Corticosteroid for IgA Nephropathy: Are They Really Therapeutic?

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Keywords

IgA nephropathy · Corticosteroid · Randomized controlled trials · Meta-analysis

Abstract

Background: IgA nephropathy (IgAN) is a common chronic glomerular disease that, in most patients, slowly progresses to end-stage kidney disease. The therapy with corticosteroid in IgAN is still a worldwide problem that is confusing the clinicians. **Methods:** MEDLINE, EMBASE, the Cochrane Library, and article reference lists were searched for randomized controlled trials (RCTs) that compared corticosteroids with placebo and any other non-immunosuppressive agents in treating IgAN. Twelve RCTs involving 1,057 patients were included. **Results:** Overall, we found that steroids had statistically significant effects in preventing the decline in renal function (relative risk 0.42, 95% CI 0.25–0.71, $p < 0.001$) and reducing proteinuria (SMD: -0.58 g/day, 95% CI -0.80 to -0.36 g/day) in patients with IgAN. The association between glucocorticoid and risk of kidney outcome was not modified

by steroids' type (prednisone or methylprednisone), dose (≤ 30 or > 30 mg/day), duration (≤ 8 or > 8 months), or serum creatinine (< 1.10 or ≥ 1.10 mg/dL). But steroids increased the risk of side effects such as gastrointestinal and endocrinium symptoms. **Conclusion:** This study provides the clear beneficial effects of the steroids therapy on the kidney function and proteinuria, although it should be used with caution.

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Background

IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide, especially in the Asian-Pacific region [1]. Up to 40% of clinically affected individuals will eventually progress to end-stage kidney disease (ESKD) within 20 years even with optimal blood pressure control and renin-angiotensin system blockade [2–6], which make the treatment of IgAN a critical area. The role of the auto-antigen/autoantibody immune-complex formation and complement ac-

tivation in the development of IgAN has supported the use of corticosteroids therapy in the management of progressive IgAN. Nonetheless, therapeutic recommendations of corticosteroids were based only on weak evidence, since the outcome of glucocorticoid therapy for IgAN has been inconclusive and conflicting. Although corticosteroid therapy was initially considered to be not delaying the progression of chronic kidney disease [7], many other randomized controlled trials (RCTs) have suggested that it may contribute to some benefit [8, 9] in protecting renal function; at the same time, a reduction in daily proteinuria, with few adverse events, could also occur. Additionally, some new RCTs are published. The Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN) trial [10] published in 2017 found that corticosteroids therapy plus supportive care was not superior to supportive care alone in patients with IgAN in delaying the progression of the kidney. However, this study that had the short follow-up for evaluating the renal function deterioration included patients who were on only >0.75 g/day of proteinuria (thus showing slow progress). Moreover, recent data from the Therapeutic Evaluation of Steroids in IgA Nephropathy Study (TESTING) [11] and Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN) [12] have provided further evidence on the benefits and side effects of corticosteroid treatment in patients with IgAN. These studies remain the latest and the largest in the world for the steroids therapy of IgAN. Several systematic reviews have evaluated the use of glucocorticoid in IgAN; however, these overviews were tested few years and lacked appropriate safety evaluation [13–15]. Among them, the study of Lv et al. [13] has not reported serious and fatal infections and death. The study of Zhou et al. [14] 8 did not evaluate the safety of steroids. And the side effects of respiratory and gastrointestinal symptoms were not documented in the study of Cheng et al. [15]. Therefore, we present the results of a systematic review summarizing currently available evidence from RCTs pertaining to the effect of glucocorticoids in the treatment of IgAN.

Materials and Methods

Date Sources, Search Strategy, and Inclusion Criteria

Relevant studies were identified by searching the following data sources: MEDLINE (OVID; from 1950 to September 2017), Embase (from 1970 to September 2017) and the Cochrane Library database (Cochrane Central Register of Active Controlled Trials;

no date restriction), and abstracts from scientific meetings. Keywords in our search included IgA glomerulonephritis, IgA nephropathy, immunoglobulin A nephropathy, and Berger disease, steroid, prednisone, glucocorticoids, proteinuria, randomized controlled trials, clinical trials, drug therapy. Trials were considered without language restrictions. To evaluate the effects of steroids on IgAN, a study must include the following criteria: (i) the study was an RCT; (ii) the study compared glucocorticoid agents (any dose, type) versus placebo/no treatment; (iii) the study contained deterioration of renal function; and (iv) the study included adverse events.

