosteroids for IgAN to provide a reference for the selection of an aggressive treatment regimen. We present the following article in accordance with the PRISMA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1028/rc).

Methods

Inclusion criteria and exclusion criteria

The inclusion criteria were: (I) RCT study type; (II) biopsy-proven IgAN patients, with no restriction on gender, age or region; (III) the intervention group was treated with immunosuppressants/corticosteroids, and the control group was treated with supportive therapy; and (IV) articles in English only.

The exclusion criteria were: (I) studies for which we were unable to access the full text, (II) prospective or retrospective study types, (III) duplicate and irrelevant literature, and (IV) literature data could not be extracted.

Outcome measures

The primary outcome measures of this meta-analysis were proteinuria excretion and ESKD, and the secondary outcome measures were glomerular filtration rate and adverse reactions. Among them, proteinuria excretion and glomerular filtration rate were the continuous effect indicators, and the effect size was the change from baseline to follow-up time point.

Literature retrieval

The literature was retrieved from English-language databases PubMed, Cochrane Library, Embase, and Web of Science, and the search time was set from the inception

of each database to August 21, 2021. The retrieval method was subject terms + free words. The subject terms searched in PubMed are shown in the Box S1. The databases were searched for published RCTs on immunosuppressants/corticosteroids versus supportive therapy in patients with IgAN, with grey literature excluded.

Literature screening and data extraction

In our study, 2 independent researchers participated in the process of literature screening. The first round of screening was carried out based on the title and abstract to exclude non-RCTs, studies which lacked control groups, and studies with interventions that did not match our theme. The articles were then screened based on reading the full text, and finally the included literature was determined.

Two researchers independently extracted data from the included literature using standardized forms. The extracted information included: basic information of the included studies (first author, publication year, country, etc.), patient information (number of patients, gender ratio, mean age), intervention measures, and outcome measures. After the information extraction was completed, the results were cross-checked by the 2 researchers, and any disagreement would be adjudicated with the assistance of a third researcher.

Risk of Bias evaluation

The 2 researchers independently used the Cochrane Collaboration Risk of Bias Tool (CCRBT) 2.0 to assess the risk of bias in the included studies. The 2 researchers cross-checked their assessments, and if there was any disagreement, a third researcher would assist with the decision. CCRBT evaluates risk of bias with 7 items from the following domains: (I) selection bias (random sequence generation and allocation concealment), (II) performance bias (blinding of participants and personnel), (III) detection bias (blinding of outcome assessment), (IV) attrition bias (incomplete outcome data), (V) reporting bias (selective reporting), and (VI) other bias. Each item is categorized as "high risk", "low risk", or "unclear" as the bias risk assessment result.

Statistical methods

Meta-analysis was performed using Stata 15.0 software. In this meta-analysis, the units of glomerular filtration rate were inconsistent, so the combined effect size was expressed by the standardized mean difference (SMD) and its 95% confidence interval (CI), i.e., SMD (95% CI). Since proteinuria excretion was dimensionally uniform, the combined effect size was expressed by weighted mean difference (WMD) and its 95% CI, i.e., WMD (95% CI). ESKD and adverse events were expressed as the relative risk rate (RR) of the comorbidity and its 95% CI, namely RR (95% CI). Q test and I^2 were used to quantify the heterogeneity among different studies and the determination of sources of heterogeneity was $P<0.05$ in two-sided. As described in the Cochrane handbook, $I^2>50\%$ may present substantial heterogeneity, and so we set this threshold as the cut-off value for model selection. When $I^2<50\%$, the fixed-effect model was used to combine the outcome measures; and when $I^2\geq50\%$, the random-effects model was employed to combine the outcome measures. The publication bias of the included studies was visually displayed by a funnel plot and analyzed by Begg's test and Egger's test. For the meta-analysis, Begg's test, and Egger's test, $P<0.05$ was considered a statistical difference.

