

## REVIEW PAPER

# Does corticosteroid treatment affect the progression of pediatric IgA nephropathy – a systematic review and meta-analysis

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## ABSTRACT

Immunoglobulin A nephropathy (IgAN) is an autoimmune disease in pediatric patients, with corticosteroid (CS) treatment remaining controversial. This meta-analysis evaluates the efficacy and safety of CS in pediatric IgAN patients. A systematic search of PubMed, ProQuest, and Wiley identified six studies with 208 patients. Outcomes included estimated glomerular filtration rate (eGFR), events of renal insufficiency, end-stage renal disease (ESRD), proteinuria, hematuria, IgA deposits, and side effects. Corticosteroid treatment showed a significant increase in eGFR (mean differences – MD: 11.84 [0.73–22.95] ml/min/1.73 m<sup>2</sup>), lower odds of having ESRD (odds ratios – OR: 0.21 [0.05–0.94]) and heavy proteinuria (OR: 0.15 [0.04–0.57]), and significant reduction in dipstick hematuria (MD: 2.89 [–3.85 to –1.93]). However, IgA deposits persisted despite CS treatment. Corticosteroid side effects were minimal. Corticosteroids may reduce glomerular damage and preserve renal function in pediatric IgAN patients, but limitations in addressing IgA deposits suggest the need for additional therapies.

## KEY WORDS:

**IgA nephropathy, pediatric, meta-analysis, treatment, corticosteroid.**

## INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is one of the most common primary glomerular diseases worldwide, especially in the Asia-Pacific area [1]. In a prior systematic literature review, the estimated global incidence of adult IgAN was found to be  $\geq 2.5/100\ 000/\text{year}$  [2]. Immunoglobulin A nephropathy is a disease that affects people of different racial and ethnic backgrounds differently. It is commonly found in East Asia, with Japan accounting for roughly 40% of all native kidney biopsies, followed by

Europe (25%), the US (12%), and central Africa (less than 5%) [3]. When it first appears in children or adolescents, it frequently progresses to chronic nephritis with a worse long-term prognosis. Young adults, who may have contracted the disease as children, make up the majority of IgAN patients in need of renal replacement therapy [4].

In 1968, IgAN was initially reported by a pathologist, Jean Berger, and an electron microscopist, Nicole Hinglais. It has been suggested that IgAN is an autoimmune illness that causes the formation of immune complexes and the generation of IgA and immunoglobulin G (IgG) auto-

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antibodies against aberrant IgA1 [5]. An increasing amount of data points to IgAN as an immune complex-mediated disease, with gut lymphocytes producing excessive amounts of galactose-deficient IgA1 (Gd-IgA1), IgG autoantibodies developing against Gd-IgA1, and immune complexes being deposited in renal mesangial tissue promoted by the dysregulation of soluble CD89 (an Fc receptor for IgA) and transglutaminase 2 [6]. Glomerulosclerosis, interstitial fibrosis, and tubular atrophy are pathologic markers indicating a bad prognosis. Age, renal insufficiency, higher degrees of proteinuria, and hypertension are clinical predictors of a poor result in patients with IgAN [7].

Clinical studies have been conducted recently in an effort to establish a connection between renal prognosis, clinical manifestations, and the three primary immunologic factors involved in IgAN pathophysiology. Potential candidate biomarkers exist that can be measured in physiological fluids to enable non-invasive disease outcome monitoring [8]. Even though the pathophysiology of IgAN is now better understood, no particular targeted therapy has been proven effective as of yet. However, there is one widely available treatment for general autoimmune-related diseases, i.e. corticosteroids (CS), which is still controversial in IgAN treatment [8]. Therefore, we aim to evaluate the efficacy and safety of CS as a non-specific immunosuppressive treatment in IgAN, specifically in the pediatric population.

## MATERIAL AND METHODS

This systematic review was performed based on the latest Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, from 2020 [9].

### ELIGIBILITY CRITERIA

Several inclusion criteria to include the relevant studies were applied as follows:

- study population consisted of pediatric patients (< 18 years old, children and adolescents) with a confirmed diagnosis of immunoglobulin A (IgA) nephropathy (IgAN),
- study intervention of any CS or CS-containing regimens compared with placebo, any other treatments, or non-CS-containing regimens as the control group,
- the measured outcomes were urinalysis, estimated glomerular filtration rate (eGFR), proteinuria, serum IgA concentration or IgA deposits, and/or biopsy results,
- study designs of randomized controlled trials (RCTs) and observational studies.

We excluded the studies when meeting several criteria:

- duplicate studies,
- inappropriate titles and/or abstracts,
- irretrievable full texts,
- incorrect study design (case reports, review articles, systematic reviews, meta-analyses, letter to editors, conference abstracts),
- non-English study.

## SEARCH STRATEGY

We conducted a systematic search of relevant studies in three electronic databases – PubMed, ProQuest, and Wiley Online Library – from inception to October 29, 2023. The key words were constructed based on Medical Subject Headings (MeSH) terms and their variants or other terms as follows: (“child” OR “children” OR “pediatric” OR “paediatric” OR “childhood” OR “adolescents”) AND (“Immunoglobulin A nephropathy” OR “IgA nephropathy” OR “IgAN” OR “immunoglobulin A glomerulonephritis” OR “IgA glomerulonephritis”) AND (“steroid” OR “corticosteroid” OR “prednisone” OR “prednisolone”). For the gray literature, we conducted the search in bioRxiv and medRxiv using the following key words: (“pediatric” OR “paediatric”) AND (“Immunoglobulin A nephropathy” OR “IgA nephropathy”) AND (“steroid” OR “prednisone”). We did not apply any language or publication date restrictions to our search. We compiled, managed, and de-duplicated the search results using Google Sheets (Google LLC, California, USA).

