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NEPHROLOGY - REVIEW

Efficacy and safety of glucocorticoids for patients with IgA nephropathy: a meta-analysis

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Abstract

Background The efficacy and safety of glucocorticoids for the treatment of patients with IgA nephropathy (IgAN) remains controversial. The aim of the study is to perform a metaanalysis of randomized controlled trials to evaluate the efficacy and safety of glucocorticoids for patients with IgAN.

Methods We searched PubMed, EMBASE and the Cochrane Library and article reference lists of Controlled Trials, and Clinical Trial Registries for randomized controlled trials comparing glucocorticoids with other non-immunosuppressive agents in patients with IgAN.

Results The present meta-analysis, including 10 RCTs and 791 patients from 12 published studies, showed that using glucocorticoids agents relatively preserves kidney function(RR 0.06, 95% CI 0.14–0.61) and plays an effective role on reducing the proteinuria(SMD, −0.69; 95% CI 0.85 to −0.53, $p < 0.00001$; heterogeneity I2 = 0%; $p = 0.09$) compared with a control group. Moreover, adverse events cannot be neglected, especially gastrointestinal tract (RR 3.10, 95% CI 1.37–6.98, $p = 0.006$; heterogeneity I2 = 0%, $p = 0.86$), and corticosteroid regimens in IgAN should be reviewed with regard to safety.

Conclusions Glucocorticoids were wildly used to treat various diseases including IgAN. Meanwhile, adverse events cannot be neglected, such as gastrointestinal adverse events, infection and so on. Corticosteroid should be used with reserve, especially in those patients with hypertension and impaired renal function or older patients.

Keywords Glucocorticoids · IgA nephropathy · Meta-analysis · Adverse events

Introduction

IgA nephropathy (IgAN) is an immune-mediated kidney disease correlated with IgA immune complex formation and deposition in the glomerular mesangium. The most frequent clinical presentation of IgAN is microscopic hematuria with variable proteinuria [1–3]. IgAN is the most common type of glomerulonephritis worldwide. However, its prevalence in some countries is underestimated due to government policy for kidney biopsy. A biopsy-based systematic review including many countries showed an overall population incidence of < 2.5/100,000 persons [4]. In China alone, the incidence ranges from 37 to 58% [5–7]. Though IgAN is considered a benign lesion, the high prevalence and chronic progression of IgAN can result in a heavy economical burden. IgAN patients have different clinical and pathological manifestations, which correspond with considerable variations in prognosis. Patients diagnosed with microscopic hematuria and stable kidney function will ultimately progress to kidney failure, and 20–40% of patients progress to end-stage renal disease (ESRD) within 10–20 years after diagnosis [4]. These challenges emphasize the urgent need for an efficient and safe strategy to reduce the progression of IgAN.

The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for glomerulonephritis suggested that anti-hypertension and anti-proteinuria drugs can be used to treat IgAN [8]. Glucocorticoids, cyclophosphamide cyclosporine A, antihypertensive agents and fish oils are included [9, 10]. Recent studies showed that, in IgAN patients who have relatively preserved kidney

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function, steroid therapy reduces proteinuria and may prevent ESRD progression [8, 11].

In addition, prospective clinical studies on the use of corticosteroids in IgAN have been conducted. However, a recent randomized clinical trial (RCT) carried out by Zhang et al. [12] suggested that corticosteroids might increase the risk of serious infections. Considering these results with those of recent studies, the efficacy and safety of glucocorticoids in IgAN treatment remain uncertain [13]. Thus, a systematic review and meta-analysis were carried out to evaluate the effect and safety of glucocorticoids in IgAN treatment and summarize the currently available data from appropriate RCTs.

Methods

Data sources and search strategy

This study was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Electronic databases were searched, including PubMed, EMBASE and the Cochrane Library. The following search terms were used (in combination with MeSH terms): glomerulonephritis IgA, Berger's disease, IgA glomerulonephritis, IgA nephropathy, immunoglobulin A nephropathy, steroid, glucocorticoid, proteinuria, prednisone, glucocorticoids, clinical trials and randomized controlled trials. Additional duplicates were found by a manual search of reference lists. Articles were evaluated by two of the authors independently (Q.G. and X.W.) to ascertain conformity with the inclusion criteria.