Results

Literature retrieval results

A total of 10,622 related studies were retrieved from various databases, and after screening, 11 RCTs were finally included (10,13-22) in this meta-analysis. The literature screening process is shown in *Figure 1*.

Basic characteristics of the included literature

The included studies were published between 2003 and 2018 and involved a total of 809 patients, including 408 in the experimental group and 401 in the control group. The included studies were all RCTs, of which 3 (10,14,16) were open-label RCTs, with the intervention group receiving immunosuppressive/steroid treatment and the control group receiving supportive treatment. All treatment lasted more than half a year (*Tables 1*,*2*).

Quality evaluation of the included literature

CCRBT 2.0 was used to evaluate the risk of bias in the included studies. The risk rating of each study in selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases are shown in *Table 3*. A graphic display was produced using RevMan 5.4 (*Figure 2*).

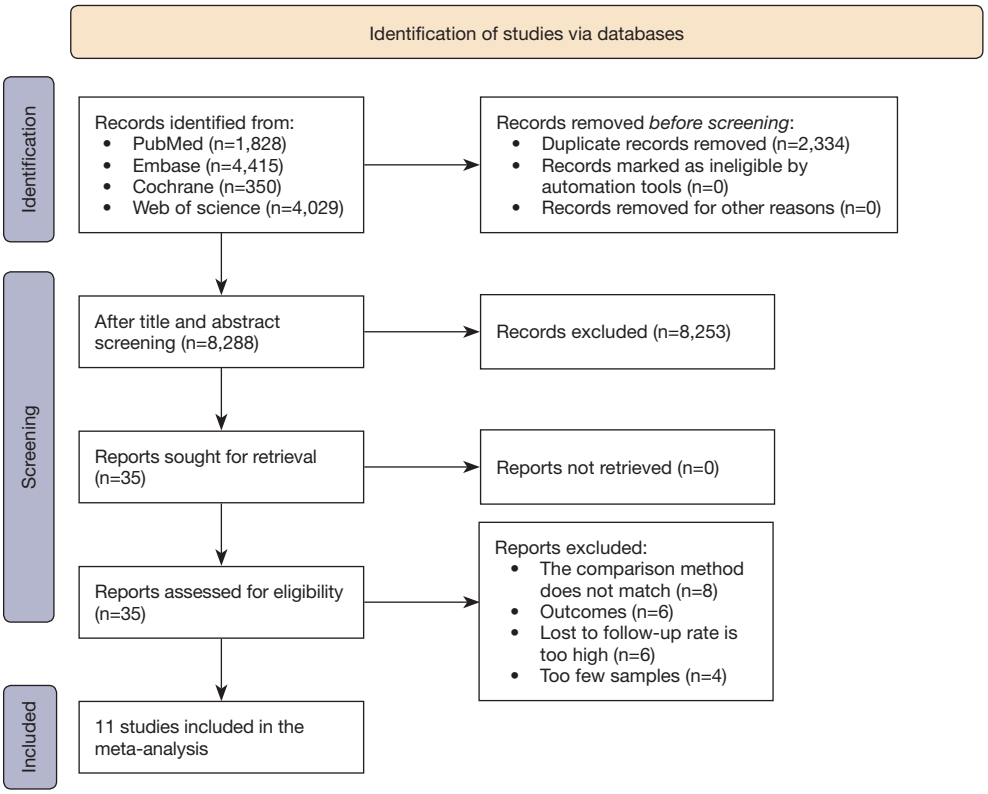

Figure 1 Flow chart of literature screening and results.

Meta-analysis

Proteinuria

Proteinuria was reported in 8 studies (13,15,16,18-22) and was represented by continuous variables (g/day). The effect size was combined using a fixed-effect model (I^2=36.0%, P=0.141). The combined results showed a statistically significant difference between the 2 groups (WMD =–0.54, 95% CI: –0.63, –0.44, Z =10.79, P<0.001), suggesting that immunosuppressant/corticosteroid treatment was significantly better than supportive therapy in reducing proteinuria in IgAN patients (*Figure 3A*).