## SELECTION PROCESS, DATA EXTRACTION, AND EVIDENCE SYNTHESIS

Independent screening was performed by six investigators (BS, CC, WRS, EAP, YEP, AP). Every investigator participated in reaching a consensus to settle any disagreements, including Andro Pramana to resolve any final decisions. Several pertinent data were extracted, including the author; the year of publication; the study location; the study design; the population and sample size; the age of the participants; intervention regimen of CS only or CS-containing regimens with control regimen of placebo, any other treatments, or non-CS-containing regimens; follow-up period; adverse effect (AE); and the measured outcomes were urinalysis, eGFR, proteinuria, serum IgA concentration or IgA deposits, and/or biopsy results for knowing the effectiveness of CS. We selected the appropriate studies, and collected and synthesized their data using Google Sheets (Google LLC, California, USA). Our data interpretation was based on the evidence we collected by summarizing each study, then presented in a tabular format.

## QUALITY ASSESSMENT OF THE INCLUDED STUDIES

The quality of the studies was assessed using the latest Cochrane’s Risk of Bias 2 (RoB 2) tool for RCTs and the Newcastle-Ottawa scale (NOS) for observational studies. Risk of Bias 2 judgments were divided into low risk of bias, some concerns, and high risk of bias, which were deduced from all domains. If every domain displayed minimal risk, the study was rated as having a low overall risk of bias. Studies were deemed to raise some concerns if at least one domain received a rating of unclear. Studies were classified as having a high risk of bias if at least one domain displayed a high risk or if there

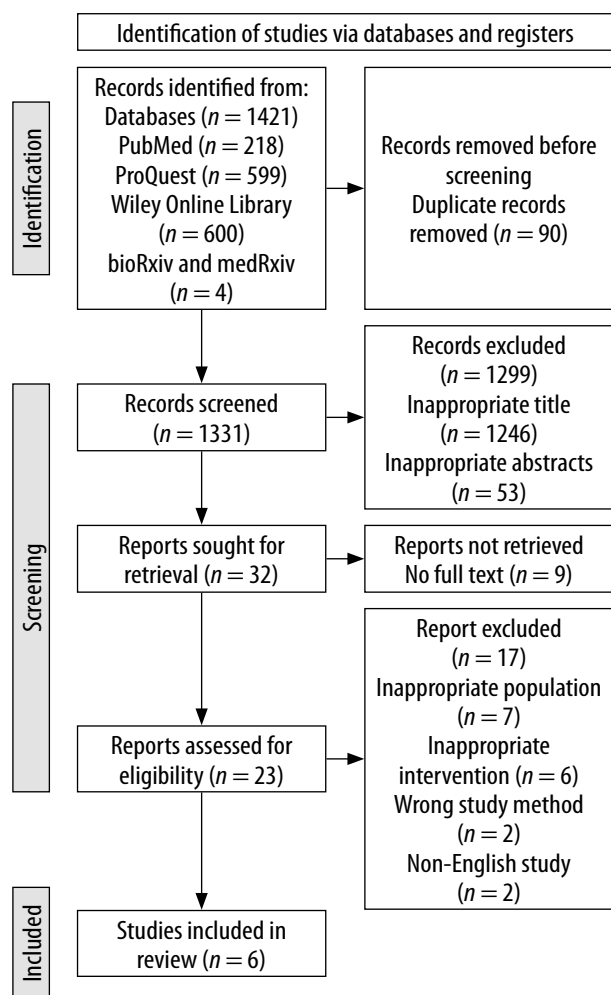


FIGURE 1. Study selection process based on PRISMA flow diagram

were issues in several domains that could significantly reduce the study's confidence in its findings. According to the NOS interpretation, the observational studies were categorized as either good (score 7–9), moderate (score 4–6), or poor (score 0–3). Six reviewers worked together to collaboratively conduct the quality assessment through a group discussion, and the decision was made according to their unanimous agreement.

### STATISTICAL ANALYSIS

We performed meta-analyses for two groups of outcomes using RevMan ver. 5.4 (The Cochrane Collab-

oration, The Nordic Cochrane Centre, Copenhagen, Denmark). The first group was the effects of CS on renal function, including eGFR, the events of renal insufficiency (eGFR < 60–70 ml/min/1.73 m<sup>2</sup>), and the events of end-stage renal disease (ESRD). The second group was the effects of CS on urinalysis, including the events of proteinuria ≥ 1 g/1.73 m<sup>2</sup>/day and hematuria detected by a urine dipstick test. We analyzed the pooled mean differences (MDs) for continuous data and pooled odds ratios (ORs) for dichotomous data. These analyses involved comparisons between post- and pre-CS-containing regimens, or between post-CS-containing regimens and post-non-CS-containing regimens. The level of heterogeneity of each analysis was quantified using Higgins' I<sup>2</sup> statistic: 0% for negligible heterogeneity, < 25% for low heterogeneity, 25–75% for moderate heterogeneity, and > 75% for high heterogeneity. We applied the random-effect model for all analyses since there was unavoidable variability and diversity among studies and the characteristics of the study participants. A *p*-value < 0.05 was considered statistically significant. The publication bias could not be assessed using a funnel plot since the number of studies included in the analysis was < 10. Sensitivity analysis was carried out using the leave-one-out method.

## RESULTS

### OVERVIEW OF LITERATURE SEARCH

The literature search yielded 1,421 studies from our initial search obtained from PubMed, ProQuest, Wiley Online Library, bioRxiv, and medRxiv. Of these, 1299 studies were initially excluded based on their titles and/or abstracts. We obtained 32 studies with eligible titles and abstracts, then we retrieved the full text for the remaining 23 studies. Finally, only 6 eligible studies were included in this study, with a total of 208 participants, consisting of 3 cohorts [8, 10, 11] and 3 RCTs [12–14]. The study selection process is shown in Figure 1. The risk of bias in our included studies is shown in Tables 1 and 2. The risk of bias of each RCT (Table 1) was low, indicated by low risk in all domains of the RoB 2 tool. The overall quality assessment of the cohort studies (Table 2) showed good quality, as indicated by a NOS score of 9.