Data Extraction and Quality Assessment

Data extraction was performed by 2 investigators (Y.L. and D.H.) independently using the standardized extraction form. If there were any different opinions between them, it would be submitted to the other reviewer (Y.L.) and the procedure would be repeated until the questions were resolved. We evaluated the quality of the studies from the Jadad scale [16–18], which is an established procedure. Its scale assigns 0 or 5 points to each of the following 5 items: (i) with or without randomization; (ii) with or without a double-blind design; (iii) the appropriateness of the randomization methods, if used; (iv) the appropriateness of double-blinding design, if used; (v) the analysis and reasons for withdrawals and dropouts.

Outcomes

The outcomes in this study were defined as follows: (i) the primary outcome was kidney outcomes, defined as a composite of ESKD, doubling in serum creatinine or 50% decreasing or more of estimated glomerular filtration rate (eGFR); (ii) the secondary outcome was daily proteinuria at the end of treatment or during the follow-up time, and (iii) adverse events of treatment.

Statistical Analysis

Dichotomous outcome data from individual trials were analyzed by using the relative risk (RR) measure. For continuous outcomes of proteinuria, we used the weighted difference in means and their 95% CI at the end of treatment. We also performed subgroup analysis to assess the potential effect for all results based on the type of control drug and duration of treatment. The random effects model using the DerSimonian-Laird method was employed [19]. Heterogeneity was analyzed using an I^2 test on $N-1$ degrees of freedom. Funnel plots and Begg's test were used to probe for publication bias. Two-sided p value <0.05 was regarded as statistically significant for all included studies. All statistical analyses were performed using Stata SE 14 and Review Manager 5.3 statistical software for the meta-analysis.

Results

Trial Flow and Study Characteristics

Our literature search retrieved 1,840 citations, of which 1,760 were excluded during an initial review. We retrieved the full text for the remaining 80 articles, and 12 clinical trials [10–12, 20–28] eligible for the

Fig. 1. Identification process for eligible studies. Results of a systematic literature search on corticosteroid therapy in IgAN. CCTR, Cochrane Central Register of Controlled Trials; IgAN, IgA nephropathy; RCTs, randomized controlled trials.

inclusion criteria (Fig. 1). These 12 clinical trials included 1,057 IgAN patients, 560 patients treated with steroid and other 497 patients with control. The follow-up for patients ranged from 12 to 120 months, and the number of patients included in every study ranged from 19 to 261. Pozzi', STOP and TESTING studies were using methylprednisolone, NEFIGAN was using budesonide, and the rest were using prednisone as the choice of steroids. There were 4 studies [20, 23, 24, 26] with a steroid dosage less than 0.5 mg/kg/day, 5 studies [11, 21, 22, 27, 28] with a steroid dosage in the range 0.8 mg/kg/day to 1 mg/kg/day, 2 studies [10, 28] with a methylprednisolone dosage of 1 g for 3 days and then tapered prednisone 0.5 mg/kg every other day, and 1 study [12] with a 8 or 16 mg dosage of targeted-release formulation (TRF)-budesonide. The duration of the treatment ranged from 4 months up to 24 months (Table 1).

Quality Assessment

A quality assessment of the primary studies is summarized in online supplemental Table S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000489580). The Jadad scores ranged from 0 to 5 points. The study quality on the whole was poor; 2 studies had a Jadad score of 5, 5 studies had a Jadad score of 3, others were less than 3. Participants and investigators were blinded in only 3 trials, 7 studies were founded allocation concealment, and 4 studies satisfy the intention-to-treat analysis criteria.

Effects on Kidney Outcomes

Data regarding the effects of glucocorticoids on kidney included ESKD, double Scr, or 50% decreasing or more of eGFR were available from 10 trials [11, 12, 19–26] with 859 patients (Figure 2). Among whom 85 events were observed, comprising 23 events in the corticoids group ($n = 436$, 5.28%) and 62 events in the control group ($n = 423$, 14.66%). Overall, glucocorticoid reduced kidney outcomes by 58% (RR 0.42, 95% CI 0.25–0.71, $p < 0.001$) in IgAN patients with no evidence of heterogeneity ($I^2 = 9.2\%$, $p = 0.36$).