We used a funnel plot to visually display the publication bias and adopted Egger's test and Begg's test to analyze the funnel plot. The analysis results of Egger's test and Begg's test did not show any bias (P>0.05). At the same time, sensitivity analysis results revealed no significant change in the effect size after excluding each study (*Figure 3B,3C*).

ESKD

Two studies (13,16) reported ESKD using dichotomous variables, and the effect size was combined using a fixed random-effect model (I^2=0%, P=0.738). The combined results showed that the difference between the 2 groups was statistically significant (RR =0.19, 95% CI: 0.06–0.61, Z =2.81, P=0.005), indicating that the risk of ESKD in IgAN patients treated with immunosuppressants/corticosteroids was significantly lower than that of supportive therapy (*Figure 4*).

Adverse reactions

Adverse reactions were reported in 8 studies (10,13,14,16,17,19,21,22) using dichotomous variables, and a fixed-effect model was utilized for the combined effect size (I^2=0%, P=0.915). The combined results showed no significant difference between the 2 groups (RR =1.06, 95% CI: 0.71–1.59, Z =0.28, P=0.777), indicating that the risk of adverse reactions in IgAN patients treated with immunosuppressants/corticosteroids was similar to that of supportive therapy (*Figure 5A*).

The publication bias was visually displayed using a funnel plot, which was further analyzed by Egger's test and Begg's test, with the results showing no bias (P>0.05). At the same time, sensitivity analysis results revealed no significant

Table 1 Basic characteristics of the included literature

No.	Study	Author country	Design	Intervention measures		Sample size		Gender (male/female)		Age		Follow-up
				T	C	T	C	T	C	T	C	
1	Rauen T 2015 (10)	Germany	RCT, open-label	Immunosuppressive, corticosteroids	Supportive therapy	82	80	61/19	58/24	45.8±12.5	42.8±13.1	3 y
2	Tang SC 2010 (13)	China	RCT	Immunosuppressants	Supportive therapy	20	20	6/14	8/12	42.1±2.6	43.3±2.8	6 m
3	Lv J 2009 (14)	China	RCT, open-label	Corticosteroids	Supportive therapy	33	33	20/13	19/11	27.8±8.9	30.43±8.8	NA
4	Pozzi C 2004 (15)	Italy	RCT	Corticosteroids	Supportive therapy	43	43	NA	NA	NA	NA	6 m
5	Manno C 2009 (16)	Italy	RCT, open-label	Corticosteroids	Supportive therapy	48	49	35/14	33/15	34.9±11.2	31.8±11.3	6 m
6	Hogg RJ 2015 (17)	USA	RCT	Immunosuppressive	Supportive therapy	25	27	14/11	18/9	31.8±11.7	32.2±13.2	6 m
7	Koike M 2008 (18)	Japan	RCT	Corticosteroids	Supportive therapy	24	24	6/18	5/19	37.9±10.1	38.3±12.7	24 m
8	Xie Y 2011 (19)	China	RCT	Immunosuppressive	Supportive therapy	35	30	14/21	14/16	33.63±11.71	33.68 ±10.29	12 m
9	Tang Y 2018 (20)	China	RCT	Corticosteroids	Supportive therapy	22	23	12/10	11/12	35.12±6.1	34.5±7.10	3 y
10	Locatelli F 2001(21)	Italy	RCT	Corticosteroids	Supportive therapy	52	50	NA	NA	NA	NA	6 m
11	Lou T 2006 (22)	China	RCT	Corticosteroids	Supportive therapy	24	22	8/16	10/12	29±11	34±11	6 m

RCT, randomized controlled trial; NA, not applicable; T, treatment group; C, control group; m, month; y, year.