TABLE 1. Quality assessment of the included randomized controlled trials using Cochrane Risk of Bias 2 tool

| Author                       | Year | Randomization process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported outcome | Overall bias |
|------------------------------|------|-----------------------|----------------------------------------|----------------------|----------------------------|-----------------------------------|--------------|
| Welch <i>et al.</i> [12]     | 1992 | Low                   | Low                                    | Low                  | Low                        | Low                               | Low          |
| Yoshikawa <i>et al.</i> [13] | 1999 | Low                   | Low                                    | Low                  | Low                        | Low                               | Low          |
| Kamei <i>et al.</i> [14]     | 2011 | Low                   | Low                                    | Low                  | Low                        | Low                               | Low          |

TABLE 2. Quality assessment of the included observational studies using Newcastle-Ottawa scale

| Author                    | Year | Selection                                |                                     |                           |                                                                          | Comparability | Outcome               |                                                   |                                  | Study quality |          |
|---------------------------|------|------------------------------------------|-------------------------------------|---------------------------|--------------------------------------------------------------------------|---------------|-----------------------|---------------------------------------------------|----------------------------------|---------------|----------|
|                           |      | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study |               | Assessment of outcome | Enough follow-up time length for outcome to occur | Adequacy of follow-up of cohorts | Total score   | Judgment |
| Cambier <i>et al.</i> [8] | 2018 | *                                        | *                                   | *                         | *                                                                        | **            | *                     | *                                                 | *                                | 9             | Good     |
| Waldo <i>et al.</i> [11]  | 1989 | *                                        | *                                   | *                         | *                                                                        | **            | *                     | *                                                 | *                                | 9             | Good     |
| Waldo <i>et al.</i> [10]  | 1993 | *                                        | *                                   | *                         | *                                                                        | **            | *                     | *                                                 | *                                | 9             | Good     |

\* – in Newcastle-Ottawa scale 1 point, \*\* – in Newcastle-Ottawa scale 2 point.

## CHARACTERISTICS AND RESULTS OF SELECTED STUDIES

This study included a total of 208 IgAN patients: 124 patients treated with CS or CS-containing regimens and 84 without CS or with non-CS-containing regimens (Table 3). We also carefully counted the total number of participants, given that there were two pairs of studies derived from similar participants, i.e. Waldo *et al.* [11] and Waldo *et al.* [10], as well as Yoshikawa *et al.* [13] and Kamei *et al.* [14].

The follow-up period of the included studies ranged from 6 months to 18 years. Of the included studies, one study compared CS with placebo [12], one study compared CS with renin-angiotensin-system blockers (RASB) [8], two studies compared CS-containing regimens with the combination of heparin and dipyridamole [13, 14], and two studies gave no treatment for the control group [10, 11].

## EFFECTS OF CORTICOSTEROIDS ON RENAL FUNCTION

Numerous impacts on renal outcomes appeared to result from the use of CS, specifically prednisone, in the treatment of pediatric IgAN patients. When compared to the RASB group, the immunosuppressive group's eGFR improved in the short-term outcome, rising from 89.9 (61.2–114.5) ml/min/1.73 m<sup>2</sup> to 110.5 (93.7–120.0) ml/min/1.73 m<sup>2</sup> in six months after treatment [8]. Furthermore, our meta-analysis showed that there was a significant increase in eGFR of approximately 11.84 (0.73–22.95) ml/min/1.73 m<sup>2</sup> after the administration of CS-containing regimens, with low heterogeneity ( $I^2 = 23\%$ ) (Figure 2A). However, when removing Cambier *et al.* [8] or Waldo *et al.* [10] from the analysis, the result changed from significant to not significant, indicating that the result was affected by those studies.

Prednisone was found to reduce mean blood creatinine concentration at the end of follow-up, according to a study conducted in 1992 by Welch *et al.* [12]. In addition, compared to patients who were not treated with prednisone, the group receiving treatment showed a greater proportion of patients with normal urinalysis, a decreased incidence of ESRD, and notable eGFR preservation [10, 11]. According to Kamei *et al.* [14], the CS-containing regimens had a reduced percentage of patients who progressed to ESRD. In the CS-containing regimens, there was a significant increase in the 10-year probability of both renal survival and eGFR 50% reduction-free survival. This was proven by our meta-analysis, which showed a significantly lower odds of having ESRD in patients receiving CS-containing regimens compared to those receiving non-CS-containing regimens, with negligible heterogeneity (OR 0.21 [0.05–0.94];  $I^2 = 0\%$ ) (Figure 2B). This implied that the usage of CS, as observed in the CS-containing regimens, might be associ-

TABLE 3. Basic characteristic of the included studies.