Study selection

Using these search terms, 105 articles were selected. The titles and abstracts of the articles were reviewed by two of the authors independently (Q.G. and X.W.). Only studies that met the following inclusion criteria were included in analyses: (1) prospective RCTs; (2) human subjects confirmed by renal biopsy data; and (3) study compared glucocorticoid agents to placebo/no treatment/any other non-immunosuppressive agents. Studies that evaluated any other immunosuppressive therapy (e.g., cytotoxic agents or mycophenolate mofetil) were excluded.

Quality assessment of articles

The quality of included studies was assessed using Cochrane Collaboration's Tool for assessing the risk of bias. The Cochrane criteria consisted of the following seven domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other sources of bias. Each study was judged to have high, low or unclear risk in these aspects.

Data abstraction

Full texts of studies meeting the inclusion criteria were analyzed, and data regarding information of author and study, trial design, drug dosage, duration of intervention, baseline characteristics of the trial population, changes in renal survival, proteinuria and adverse events between treatment group and control group were extracted. The primary outcome was renal survival [defined by impairment of renal function reaching a doubling of serum creatinine and/or 50% decrease in estimated glomerular filtration rate (eGFR) and/or progression to ESRD requiring dialysis therapy or transplantation at any time during treatment], with the log-rank p value of renal survival analyzed by means of the Kaplan–Meier method. The secondary outcome was daily proteinuria (g/24 h) at the end of treatment [measured from timed urine specimens for proteinuria and albuminuria and spot urine specimens (protein to creatinine or albumin to creatinine ratio) and converted to g/24 h].

Statistical analysis

For the dichotomous outcome, the relative risk (RR) measure was calculated for individual trials. Continuous outcomes from individual trials were analyzed using the difference in means at the end of treatment, and the standardized mean difference (SMD) was used as a summary estimator. All summary effects are presented with 95% confidence interval (CI).

The fixed-effect model weighted by the Mantel–Haenszel method was used, followed by a test of homogeneity [14]. Heterogeneity was analyzed using the χ^2 test on $N-1$ degrees of freedom. A p value of 0.05 was regarded as the critical value for homogeneity. If the hypothesis of homogeneity was rejected (p value < 0.05), then the random effect model using the DerSimonian–Laird method was employed. Forest plots were used for graphic representation of data. Vertical lines in these plots—positioned at 1 for RR—represent equivalence in efficacy between experimental and control treatments. A solid square and horizontal line represent the RR with 95% CI, respectively. The surface area of the black square represents the relative quantitative contribution of the trial to the analysis (weight). The horizontal line indicates the 95% CI. The diamond-shaped symbol is the summary estimate of effect expressed as the RR with 95% CI, which is a weighted average of the pooled treatment effects across all trials. p values < 0.05 were considered statistically significant. In our analysis, all glucocorticoids were

combined regardless of dosages with an assumed class effect and analyzed regardless of the types of controls.

To determine the robustness of our pooled effects, we compared our primary analysis with fixed effects and random effects models. Pooled estimates were also recalculated after excluding RCTs with poor quality. All statistical analyses were performed using Review Manager 5.3 statistical software for the meta-analysis.

Results

Summary of included studies

As shown in Fig. 1, our search strategy identified 105 potentially relevant studies using combined searches in PubMed, EMBASE and Cochrane Library databases. After two authors independently screened each title and abstract, 93 studies were removed because of repetition, not a relevant disease, absence of renal outcomes, review articles, basic research studies, inappropriate patient enrollment and combination of immunosuppressive medication.

Characteristics of Included Studies (Table 1)

After the assessment, 12 articles (10 trials) [12, 14–22], enrolling a total of 791 patients, met the inclusion criteria and were incorporated into this meta-analysis. Details of the included studies are listed in Table 1, and three of the studies were derived from the same trial.