Table 2 Characteristics of the treatment group and control group

No.	Study	Treatment group		Control group
		Immunosuppressants	Corticosteroids	Supportive therapy
1	Rauen T 2015 (10)	Cyclophosphamide, Azathioprine	Methylprednisolone, Prednisolone	ACE-I without ARB, ARB without ACE-I, ACE-I plus ARB
2	Tang SC 2010 (13)	Mycophenolate mofetil (MMF)	NA	Blockers of the renin–angiotensin system
3	Lv J 2009 (14)	NA	Prednisone	ACE-I (cilazapril)
4	Pozzi C 2004 (15)	NA	Imethylprednisolone, Prednisone	Diuretics, antihypertensive (ACE-I or ARB), antiplatelet agents
5	Manno C 2009 (16)	NA	Prednisone	Ramipril
6	Hogg RJ 2015 (17)	Mycophenolate mofetil (MMF)	NA	Lisinopril (or losartan) plus omega-3 fatty acid
7	Koike M 2008 (18)	NA	Prednisolone	ACE-I, dipyridamole or zilazep
8	Xie Y 2011 (19)	Mizoribine (MZR)	NA	Losartan
9	Tang Y 2018 (20)	NA	Methylprednisolone	ACE-I (Lotensin) and/or ARB (Losartan)
10	Locatelli F 2001(21)	NA	Methylprednisolone	Diuretics, antihypertensive (ACE-I or ARBs), antiplatelet agents
11	Lou T 2006 (22)	NA	Leflunomide	Fosinopril

NA, not applicable; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

Table 3 Risk of bias assessment of the included studies

Author	Year	v1	v2	v3	v4	v5	v6	v7
Hogg RJ (17)	2015	Low	Low	Low	Low	Low	Low	Low
Koike M (18)	2008	Low	Low	Unclear	Unclear	Low	Low	Low
Locatelli F (21)	2001	Low	Low	Unclear	Unclear	Low	Low	Low
Lou T (22)	2006	Low	Low	Unclear	Unclear	Low	Low	Low
Lv J (14)	2009	Low	High	High	High	Low	Low	High
Manno C (16)	2009	Low	High	High	High	Low	Low	Low
Pozzi C (15)	2004	Low	Low	Unclear	Unclear	Low	Low	Low
Rauen T (10)	2015	Low	High	High	High	Low	Low	Low
Tang SC (13)	2010	Low	Unclear	Unclear	Unclear	Low	Low	Low
Tang Y (20)	2018	Low	Low	Unclear	Unclear	Low	Low	Low
Xie Y (19)	2011	Low	Low	Unclear	Unclear	Low	Low	Low

v1-v7 in the table represent, in turn, random sequence generation, allocation concealment, performance blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

change in the effect size after excluding each study (*Figure 5B*,*5C*).

Glomerular filtration rate

Five studies (16,17,19,20,22) reported glomerular filtration rate (mL/min/1.73 m^2 or mL/min) using continuous variables, and a fixed-effect model was used for the combined effect size (I^2=0%, P=0.752). The combined results showed that the difference between the 2 groups was statistically significant (SMD =0.32, 95% CI: 0.09–0.54,