In order to further find the influence of various factors on the incidence of kidney events, we performed subgroup analysis and found that the association between glucocorticoid and risk of kidney outcome was not modified by sample size, age, follow-up time, usage of steroid, steroid dose, type of steroid, steroid duration, using ACEi or ARB in control, baseline proteinuria, serum creatinine, and systolic BP (Fig. 3).

Effects on Proteinuria

The STOP-IgAN Trial showed corticosteroid monotherapy transiently reduced the protein-to-creatinine ratio at 12 months. However, data on 24 h proteinuria associated with steroid were collected to make a statistical analysis in our paper, not protein-to-creatinine ratio. Six studies [11, 20, 21, 25–27] assessed 24-h proteinuria in a total of 461 patients, comprising 238 patients in the glucocorticoid treatment group and 223 patients in the control group. Findings suggest that proteinuria at the end

Table 1. Characteristics of RCTs involved in the study

RCTs	Baseline characters		Drugs	Duration of therapy, month	Follow-up, month	Number of patients		Events***
	serum creatinine (mg/dL) or eGFR (mL/min/1.73 ²)*	proteinuria (g/day) or UPC ratio (mg/dL)**				sample sizes (steroid/ control group)	sample sizes (steroid/ control group)	
Lai et al. [21], 1986	1.36±0.59	5.6±2.21	Prednisone or prednisolone: initial dose, 40–60 mg/day, then tapered	4	38	17/17	2/0	
Julian and Barker [26], 1993	1.54±0.19	3.35±0.6	Prednisone: initial, 60 mg every other day for 3 months, then tapered	24	6–24	17/18	1/2	
Shoji et al. [27], 2000	0.74±0.22	0.75±0.31	Prednisolone: 0.8 mg/kg/day, then tapered;	12	12	11/8	0/0	
Katafuchi et al. [24], 2003	0.91±0.22	1.63±1.53**	Prednisolone: 20 mg/day, gradually tapered to 5 mg/day	24	65	43/47	3/3	
Pozzi et al. [28], 2004	1.10 (IQR 0.90–1.30) ^a	2.0 (IQR 1.6–2.4) ^b	Methylprednisolone: 1.0 g i.v. ×3 day at start month of 2, 4; prednisone: 0.5 mg/kg every other day	6	120	43/43	1/13	
Hogg et al. [23], 2006	108.5±3.1*	1.81±1.98**	Prednisone: initial, 60 mg every other day for 3 months, then tapered	24	24	33/31	2/4	
Koike et al. [20], 2008	1.04±0.31	0.93±0.63	Prednisolone: 0.4 mg/kg/day, gradually tapered to 5–10 mg/day	24	24	24/24	NA/NA	
Manno et al. [22], 2009	1.07±0.29	1.7 (IQR 1.2–2.5) ^b	Prednisone: initial, 1 mg/kg/day for 2 months, then tapered	6	96	48/49	2/13	
Lv et al. [25], 2009	1.1±0.3	2.26±0.85	Prednisone: 0.8–1 mg/kg/day for 8 week, then tapered	6–8	27.3	33/30	1/7	
TESTING 2017	59.30±25.01*	2.40±1.93	Methylprednisolone: 0/6–0.88 mg/kg/day for 2 months, then tapered	6–8	25	136/126	10/15	
NEFIGAN 2017	78.03±25.16*	1.20±2.10	TRF-budesonide 8 or 16 mg per day for 9 months, then continued optimized RAS blockade treatment	9	12	100/50	NA/NA	
STOP 2017	91.2±30.4*	0.9±0.5**	Methylprednisolone: 1.0 g i.v. ×3 day at start month of 1, 3, 5; prednisone: 0.5 mg/kg orally/48 h for 6 months on the remaining days	6	36	55/54	1/5	

* eGFR, estimated glomerular filtration rate (mL/min/1.73 m²).

** UPC ratio, the urine protein to creatinine ratio (mg/dL).

*** Events, ESRD or doubling of serum creatinine or 15% decreasing of GFR.

^a Median serum creatinine (mg/dL) in the steroid group.

^b Median proteinuria (g/day) in the steroid group.

RCT, randomized controlled trial; UPC, urine protein-to-creatinine; NA, not available; IQR, interquartile range.