Risk of bias

Systematic assessment of the risk of bias in the included studies is presented in Fig. 2. These trials manifested high variations in overall quality because of differences in their study design, structure and methodology. Overall, study quality was average. Three of the included RCTs did not describe the process of random sequence generation in detail and five RCTs were estimated as low-risk

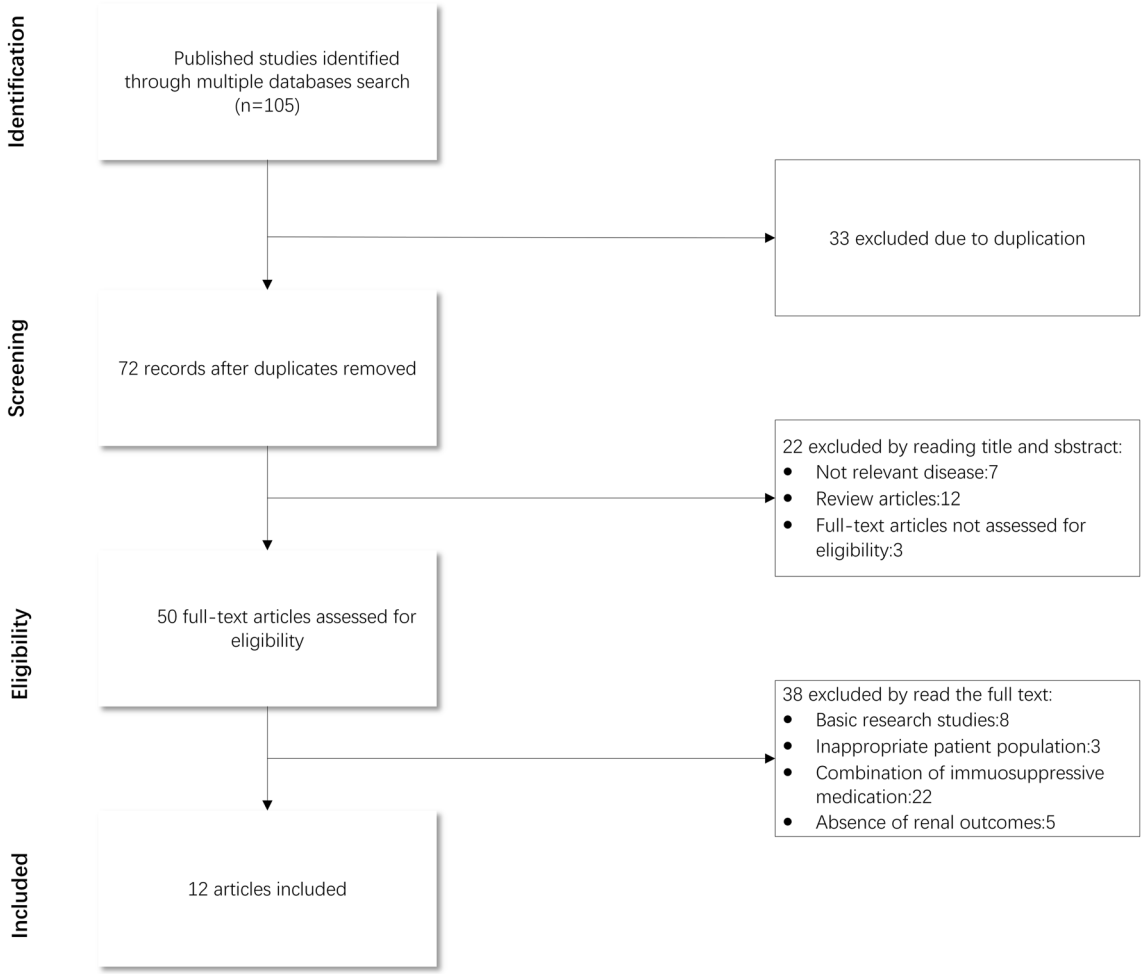

Fig. 1 Flow diagram of studies considered for inclusion

Table 1 Characteristics of interventions and population at baseline and end of treatment in included RCTs