| Author                    | Year | Study location | Study design               | Age (year)       | Number of patients (CS/no-CS) | When to treat                                                                                                                                       | Intervention regimen                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Comparator regimen                                                                                                    | Follow-up period    | Outcome                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | AE CS                                                                                                                                  | Conclusions                                                                                                                                                                                                                   |
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| Welch <i>et al.</i> [12]  | 1992 | Cincinnati     | RCT (crossover trial)      | Mean age of 13   | 20                            | N/A                                                                                                                                                 | <p>The prednisone phase of the crossover trial is below listed; each patient had two 3-month therapy courses followed by a 3-month rest period.</p> <ul style="list-style-type: none"> <li>• three-month courses of prednisone 2 mg/kgBW for 2 weeks, followed by the same amount as a single every-other-morning dose for 10 weeks</li> <li>• three-month rest period</li> <li>• three-month placebo period</li> <li>• in the same way</li> </ul>                                                                                                                                                                                                                                                                                                                                 | Crossover trial with a placebo phase (two 3-month therapy courses followed by a 3-month rest period) for each patient | 24 weeks            | <p>Even though no significant change from week 0–12 in urinary erythrocyte excretion during prednisone phase (<math>p = 0.29</math>) and placebo phase (<math>p = 0.42</math>) were observed, the prednisone phase was able to reduce the degree of hematuria in this study. During the prednisone phase, there were 20 individual episodes of gross hematuria; during the placebo phase, there were 28.</p> <p>There were no notable changes in the excretion of urinary protein throughout the prednisone (<math>p = 0.19</math>) or placebo phases (<math>p = 0.12</math>). The average serum creatinine concentration was 70 <math>\mu\text{mol/l}</math> (0.8 mg/dl) at the beginning of the follow-up and 60 <math>\mu\text{mol/l}</math> (0.7 mg/dl) at the end</p> | <p>One patient experienced acne and one patient experienced weight gain during prednisone phase. They were excluded from the study</p> | The corticosteroid treatment was well tolerated in this controlled study. However, it was not linked to any significant alterations in proteinuria or hematuria. There was no proof that treatment for IgA nephropathy worked |
| Cambier <i>et al.</i> [8] | 2018 | Paris          | Retrospective cohort study | Mean age of 10.6 | 82 (51/31)                    | <p>When there is a biopsy sample demonstrating glomerular inflammation, when proteinuria exceeds 0.5 g/l, or when eGFR decrease below 70 ml/min</p> | <p>IV pulse steroid therapy with MP 500 mg/m<sup>2</sup> for three days in a row</p> <p>Oral steroid therapy :</p> <ul style="list-style-type: none"> <li>• prednisolone for the first month at Necker Hospital (30 mg/m<sup>2</sup> daily) or Robert-Debré Hospital (60 mg/m<sup>2</sup> daily), then one day every two for the next two months</li> <li>• the dosage of prednisolone is 15 mg/m<sup>2</sup> for one of the two days (Necker Hospital), or 30 mg/m<sup>2</sup> everyday for the next two months (Robert-Debré Hospital), and 15 mg/m<sup>2</sup> everyday for the next eighteen months (Robert-Debré Hospital)</li> </ul> <p>Patients who did not respond to oral and pulse steroid therapy for chronic nephrotic syndrome were treated with cyclophosphamide</p> | RASB (ACE-I and/or ARB) or without any treatment                                                                      | 3.3 (1.9–5.9) years | <p>Six months after starting therapy, the immunosuppressive group's eGFR improved from 89.9 (61.2–114.5) ml/min/1.73 m<sup>2</sup> at the time of biopsy (M0) to 110.5 (93.7–120.0) ml/min/1.73 m<sup>2</sup> (<math>p \leq 0.0001</math>). In contrast, the RASB group's eGFR remained stable with no improvement (<math>p = 0.12</math>). In the immunosuppressive group, proteinuria decreased (from 1.6 [1–4.3] g/g to 0.3 [0.2–0.7] g/g; <math>p &lt; 0.0001</math>), but not in the RASB group (<math>p = 0.4</math>)</p> <p>The reduction of proteinuria in the immunosuppressive group remained significant (from 1.1 [0.43–1.6] g/g to 0.3 [0.13–0.5] g/g, <math>p = 0.0015</math>) when the severe manifestations (nephrotic syndrome and AKI) were excluded</p> | <p>These show that steroids are generally safe and effective, when combined with other drugs, it can support their efficacy</p>        | <p>Children with severe primary IgAN may have experienced a fast improvement in eGFR and decreased proteinuria as a result of immunosuppressive treatment utilizing the Paris protocol</p>                                    |

TABLE 3. Cont.

| Author                       | Year | Study location | Study design | Age (year)                                                      | Number of patients (CS/no-CS) | When to treat                                                                                                                                                                                                                                                                                                                                                   | Intervention regimen                                                                                                                                                                                                                                                                                                                                 | Comparator regimen                                                                                                                                             | Follow-up period | Outcome                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | AE CS | Conclusions                                                                                                                                                                                                                                                           |
|------------------------------|------|----------------|--------------|-----------------------------------------------------------------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Yoshikawa <i>et al.</i> [13] | 1999 | Japan          | RCT          | Group with CS<br>12.2 ± 3<br><br>Group without CS<br>11.6 ± 2.3 | 78<br>(40/38)                 | Had undergone a biopsy and were recently found to have diffuse mesangial proliferation and IgA nephropathy, the following conditions were complied with:<br>• sufficient kidney biopsy tissue accessible for histological evaluation (≥ 10 glomeruli)<br>• age 15 years at study entrance<br>• no history of corticosteroid or immunosuppressive medication use | Prednisolone orally 2 mg/kgBW/d in 3 divided doses (max. 80 mg/d) for 4 wk, following that a single dosage of 2 mg/kgBW/2 d was administered in the morning of every other day on alternate days for 4 weeks, followed by 1.5 mg/kgBW/2 d for 4 weeks, and 1 mg/kgBW/2 d for 21 months<br>Other drugs (azathioprine, heparin-warfarin, dipyridamole) | Heparin IV for 28 d, then single morning dosage of oral warfarin for 23 mo<br><br>Dipyridamole orally 5 mg/kgBW/d in 3 divided doses (max. 400 mg/d) for 24 mo | 24 months        | The mean excretion of urine protein decreased considerably in patients in group 1 (1.35 ± 1.01 g/d at treatment initiation to 0.22 ± 0.31 g/d at treatment conclusion; $p < 0.0001$ ), but did not alter in patients in group 2 ( $p = 0.16$ )<br>The mean serum IgA concentration remained stable in group 2 patients ( $p = 0.88$ ), but dramatically decreased in group 1 patients (290 ± 115 mg/dl at treatment initiation to 229 ± 87 mg/dl at treatment completion; $p = 0.0002$ )<br>All patients in group 2 had normal BP and GCrI at the end of the experiment, with the exception of one who had chronic renal insufficiency in group 2 patients ( $p = 0.006$ )<br>In patients in group 1, the glomerular sclerosis did not alter ( $p = 0.65$ ); in patients in group 2, however, it dramatically increased ( $p = 0.006$ )<br>In group 1 patients, there was a significant difference in the severity of mesangial IgA deposits between the beginning and the end of treatment ( $p = 0.02$ ), and at the end of treatment, there were no more IgA deposits in 7 patients (21%) while there was no significant difference in group 2 patients ( $p = 0.31$ ) | N/A   | Prednisolone-containing regimen (with azathioprine, heparin-warfarin, dipyridamole) inhibits immunologic renal injury and the growth of sclerosed glomeruli, and in children with severe IgAN, it may result in a 2-year remission early in the course of the disease |

TABLE 3. Cont.