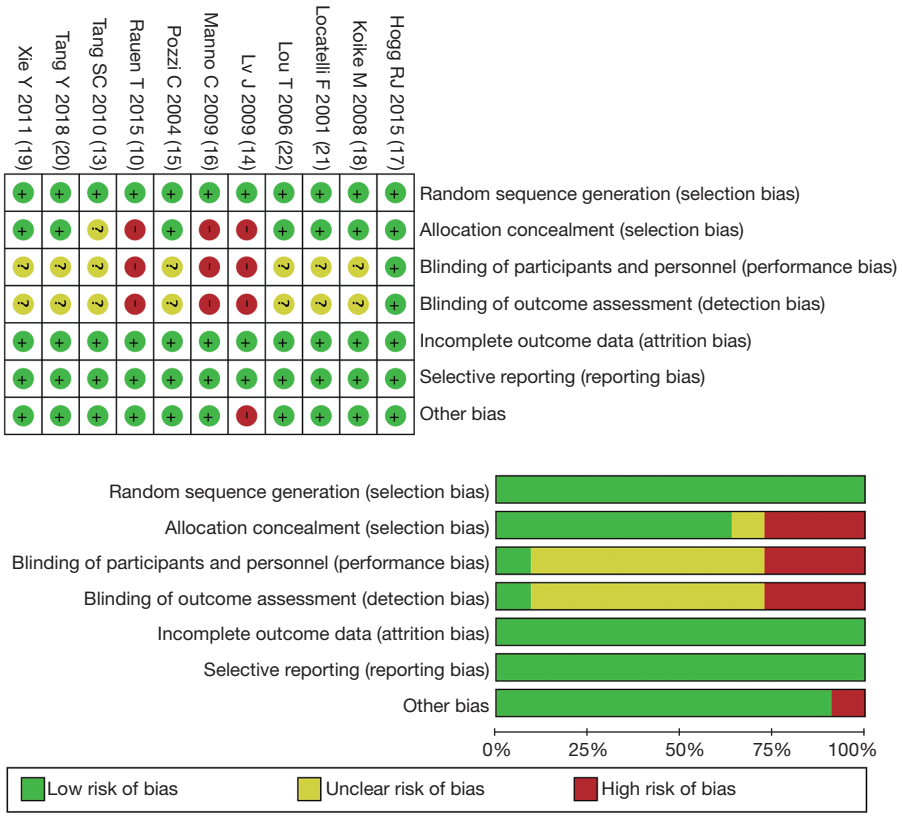

Figure 2 Risk of bias summary.

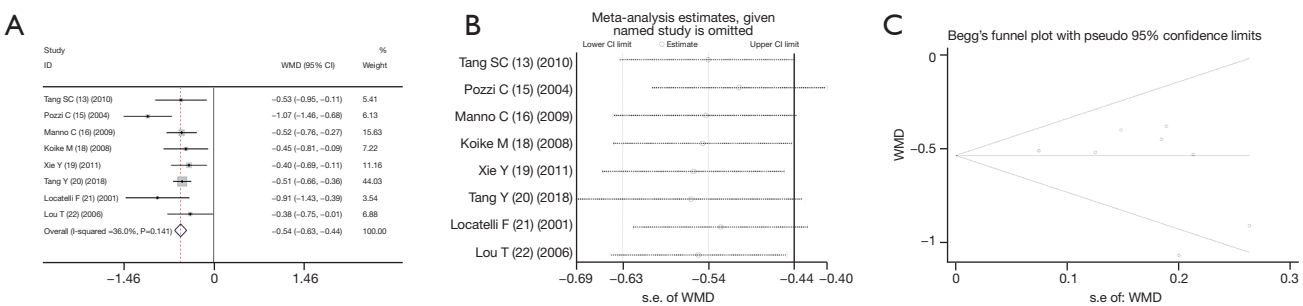

Figure 3 Forest plot, sensitivity analysis, and funnel plot of meta-analysis of proteinuria. WMD, weighted mean difference.

Z =2.48, P=0.013), suggesting that immunosuppressants/corticosteroids significantly increased the glomerulus filtration rate in IgAN patients (*Figure 6A*).

We used a funnel plot to visually display the publication bias, and adopted Egger's test and Begg's test to analyze the funnel plot. The results of Egger's test and Begg's test did not show any bias (P>0.05), and the results of sensitivity analysis indicated that the effect size did not change significantly after excluding each study (*Figure 6B,6C*).