Sr. No.	Author (year) [Ref.]	Intervention and sample size		Baseline characteristics	Follow-up months	Treatment group		Control group	
		Treatment group	Control group			Sample sizes	DRF/UH	Samplesizes	DRF/UH
1	Lv et al. (2017) [12]	Methylprednisolone 0.6–0.8 mg/kg/day for 2 months, then tapered by 8 mg/day each month, with a total treatment period of 6–8 months	Placebo	Proteinuria > 1 g/day and eGFR between 20 and 120 mL/min/1.73 m^2; M:F = 39:24	25	134	8	126	20
2	Manno et al. (2009) [16]	Oral prednisone 1.0 mg/kg/day for 2 months and then the dose was tapered by 0.2 mg/kg/day for 4 months. The maximal prednisone dose was 75 mg/day	Ramipril	Proteinuria ≥ 1.0 g/day for at least 2 months and eGFR ≥ 50 ml/min/1.73 m^2, Age 16–70 years	96	48	2	49	13
3	Koike et al. (2008) [23]	Prednisolone 0.4 mg/kgBW/day (20–30 mg/day), gradually tapered to 5–10 mg/day over 24 months. plus anti-platelet agent 150–300 mg/day	Dipyridamole or zilazep hydrochloride	Proteinuria ≥ 1.0 g/day for at least 2 months and eGFR ≥ 50 ml/min/1.73 m^2,M:F = 3:1	24	24	9	24	9
4	Hogg et al. (2006) [15]	Prednisone 60 mg/m^2 every other day for 3 months, then 40 mg/m^2 every other day for 9 months, then 30 mg/m^2 every other day for 12 months	Placebo	Persistent severe proteinuria, (UP/C) ratio > 1.0 or moderate proteinuria, i.e., UP/C ratio > 0.5, age < 40 years; M:F 26:13	24	30	2	29	4
5	Katafuchi et al. (2003) [19]	Prednisolone 20 mg/day, for 1 month, followed by15 mg/day for 1 month, 10 mg/day for 1 month, 7.5 mg/day for 3months, and 5 mg/day for 18 months,plus dypiridamole 150–300 mg/day	Dypiridamole 150–300 mg/day	Plasma creatinine concentrations < 1.5 mg/dl. Age < 60 years	65 ± 25	43	3	47	3
6	Shoji et al. (2000) [22]	Prednisolone 0.8 mg/kg/day and tapering to 10 mg q.o.d. 1 year	Dypiridamole 300 mg/day	Proteinuria less than 1.5 g/day; plasma creatinine concentrations < 1.5 mg/dl. Age 15 and 55 years	12	11	0	8	0

Table 1 (continued)

Sr. No.	Author (year) [Ref.]	Intervention and sample size		Baseline characteristics	Follow-up months	Treatment group		Control group	
		Treatment group	Control group			Sample sizes	DRF/UH	Samplesizes	DRF/UH
7	Pozzi et al. (2004) [17]	Methylprednisolone 1 g i.v. for 3 consecutive days, then prednisone 0.5 mg/kg/day for 6 months	Supportive therapy	Urinary protein excretion of 1.0–3.5 g daily for at least 3 months, and plasma creatinine concentrations ≤ 133 mol/l (1.5 mg/dl); age 15–69 years	60	43	10	43	23
8	Lv et al. (2009) [20]	Prednisone 0.8 to 1.0 mg/kg/day for 8 weeks, then the dose was tapered by 5 to 10 mg every 2 weeks; plus cilazapril	Cilazapril	Urine protein excretion of 1 to 5 g/day; eGFR > 30 ml/min; age 18–65 years	28	33	1	30	7
9	Julian and Barker (1993) [18]	Alternate day prednisone 60 mg 3 months	No treatment	Creatinine clearance > 25 ml/min /1.73 m^2	6–24	18	1	17	2
10	Lai et al. (1986) [21]	Prednisolone 40–60 mg/day for 2 months, then 1/2 dose in subsequent 2 months	Supportive therapy	IgA nephropathy with nephrotic syndrome; age 11–59 years; M:F = 40:35	38	17	2	17	3