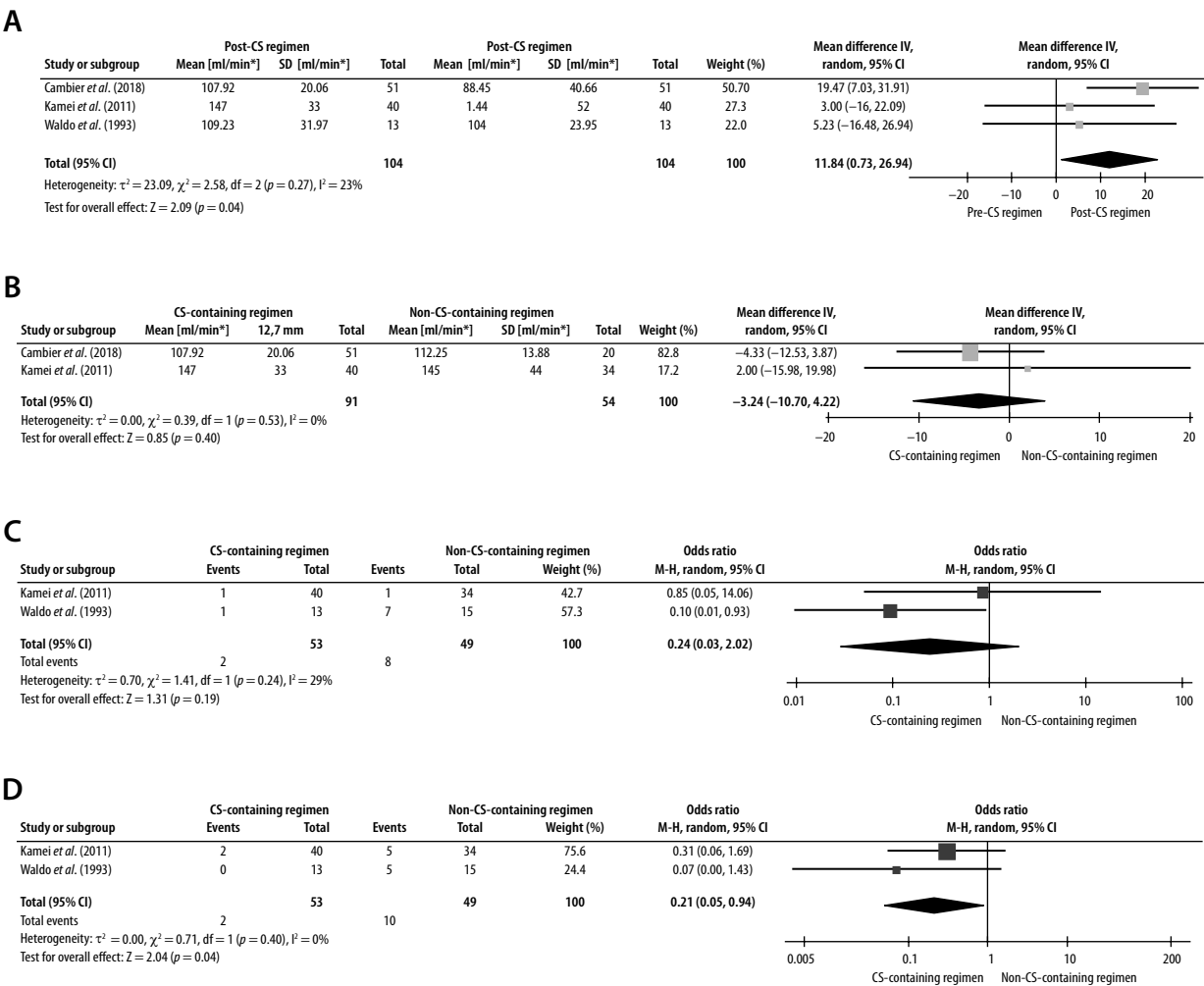
| Author                   | Year | Study location | Study design             | Age (year)                                                                                                     | Number of patients (CS/no-CS) | When to treat                                                                                                                                                                                                                                                                                                                                                   | Intervention regimen                                                                                                                                                                                                                                                                                                                                 | Comparator regimen                                                                                                                                         | Follow-up period  | Outcome                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | AE CS               | Conclusions                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|--------------------------|------|----------------|--------------------------|----------------------------------------------------------------------------------------------------------------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kamei <i>et al.</i> [14] | 2011 | Japan          | RCT                      | Group with CS 12.2 ± 3<br>Group without CS 11.6 ± 2.3                                                          | 78 (40/38)                    | Had undergone a biopsy and were recently found to have diffuse mesangial proliferation and IgA nephropathy, the following conditions were complied with:<br>• sufficient kidney biopsy tissue accessible for histological evaluation (≥ 10 glomeruli)<br>• age 15 years at study entrance<br>• no history of corticosteroid or immunosuppressive medication use | Prednisolone orally 2 mg/kgBW/d in 3 divided doses (max. 80 mg/d) for 4 wk, following that a single dosage of 2 mg/kgBW/2 d was administered in the morning of every other day on alternate days for 4 weeks, followed by 1.5 mg/kgBW/2 d for 4 weeks, and 1 mg/kgBW/2 d for 21 months<br>Other drugs (azathioprine, heparin-warfarin, dipyridamole) | Heparin IV for 28 d, then single morning dosage of oral warfarin for 23 mo<br>Dipyridamole orally 5 mg/kgBW/d in 3 divided doses (max. 400 mg/d) for 24 mo | 10 (0.5–18) years | The number of patients progressing to ESRD was lower in the group 1 ( $n = 2$ ; 5.0%) than group 2 ( $n = 5$ ; 14.7%)<br>The 10-year renal survival probability in the group 1 (97.1% [95% CI = 81.4–99.6%]) was significantly higher than group 2 (84.8% [95% CI, 55.4–95.5%]) ( $p = 0.03$ )<br>The 10-year probability of eGFR 50% reduction-free survival in the group 1 (94.5% [95% CI, 79.8–98.6%]) was significantly higher than group 2 (84.6% [95% CI, 62.0–94.3%]) ( $p = 0.03$ )<br>Combination therapy appears to be most beneficial over the long run when it comes to lowering urine protein excretion and slowing the course of glomerular sclerosis |                     | In addition to improving the acute phase of nephritis, a 2-year combination therapy comprising prednisolone, azathioprine, dipyridamole, and heparin-warfarin also improves the long-term prognosis of pediatric IgA nephropathy with diffuse mesangial proliferation.<br>Combination therapy appears to be most beneficial over the long run when it comes to lowering urine protein excretion and slowing the course of glomerular sclerosis |
| Waldo <i>et al.</i> [11] | 1989 | USA            | Prospective cohort study | Treated patients with mean age (range) of 11 (9–13)<br>Untreated patients with mean age (range) of 12.2 (1–18) | 21 (6/15)                     | 1. Proteinuria > 1 g/1.73 m <sup>2</sup> per day<br>2. More than minimal interstitial fibrosis or tubular atrophy<br>3. More than minimal glomerular sclerosis                                                                                                                                                                                                  | Oral prednisone 60 mg/m <sup>2</sup> every other morning for 1–3 months, followed by 30 mg/m <sup>2</sup> over the next 9–11 months, 15 mg/m <sup>2</sup> between 12–14 months, and gradually reduced or discontinued between 2 and 4 years based on current biopsy result and clinical evidence of disease activity                                 | Untreated                                                                                                                                                  | 54 (28–60) months | The quantity of patients whose urinalyses are normal at the follow-up was observed significantly higher in prednisone-treated group ( $n = 6$ ; 100%) in contrast to individuals who received no treatment ( $n = 1$ ; 6%) ( $p = 0.03$ )<br>The absence of patients with active renal illness indicates that prednisone protects against ESRD and renal insufficiency in the follow-up of prednisone-treated group<br>The underlying immunopathology is not eradicated by prednisone (the IgA immunofluorescence in the patients persisted and mesangial deposits by electron microscopy)                                                                          | No steroid toxicity | Patients with IgAN benefit from long-term prednisone treatment in terms of normal urinalysis and reduced glomerular inflammation at the end of the follow-up period                                                                                                                                                                                                                                                                            |