Discussion

The present study involved a meta-analysis of RCTs to investigate the efficacy and safety of immunosuppressants/corticosteroids in IgAN patients compared with supportive therapy. A total of 11 RCTs were included in the meta-analysis. The results showed that compared with supportive therapy, immunosuppressants/corticosteroids significantly reduced the risk of proteinuria and ESKD and significantly

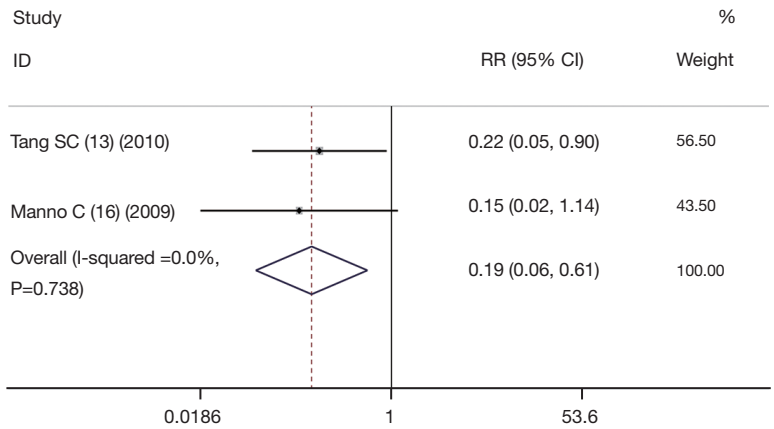

Figure 4 Forest plot of meta-analysis of end-stage kidney disease. RR, relative risk.

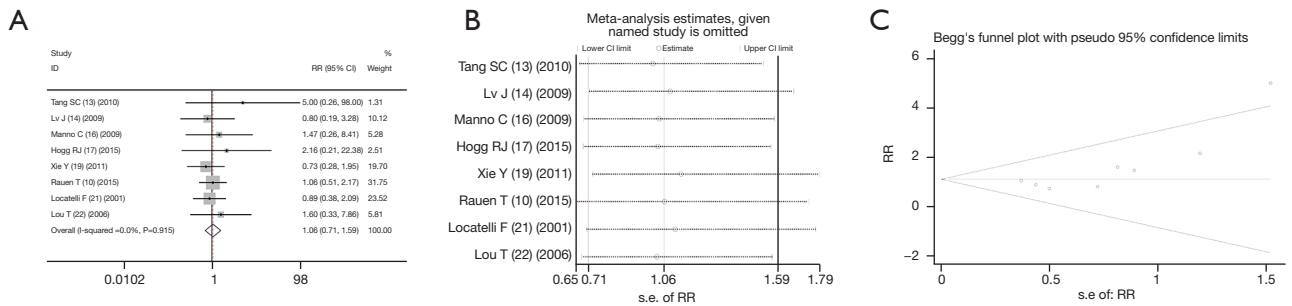

Figure 5 Forest plot, sensitivity analysis, and funnel plot of meta-analysis of adverse reactions. RR, relative risk.

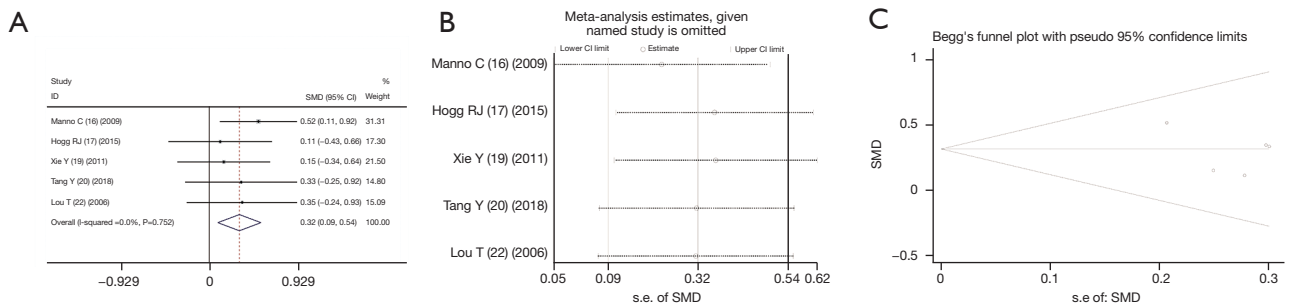

Figure 6 Forest plot, sensitivity analysis, and funnel plot of meta-analysis of glomerular filtration rate. SMD, standardized mean difference.

alleviated the decrease in glomerular filtration rate. The 2 groups were similar in terms of adverse reactions.