DRF Deteriorated renal function; *UH* uremia and/or hemodialysis; *M:F* male:female

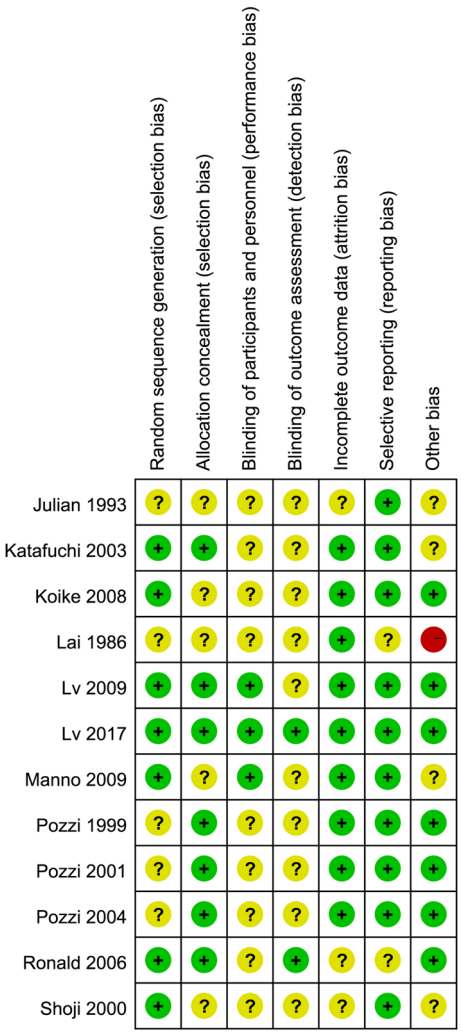

Fig. 2 Quality assessment of RCTs included in the review

on allocation concealment. Only two of ten trials implemented a double-blind strategy. No obvious problem was detected on the bias of incomplete outcome data and selective reporting, except for research conducted by Lai in 1986 [21]. Because this study included essential data, we ultimately included it in this meta-analysis.

We removed three studies with low Cochrane criteria scores from our analysis. In addition, no obvious differences in effects of glucocorticoid agents on renal function and proteinuria were observed when compared with the control group.

Outcomes

As shown in Table 2, we performed a meta-analysis on some baseline data, including age, creatinine clearance and mean systolic blood pressure. No remarkable heterogeneity was found, thus, we evaluated these ten RCTs in one meta-analysis using a fixed-effect model. Analysis of baseline data suggested that no significant difference existed between treatment and control groups.

Renal survival

Six studies reported renal survival data with Kaplan–Meier survival curves. Because results may be influenced by the various steroid regimens employed, we carried out subgroup analysis to decrease clinical heterogeneity.

As shown in Fig. 3, compared with control groups, renal function improved with glucocorticoid treatment in the subgroup for oral prednisone treatment (four trials, RR 0.34, 95% CI 0.13–0.89). In addition, compared with control groups, renal function improved with glucocorticoid treatment in the subgroup for oral methylprednisolone treatment (RR 0.37, 95% CI 0.12–1.15) and the subgroup for oral prednisone plus intravenous methylprednisolone treatment (RR 0.08, 95% CI 0.01–0.56). Given the subgroups were combined, the hazard of deterioration in renal function was significantly decreased in treatment groups (RR 0.30, 95% CI 0.14–0.61) when the weight of each individual study was taken into account.

Daily proteinuria

Eight of 12 RCTs evaluated daily proteinuria in 637 patients (control group = 313 patients; treatment group = 324 patients). As no heterogeneity of the effects on daily proteinuria was found, we did not use univariate study-level meta-regression and subgroup analyses for heterogeneity analysis.

As shown in Fig. 4, the glucocorticoid treatment group exhibited a greater reduction in proteinuria compared with the control group (SMD −0.69, 95% CI, 0.8 to −0.53, $p < 0.00001$; heterogeneity $I^2 = 0\%$, $p = 0.09$).