TABLE 3. Cont.

| Author                   | Year | Study location | Study design             | Age (year)                                                                                               | Number of patients (CS/no-CS) | When to treat                                                                                                                                                  | Intervention regimen                                                                                                                                                                                                                                                                                                   | Comparator regimen | Follow-up period   | Outcome                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | AE CS                                                                                                                                                                                                             | Conclusions                                                                                                                                                                                                         |
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| Waldo <i>et al.</i> [10] | 1993 | USA            | Prospective cohort study | Treated patients with mean age (range) of 11.1 (7–17)<br>Untreated patients with mean age of 12.2 (1–18) | 28 (13/15)                    | 4. Proteinuria > 1 g/1.73 m <sup>2</sup> per day<br>5. More than minimal interstitial fibrosis or tubular atrophy<br>6. More than minimal glomerular sclerosis | Prednisone orally 60 mg/m <sup>2</sup> every other morning for 1–3 months, followed by 30 mg/m <sup>2</sup> over the next 9–11 months, 15 mg/m <sup>2</sup> between 12–14 months, and gradually reduced or discontinued between 2 and 4 years based on current biopsy result and clinical evidence of disease activity | Untreated          | 67 (37–120) months | After 2 years of treatment in prednisone-treated patient, there was a significant reduction in the activity score 5.2–4.3 ( $p = 0.03$ )<br>The chronicity score increased 2.2–2.8 ( $p > 0.05$ ) in prednisone-treated patients<br>Glomerular immunofluorescence for IgA remained positive in all prednisone-treated patients, but declined in intensity from 2.8+ to 2.1+ ( $p = 0.08$ ) on the follow-up biopsy<br>The number of patients with normal urinalysis at the follow-up was observed significantly higher in prednisone-treated group ( $n = 12$ ; 92.31%) compared to those who were untreated ( $n = 1$ ; 6.67%) ( $p < 0.00001$ )<br>In the untreated group, there was a greater number of patients with proteinuria 1–3 g/1.73 m <sup>2</sup> /day ( $n = 4$ ; 26.67%).<br>No statistically significant distinction between the two groups: incidence of proteinuria > 3 g/1.73 m <sup>2</sup> /day ( $p = NS$ )<br>There was no patient with ESRD in prednisone-treated group, which significantly different from the untreated group ( $n = 5$ ; 33.33%) ( $p = 0.04$ )<br>In the prednisone-treated group, resulted in significant preservation of eGFR as evidenced by significantly decreased number of prednisone-treated patients with eGFR < 70 ml/min/1.73 m <sup>2</sup> ( $n = 1$ , 7.69%) compared to untreated patients ( $n = 7$ ; 46.67%) ( $p = 0.03$ ) | Mild weight gain during the first 6–12 months<br>No patients developed hypertension requiring therapy<br>No patients developed cataracts or clinically apparent bone disease<br>No evidence of growth retardation | Alternate-day prednisone reduced the hypercellularity and matrix expansion, prevented sclerosis development, preserved renal function, normalized the urinalysis, and had benefit to patients with more severe IgAN |