Fig. 2. Effect of steroids on composite renal endpoint (ESRD or doubling of serum creatinine or 50% decrease of GFR) in patients with IgAN. Boxes and horizontal lines represent RR and 95% CI, respectively, for each trial. The size of boxes is proportional to the weight of that trial result. Diamonds represent the 95% CI for

pooled estimates of effect and are centered on pooled RR. Dotted lines on the center of the diamonds represent pooled RR. Solid lines represent that the RR is 1. GFR, glomerular filtration rate; IgAN, IgA nephropathy; RR, relative risk; ESRD, end-stage renal disease.

of treatment or during follow-up was significantly lower in steroid group than in the control groups (weighted mean difference, -0.58 g/day [95% CI -0.80 to -0.36 g/day], $p < 0.001$; $I^2 = 51\%$, p for heterogeneity = 0.07 ; Fig. 4).

Adverse Events

Data on adverse outcomes potentially associated with steroid were collected from 11 RCTs [11, 12, 21–28]. Adverse events such as infections, death, hypertension, cough, insomnia, gastrointestinal bleeding, increased appetite, heartburn, perspiration, palpitations, headache, diabetes mellitus, and cushingoid features reported in the included studies are provided in Table 2. The result showed that steroid therapy was associated with an increased risk for adverse events (RR 1.15, 95% CI 1.01–1.30; $p = 0.03$; Fig. 5). This analysis was dominated by the NEFIGAN study (133 patients; accounting for 48.0% of the weight). Exclusion of this study did not eliminate the higher risk of adverse events (RR 1.50, 95% CI 1.12–2.01; $p < 0.001$) associated with steroid therapy but dropped heterogeneity to 31.3% ($p = 0.16$; online

suppl. Fig. S1). In all kinds of adverse events, we found that gastrointestinal symptom (RR 1.62, 95% CI 1.07–2.47) and endocrine symptoms (RR 1.86, 95% CI 1.23–2.80) contributed more. Other side effects, such as cardiovascular symptoms, respiratory symptoms, endocrine symptoms, neurological symptoms, bone disorders, infections, and even death in glucocorticoid group had increased tendency, but p value is >0.05 , which is without any statistical differences.

In order to further find the influence of various factors on the incidence of adverse events, we analyzed related subgroup analysis of side effects. Subgroup analysis results show that the adverse effects cannot be influenced by sample size, age, follow-up time, usage of steroid, type of steroid, steroid dose, steroid duration, using ACEi or ARB in control, baseline proteinuria, serum creatinine, and systolic BP (online suppl. Fig. S2).

Risk of Bias

The Funnel plots and Begg's test applied to individual trials did not disclose any publication bias ($p = 0.93$; online suppl. Fig. S3).

Fig. 3. Subgroup analysis for the effect of corticosteroid on composite renal endpoint (ESRD or 15% decreasing in serum creatinine or halving of GFR). GFR, glomerular filtration rate; RR, relative risk; ESRD, end-stage renal disease.

Discussion

The use of steroid is supported by experimental insights into IgAN pathogenesis that suggest an autoimmune component in disease development and progression. Unfortunately, published studies examining the efficacy and safety for corticosteroids therapy in IgAN have reported inconsistent results [21, 24]. In this meta-analysis, quantitative systematic review comprising 12 trials and 1,057 individuals, we have clearly demonstrated that glucocorticoid had statistically significant effects in protecting the renal function and reducing proteinuria in patients with IgAN. On the contrary, it may increase the risk of side effects such as gastrointestinal symptoms and endocrinium symptoms. The results of this study suggest that glucocorticoid is effective in IgAN patients generally but should be used with caution.

Given that both the pathogenesis and progression of IgAN are linked to defects in mucosal immune regulation and inflammation [29], the use of corticosteroid to prevent kidney failure is well founded. Kidney Disease: Improving Global Outcomes guidelines for glomerulonephritis recommend patients with persistent proteinuria ≥1 g/day, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR >50 mL/min/1.73 m², receive a 6-month course of corticosteroid therapy (prednisone 0.8–1 mg/kg/day for 2 months and then reduced by 0.2 mg/kg/day per month for the next 4 months) [30]. The quality of the evidence was generally low (2C). The question of whether corticosteroids exert a benefit if added after optimization of supportive treatment remains unresolved. We defined kidney events as ESKD, double Scr, or 50% decreasing or more of eGFR which included 10 studies in which

Fig. 4. Effect of steroids on proteinuria in patients with IgAN. Boxes and horizontal lines represent mean difference and 95% CI, respectively, for each trial. The size of boxes is proportional to the weight of that trial result. Diamonds represent the 95% CI for

pooled estimates of the effect and centered on the pooled mean difference. Dotted line on the center of the diamond represents pooled mean difference. Solid line represents that the mean difference is 0. IV, inverse variance; IgAN, IgA nephropathy.