Table 2 Meta-analysis of age, creatinine and mean systolic BP clearance at baseline

Treatment group versus control group	No. of studies	*p* for heterogeneity	Pooled estimate	95% Confidence interval	*p* for test for overall effect
Age	9	0.003	−0.49	−2.93 to 1.95	0.69
Serum creatinine	8	0.34	−0.03	−0.08 to 0.02	0.25
Mean systolic BP	6	0.02	−1.68	−4.48 to 1.12	0.24

Adverse events

As shown in Table 3, compared with the control group, adverse effects of steroid treatment were recorded in 7 of 10 RCTs. Adverse effects (mentioned ≥ 2 times) included gastrointestinal tract reactions, type 2 diabetes mellitus (2DM), hypertension, insomnia and perspiration. No significant differences were observed between treatment and control

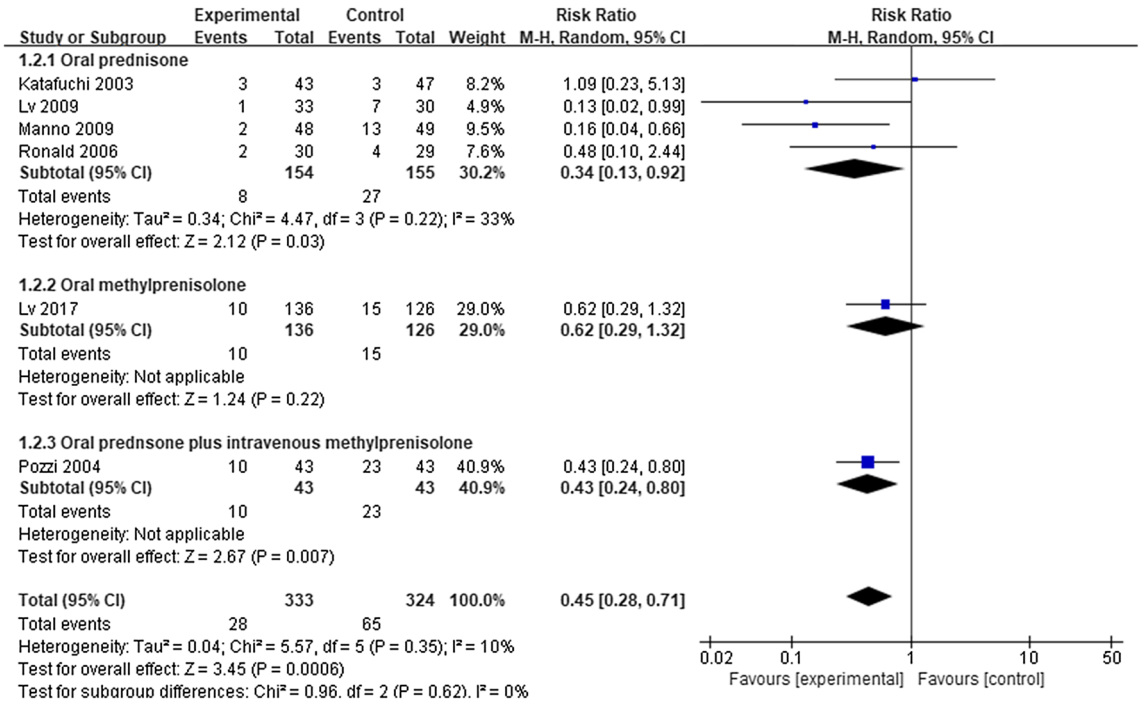

Fig. 3 Comparison of glucocorticoids versus controls on renal survival

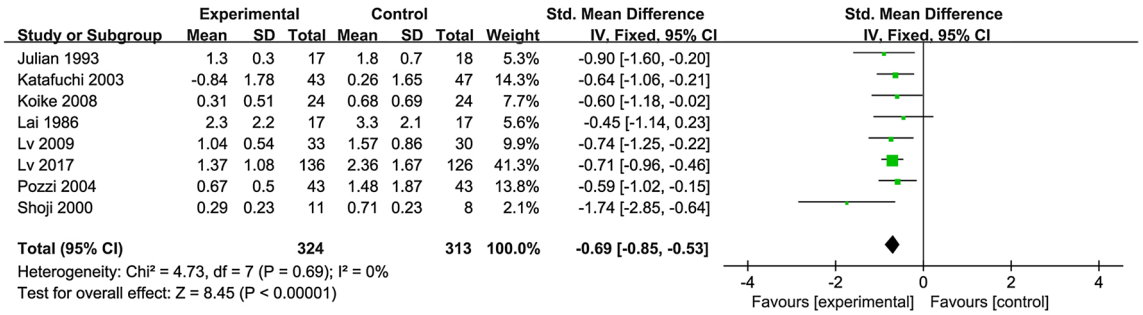

Fig. 4 Comparison of glucocorticoids versus controls on daily proteinuria

Table 3 Meta-analysis of patient adverse events

Adverse events	No.of studies	Treatment group	Control group	*p* for heterogeneity	Pooled estimate	95% Confidence interval	*p* for test for overall effect
DM	3	5	4	0.58	1.2	0.36 to 4.02	0.77
Hypertension	4	12	12	0.79	1.01	0.49 to 2.08	0.99
Gastrointestinal tract	2	20	6	0.86	3.1	1.37 to 6.98	0.006
Insomnia, perspiration	3	5	0	0.94	4.44	0.78 to 25.31	0.09

groups by the meta-analysis. These results suggested that patients receiving steroid therapy did not have an increased risk of developing 2DM, hypertension, insomnia and perspiration. However, glucocorticoid use was found to be linked to a marked increase in the risk of gastrointestinal adverse events (RR 3.10, 95% CI 1.37–6.98, $p=0.006$; heterogeneity $I^2=0\%$, $p=0.86$). Furthermore, while some adverse events were only mentioned once, they cannot be neglected, such as serious adverse outcomes due mainly to an increased risk of serious infections. These adverse events will be further explained in Sect. 4.

Discussion

The present meta-analysis, which included 10 RCTs and 791 patients from 12 published studies, showed that glucocorticoid treatment relatively preserves kidney function and plays an effective role in reducing proteinuria compared with the control group. Moreover, adverse events cannot be neglected, especially gastrointestinal tract reactions, and corticosteroid regimens in IgAN should be reviewed for safety. This evidence directly originated from the majority of included studies, despite their heterogeneity and average quality.