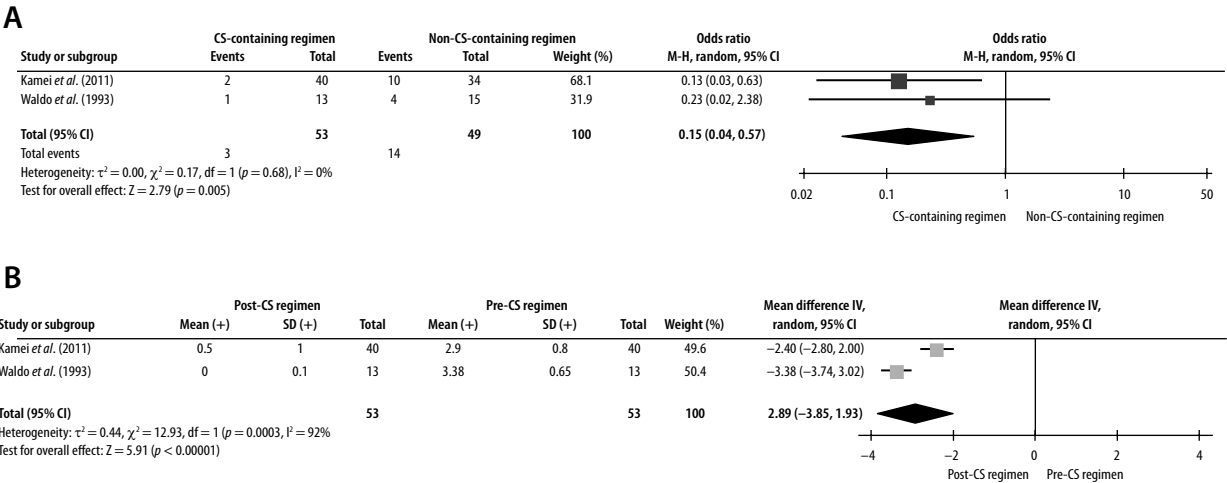
CS – corticosteroid, eGFR – estimated glomerular filtration rate, ESRD – end-stage renal disease, IgAN, – immunoglobulin A nephropathy, N/A – not available, NS – not significant, RCT – randomized controlled trial





**FIGURE 2.** Forest plots of the effect of corticosteroids (CS) on renal function. (A) Estimated glomerular filtration rate (eGFR) following post-CS-containing regimens vs. pre-CS-containing regimens. (B) eGFR following post-CS-containing regimens vs. post-non-CS-containing regimens. (C) Events of renal insufficiency (eGFR < 60–70 ml/min/1.73 m<sup>2</sup>) following post-CS-containing regimens vs. post-non-CS-containing regimens. (D) Events of end-stage renal disease following post-CS-containing regimens vs. post-non-CS-containing regimens

CI – confidence interval, IV – inverse variance; M-H – Mantel-Haenszel, SD – standard deviation  
\* The unit of eGFR is ml/min/1.73 m<sup>2</sup>



**FIGURE 3.** Forest plots of the effect of corticosteroids (CS) on urinalysis. (A) Events of proteinuria  $\geq 1$  g/1.73 m<sup>2</sup>/day following post-CS-containing regimens vs. post-non-CS-containing regimens. (B) Hematuria detected by urine dipstick test following post-CS-containing regimens vs. pre-CS-containing regimens

CI – confidence interval, IV – inverse variance; M-H – Mantel-Haenszel, SD – standard deviation

ated with a better prognosis for the renal over the long-term outcome, including a decreased risk of ESRD and a higher likelihood of sustaining a steady eGFR over time. However, the latter result changed from significant to not significant when removing Kamei *et al.* [14] or Waldo *et al.* [10] from the analysis, indicating that the result was affected by those studies.

#### EFFECTS OF CORTICOSTEROIDS ON URINALYSIS

In comparison to the RASB group, the immunosuppressive group also showed positive short-term results, such as a decrease in proteinuria. Despite excluding the more severe manifestations of the illness (nephrotic syndrome and acute kidney injury), the reduction in proteinuria was still considerable [8]. The average urinary protein excretion was found to be much lower in the CS-containing regimens, but remained unchanged in the non-CS-containing regimens, according to the study by Yoshikawa *et al.* [13]. Our result showed that patients receiving CS-containing regimens had a significantly lower odds of having heavy proteinuria  $\geq 1 \text{ g}/1.73 \text{ m}^2/\text{day}$  than patients receiving non-CS-containing regimens, with negligible heterogeneity (OR 0.15 [0.04–0.57];  $I^2 = 0\%$ ) (Figure 3A). This result was affected by Kamei *et al.* [14] due to a change of result from significant to not significant when removing that study from the analysis.

According to Welch *et al.* [12], although there was no significant difference in urinary erythrocyte excretion between the prednisone and placebo phases, the prednisone phase still showed a substantial decrease in hematuria from  $7.5 \text{ cells} \times 10^{-7}/12 \text{ hour}$  to  $4.1 \text{ cells} \times 10^{-7}/12 \text{ hour}$  in approximately 12 weeks of observation. This was supported by our finding of a significant reduction in dipstick hematuria in the patients received CS-containing regimens (MD:  $-2.89$  [ $-3.85$  to  $-1.93$ ]), with high heterogeneity ( $I^2 = 92\%$ ) (Figure 3B). This result was robust, since no change of result was seen when removing any of the included studies. Compared to the untreated group, the prednisone-treated group also had a considerably larger number of patients with normal urinalysis at the follow-up [10, 11].

#### EFFECTS OF CORTICOSTEROIDS ON GLOMERULAR PATHOLOGY

In two studies with a total of 49 patients [10, 11], 19 patients were assigned to the treatment group. According to the analyses, CS treatment did not eliminate the underlying immunopathology. Biopsy data indicated that patients continued to have positive IgA immunofluorescence and mesangial deposits [11]. Glomerular immunofluorescence for IgA remained positive in all CS-treated patients, but still carried a slight decline in intensity from 2.8+ to 2.1+, although this was not significant ( $p = 0.08$ ) in the follow-up biopsy [10].

#### ADVERSE EFFECTS OF CORTICOSTEROID TREATMENT

For the CS vs. control group, some patients experienced weight gain during the CS phase [12] and mild weight gain during the first 6–12 months [10]. One patient experienced acne [12]. Overall, 3 studies reported that CS treatment was well tolerated and relatively safe [8, 11, 12]. No patients developed hypertension requiring therapy, and no patients experienced growth retardation, acquired cataracts, or clinically noticeable bone damage [10].