IgAN is an important cause of progression to ESKD. There is no uniformly agreed upon definition to determine ESKD, and in this study, ESKD was defined as the need to start dialysis or undergo kidney transplantation. ESKD remains the most unambiguous and clinically relevant endpoint for clinical trials (23), and although the significant loss of renal function has been accepted as an alternative endpoint for progression to ESKD, clinical trials in this area may take a long time to demonstrate therapeutic efficacy for this endpoint. A review by Thompson *et al.* (24) pointed out that proteinuria should be used as an early endpoint for the treatment of IgAN and as a reliable predictor of interventions for the long-term renal outcomes of IgAN. Inker *et al.* (25) conducted a meta-analysis based on 11

RCTs involving 4 interventions (ARB, fish oil, steroids, and other immunosuppressants), finding an association between the effect of changes in proteinuria from baseline to approximately 9 months (which can be measured between 7 and 12 months) and the effect of treatment on clinical endpoints of interest. Le *et al.* (26) concluded proteinuria was a predictor of renal outcome based on a 20-year cohort study of 1,155 Chinese adult IgAN patients. On this basis, proteinuria and ESKD were used as the primary outcome measures in this meta-analysis.

Sridharan *et al.* (27) recently published a network meta-analysis confirming that proteinuria remission rates of unsaturated fatty acids, corticosteroids/ARB, ARB, ACE, ARB/ACE, corticosteroids/ACE inhibitors (ACEI), and hypolipidemic drugs/ARB were significantly higher than those of standard treatment. Meanwhile, it was also noted that these results may change as future head-to-head clinical trials are conducted. The network meta-analysis by Tan *et al.* (28) showed that immunosuppressants/corticosteroids seemed to reduce proteinuria levels. Our study confirmed that compared with supportive therapy, immunosuppressant or corticosteroid treatment for IgAN patients could significantly reduce proteinuria, with only low heterogeneity among studies and no publication bias. Further, the risk of ESKD within 6 years was significantly reduced, which seems to support an association between long-term renal outcomes and proteinuria in IgAN patients. In addition, a multicenter, large-scale, long-term follow-up observational cohort study showed that immunosuppressant/corticosteroid treatment in IgAN patients had better long-term renal outcomes (29). Meanwhile, a 15-year follow-up study of 1,243 children with IgAN in China showed that immunosuppressant/corticosteroid therapy improved long-term renal outcomes (30). In general, these results indicated that immunosuppressive agents/corticosteroids could effectively alleviate proteinuria levels in IgAN patients and reduce the risk of ESKD.

Moreover, our results also showed that the 2 treatment regimens had a similar risk of adverse events, which was different from the results of other studies. The meta-analyses using non-immunosuppressants/corticosteroids as a reference showed that immunosuppressants/corticosteroids significantly increased the incidence of adverse events (30,31). The possible reason may be that our reference objects were patients receiving a single supportive treatment, and the types of adverse events in this study were diverse and mainly mild with good tolerance, including diarrhea, gastrointestinal discomfort, cough, insomnia, nausea, and mild hair loss. However, a very small number of patients also experienced adverse reactions such as urinary tract infections and severe diarrhea. Overall, this meta-analysis showed that immunosuppressants/corticosteroids had a similar safety profile to supportive therapy. Glomerular filtration rate is critically important for determining drug dosing as well as prognosis and treatment in patients with kidney disease. Low glomerular filtration rate predicts cardiovascular disease, end-stage renal disease (a requirement for dialysis or transplantation), and death. A recent Cochrane systematic review (32,33) showed that the effect of immunosuppressants/corticosteroids on glomerular filtration rate in IgAN patients was not clear compared with other treatment options, whereas our study showed that this treatment regimen effectively alleviated the reduction of glomerular filtration rate compared with supportive therapy.