Data on adverse outcomes potentially associated with treatment were collected from the trials but were inconsistently reported (Table 2). Several adverse events were reported, such as severe infections, DM or impaired glucose intolerance, hypertension, gastrointestinal bleeding, cushingoid features, insomnia, headache and weight gain. However, only four adverse events were mentioned several times, including DM, hypertension, gastrointestinal bleeding and insomnia. Furthermore, glucocorticoid use was found to be linked to a marked increase in the risk of gastrointestinal adverse events. A trend toward increases in other risks (i.e., DM and hypertension) was observed but did not reach statistical significance.

Of note, the results from only one of the studies included in the meta-analysis were inconsistent with those of the other studies. Zhang et al. [12] reported that glucocorticoid use might cause a nearly fivefold higher risk of serious adverse events. In this trial, the difference in the rate of infections may be explained by differences in trial population or specific treatment regimen employed. More important, the incidence of infections in the study by Zhang et al. was consistent with the supportive versus immunosuppressive therapy for the treatment of progressive IgA nephropathy (STOP-IgAN) trial [24]. The STOP-IgAN trial also collected detailed adverse event data and found similarly high rates of severe infections among the immunosuppression group (8.1% vs. 9.8%), including one death in the combination immunosuppression group. In a subsequent reanalysis examining the two immunosuppression regimens separately, it was shown that the increase in full clinical remission was driven exclusively by the glucocorticoid monotherapy arm, which produced a transient reduction in proteinuria in patients with relatively well preserved GFR [25]. However, there were limitations to both studies. Primarily, neither study used renal biopsy features when determining patient eligibility and the follow-up time for both studies was relatively short for a disease that typically is slowly progressive.