#### DISCUSSION

This systematic review provides some evidence that treating pediatric IgAN patients with CS reduces the risk of ESRD and preserves eGFR. This study shows that CS has significant effects on renal function. The patients who received CS-containing regimens also had a substantial reduction in protein excretion and hematuria. This might slow the progression of glomerular sclerosis by reducing hypercellularity and matrix expansion in the renal tissue. However, all patients receiving glucocorticoids still have positive glomerular immunofluorescence for IgA, which means that CS still carries a limitation in terms of treating the underlying immunopathology.

Glucocorticoids are a class of non-specific immunosuppressive drugs that may be beneficial due to their effects on the autoimmune pathophysiology of IgAN. Corticosteroid therapy can reduce proteinuria and prevent kidney failure. Therefore, CS helps improve kidney prognosis in IgAN patients [15]. By the end of the follow-up, patients who received prednisone had a lower mean blood creatinine concentration than those who did not. Additionally, the group receiving treatment had a higher percentage of patients with normal urinalysis, a lower incidence of ESRD, and notable preservation of eGFR [8, 11, 12]. According to the Kidney Disease Improving Global Outcome (KDIGO) 2021 guidelines [16], corticosteroid therapy is also considered relevant in pediatric IgAN patients with persistent proteinuria despite optimized supportive care, provided that renal function remains adequate and the risks of therapy are carefully assessed. However, CS therapy in our included studies is mainly administered to IgAN patients with several features, such as heavy proteinuria, significantly reduced eGFR, and the presence of glomerular inflammation, diffuse mesangial proliferation, interstitial fibrosis, tubular atrophy, and/or glomerular sclerosis on biopsy samples. This highlights that even though CS therapy is beneficial in IgAN, pediatric patients with milder conditions might not need CS in their therapeutic regimens.

Although complement and calcineurin inhibitor directly affect the location of glomerular injury, most immunosuppressive medications primarily affect lymphoid organs. Both adaptive immunity in lymphoid organs and renal local inflammation are suppressed by gluco-

corticoids [17]. Recent advances in the pathophysiology of IgAN have brought attention to the immunologic basis of the disease. Circulating immune complexes consisting of a glycan-specific IgG antibody and Gd-IgA1 are the characteristics of IgAN. These immune complexes cause the mesangioproliferative glomerulonephritis (GN) that is specific to IgAN by depositing themselves in the mesangial part of the glomerulus. Complement activation through the lectin pathway, the identification of a particular autoantigen/autoantibody (characteristic of autoimmune diseases), and the existence of immune complex-mediated GN have all clearly demonstrated the potential benefit of immunosuppressive therapy in the treatment of progressive IgAN [18]. Due to the nearly universal expression of glucocorticoid receptors (GRs), glucocorticoids have both local and systemic effects. Glucocorticoids in the kidney may protect podocytes through the GRs, in addition to directly preventing the overproduction of inflammatory mediators. The renal protective effect provided by glucocorticoids is through increasing total cellular actin, which plays a role in tissue stability and in increasing the expression of three major proteins, i.e. ciliary neurotrophic factor,  $\alpha$ B-crystallin, and HSPB1, which have been shown to increase cell viability [19].

Our findings suggest that the current treatment is not sufficient to completely counteract the underlying immune response causing IgA deposits in the kidneys. According to the glomerular pathology, it was found that glomerular IgA immunofluorescence of all CS-treated patients remained positive, but there was a minor decrease in intensity on the follow-up biopsy, even though it was not statistically significant [10]. According to the autopsy results, the mesangial deposits and positive IgA immunofluorescence persist [11]. Related to the previous discussion regarding the pharmacological effects of glucocorticoids, systemic glucocorticoids may also reduce the autoantibody production in response to aberrant IgA1 molecules. IgA-IgG immune complex levels are significantly lower in patients treated with systemic glucocorticoids or immunosuppressants than the untreated ones. However, there is no significant change in total plasma IgA levels during treatment, which may indicate that systemic glucocorticoids have a minimal influence on mucosal production of antibodies against aberrant IgA [20, 21]. Therefore, this may also be the reason for the IgA persistence in the glomerulus of IgAN patients.

Corticosteroids are associated with greater clinical remission; however, this comes at the expense of additional side effects. Many side effects of glucocorticoids can be linked to the capacity of GRs to transcribe inflammatory genes that cause metabolic consequences, such as infections, abnormalities in glucose metabolism, and weight gain [22]. In this review, the AEs of CS did not show up significantly, due to the small number of participants included, and most of the studies use alternate dose or low pulse dose CS [10, 11]. Data on potential AEs of CS are not provided.

Furthermore, it is challenging to accurately assess the AEs of CS therapy in our included studies; however, there are a few reported AEs, such as weight gain and acne [11, 12]. Serious AEs of CS, such as infection, diabetes, and osteonecrosis, were observed in a study involving adult IgAN [23]. Despite concerns about possible AEs of CS in children, no issues have been detected. In particular, growth rates are unchanged, and no indications of diabetes, hypertension, cataracts, or bone disease are present [11]. While the renal outcomes in this study appear promising, it is important to note that these findings are based on a limited sample size and a limited number of included studies. To confirm these results, further studies with longer follow-up periods and larger sample sizes are necessary. Additionally, comparing the included studies is challenging due to inconsistencies in the timing and indications for CS use, making it still unclear when to initiate CS therapy.

## CONCLUSIONS

This study shows that CS treatment may provide good preservation of eGFR and reduce the risk of ESRD in pediatric IgAN patients. This is further supported by a good improvement in urinalysis parameters (considerable reduction in hematuria and proteinuria), and a significant increase in the 10-year probability of both renal survival and eGFR 50% reduction-free survival, with minimal side effects. However, CS is not sufficient to decrease the IgA deposits in the glomerulus; therefore, other therapeutic regimens are still needed to improve the efficacy of CS. Further studies with a larger IgAN sample size and scope of CS treatment are still warranted in order to obtain more comprehensive results.

## DISCLOSURES

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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