This meta-analysis had the following advantages. First, this meta-analysis conducted a comprehensive and systematic evaluation of the efficacy and safety of inhibitors/corticosteroids compared with supportive therapy in IgAN patients based on RCTs, providing a reference for the selection of subsequent clinical treatment plans. Second, the heterogeneity of each outcome measure in this study was quite small, and there was no publication bias, which ensures the accuracy of the results of this study. Nevertheless, our study had some limitations. First, although we conducted a comprehensive search of mainstream databases, there were still few RCTs that could be included in this meta-analysis, otherwise only English language database were searched which that would have language bias. Second, adverse events covered a large range and were not combined with treatment-related adverse events, which may result in a certain bias in the safety review. Third, there was some variation in the interventions included in the studies, such as differences in the type, dose, and duration of immunosuppressive and supportive therapies, which may lead to clinical heterogeneity, and the number of included studies prevented a more in-depth subgroup analysis, which may have affected the accuracy of the results and needs to be clarified in future studies.

Conclusions

Compared with supportive therapy, immunosuppressants/corticosteroids can significantly reduce the risk of proteinuria and ESKD in IgAN patients and appear to have a similar safety profile. However, few studies were included in this meta-analysis and treatment-related adverse events

were not effectively assessed. Therefore, we hope that more reasonably designed multicenter RCTs not limited to short-term treatment outcomes will be conducted in the future.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1028/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1028/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Box S1 PubMed search strategy

#1	"Glomerulonephritis, IGA"[Mesh]
#2	((((((((((Glomerulonephritides, IGA[Title/Abstract]) OR (Berger's Disease[Title/Abstract])) OR (Bergers Disease[Title/Abstract])) OR (IGA Glomerulonephritis[Title/Abstract])) OR (Nephropathy, IGA[Title/Abstract])) OR (Iga Nephropathy 1[Title/Abstract])) OR (Nephropathy 1, Iga[Title/Abstract])) OR (Immunoglobulin A Nephropathy[Title/Abstract])) OR (Nephropathy, Immunoglobulin A[Title/Abstract])) OR (Nephritis, IGA Type[Title/Abstract])) OR (IGA Type Nephritis[Title/Abstract])) OR (Berger Disease[Title/Abstract])) OR (IGA Nephropathy[Title/Abstract])
#3	#1 OR #2
#4	"Glucocorticoids"[MeSH Terms]
#5	((((Glucocorticoid[Title/Abstract]) OR (Glucocorticoid Effect[Title/Abstract])) OR (Effect, Glucocorticoid[Title/Abstract])) OR (Glucorticoid Effects[Title/Abstract])) OR (Effects, Glucorticoid[Title/Abstract])
#6	#4 OR #5
#7	"Immunosuppressive Agents"[Mesh]
#8	((((Agents, Immunosuppressive[Title/Abstract]) OR (Immunosuppressants[Title/Abstract])) OR (Immunosuppressive Agent[Title/Abstract])) OR (Agent, Immunosuppressive[Title/Abstract])) OR (Immunosuppressant[Title/Abstract])
#9	#7 OR #8
#10	"Palliative Care"[Mesh]
#11	((((((Care, Palliative[Title/Abstract]) OR (Palliative Treatment[Title/Abstract])) OR (Palliative Treatments[Title/Abstract])) OR (Treatment, Palliative[Title/Abstract])) OR (Therapy, Palliative[Title/Abstract])) OR (Palliative Supportive Care[Title/Abstract])) OR (Surgery, Palliative[Title/Abstract])
#12	#10 OR #11
#13	Randomized controlled trial
#14	Controlled clinical trial
#15	Randomized
#16	Randomly
#17	Trials
#18	RCT
#19	#13 OR #14 OR #15 OR #16 OR #17 OR #18
#20	#3 AND #6 AND #9 AND #12 AND #19

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