Other research has reported that steroid therapy is associated with an increased risk for adverse events, mainly because of an increased risk for cushingoid features. A trend toward increases in other risks (i.e., DM and weight gain) was observed but did not reach statistical significance [11].

Glucocorticoid treatment has similar side effects in other diseases. In asthmatic patients, glucocorticoid-associated adverse effects were common and included cataracts, DM, myocardial infarction, osteoporosis, peptic ulcer or stroke [26]. In patients with rheumatoid arthritis, glucocorticoid use has been associated with adverse events, such as osteoporosis, fracture, aseptic necrosis of the bone, 2DM, ulcer/gastrointestinal bleeding, infection, myocardial infarction or stroke [27]. In addition, in systemic lupus erythematosus patients, higher doses of glucocorticoids were associated with an increased risk of osteonecrosis bacterial infection, cushingoid syndrome and sleep disorder [28].

Immunosuppressants have been clinically used to treat IgAN, [29, 30] however, the immunosuppressant treatment proposal for IgAN patients with impaired kidney function and remarkable proteinuria (proteinuria > 1 g/24 h) has been controversial. Some studies indicated that corticosteroids and immunosuppressants might not provide substantial kidney-related benefits [31, 32], whereas other reports indicated that the combination of the two might have a positive synergistic effect. Pozzi et al. reported a small group of IgAN patients treated with methylprednisolone plus azathioprine or steroid alone and concluded that while 6-year renal survival rates were similar between the two groups, the addition of azathioprine may be slightly more effective than steroids alone in patients with chronic renal failure [33]. Although KDIGO advised that mycophenolate mofetil (MMF) should not be used for IgAN treatment, it was recognized that the evidence base on which the decision had been made was very poor. KDIGO recommended that an RCT comparing MMF and corticosteroids versus corticosteroids alone in patients receiving optimal antihypertensive and antiproteinuric therapy should be performed, as well as an RCT to investigate the efficacy of MMF in Asians compared with Caucasians, including evaluation of drug and metabolite levels. Two new studies of MMF in IgAN [34, 35] have been published since 2012 and these are reviewed. Tan et al. [36] reported that

immunosuppressive treatment (corticosteroids and immunosuppressive therapy) might be superior to glucocorticoids alone.

Overall, glucocorticoids are broadly used to treat various diseases including IgAN. This therapy is inexpensive, appears to be mostly well tolerated and offers great promise as a method of substantially reducing the burden of ESRD worldwide. Nevertheless, adverse events cannot be neglected, such as gastrointestinal adverse events and infection. Corticosteroids should be used with reserve, especially in patients with hypertension and impaired renal function or older patients.

There are several limitations to this analysis. There was heterogeneity in many comparisons, which may have introduced potential interference in the analysis. Although we minimized the likelihood of an effect by performing a careful search for published studies, using strict study inclusion criteria, performing precise data extraction and carefully analyzing data, significant study heterogeneity existed in some comparisons (e.g., dosage and drug type, duration of intervention and follow-up time). Studies should have adequate follow-up and clearly report adverse events in greater detail. Long-term follow-up studies that evaluate the true outcome of renal death (i.e., ESRD) might yield different results because durations of the included studies were not long enough to assess ESRD. Finally, most participants in the included studies received concomitant drugs, such as thiazide diuretics agents, beta-blockers or renin-angiotensin system blockers.

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Author contributions HZ, YL conceived the idea for this systematic review. GQ, XZ and WX developed the methodology for the systematic review, and YL and XZ supervised the methodological process. The manuscript was drafted by GQ and XZ. All authors critically reviewed and approved the final manuscript.

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Compliance with ethical standards

Conflict of interests The authors declare that they have no competing interests.

Ethical approval Ethics approval is not required because this is a protocol for a systematic review and meta-analysis in which no primary human data will be collected.

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