Fig. 5. Adverse events reported in the included trials. Boxes and horizontal lines represent RR and 95% CI, respectively, for each trial. The size of boxes is proportional to the weight of that trial result. Diamonds represent the 95% CI for pooled estimates of ef-

fect and are centered on pooled RR. Dotted lines on the center of the diamonds represent pooled RR. Solid lines represent that the RR is 1. RR, relative risk.

Table 2. Adverse events reported in the included studies

Adverse events	Studies reporting, <i>n</i>	Steroid group, <i>n/n</i>	Control group, <i>n/n</i>	RR (95% CI)*	<i>p</i> value
Total patients with adverse events	10	183/536	94/473	1.15 (1.01–1.30)	0.03
<i>Specific adverse events</i>					
Cardiovascular symptoms (hypertension, pulmonary embolism, deep vein thrombosis)	6	28/372	15/296	1.11 (0.60–2.06)	0.60
Respiratory symptoms (cough, respiratory infection, pneumonia)	2	2/81	3/79	1.57 (0.15–15.87)	0.47
Gastrointestinal symptoms (gastrointestinal bleeding, increased appetite, heartburn, duodenal ulcer, gastric perforation, dyspepsia, nausea, increase of liver enzymes)	5	46/341	25/298	1.62 (1.07–2.47)	0.02
Neurological symptoms (insomnia, perspiration, palpitations, headache, <i>Cryptococci meningitis</i>)	6	22/340	3/279	3.43 (0.87–13.49)	0.08
Endocrinium symptoms (diabetes mellitus/impaired glucose intolerance, acne, cushingoid features)	8	63/404	21/388	1.86 (1.23–2.80)	0.00
Bone disorders (fracture, osteonecrosis, avascular necrosis, osteochondroma)	2	4/191	0/180	96.42 (0.00–2.21e + 07)	0.89
Infections	3	20/291	5/230	1.21 (0.42–3.49)	0.73
Death	2	2/191	2/180	1.64 (0.16–17.35)	0.54

* RR, relative risk.

859 patients were analyzed to understand the relationship between glucocorticoid treatment and the progression of IgAN. The benefits of corticosteroid for the kidney protection by which steroids reduced the risk of kidney outcomes by 58% compared with supportive therapy and this finding was confirmed. Subgroup analysis revealed that the association between steroid and risk of kidney outcome was not modified by steroid dose or duration. Some findings indicate that glycan-specific antibodies are associated with the development of IgAN and may represent a disease-specific marker and potential therapeutic target. These findings support a predominant role of an autoimmune mechanism in the pathogenesis of IgAN, which provide strong evidence that steroids may add effectiveness to this autoimmune mechanism. Proteinuria is another important factor to judge the prognosis of glucocorticoid treatment effect in IgAN [31]. So when we analyzed the proteinuria to evaluate the effect of glucocorticoid treatment of IgAN, our research shows that steroids can significantly reduce proteinuria. But it should be noted that steroid therapy can increase the risk of adverse events by 15%. The incidence of gastrointesti-

nal symptom, such as gastrointestinal bleeding, increased appetite and heartburn, which are also major side effects, and these side effects increased by 105% in the steroid group. Also, endocrinium symptoms, including diabetes mellitus/impaired glucose intolerance, acne, hirsutism, and cushingoid features, increased by 86% in the steroid group. The infection was the most disconcerting side effect; however, few trials reported the incidence of infection even though this was a common adverse event. The recent TESTING trial had showed 11 severe infections (of 136, 8.1%) in the steroid group and 0 in the placebo group. In the STOP trial [32], 8 patients (of 82, 9.8%) had severe infection in the corticosteroid group or corticosteroid plus immunosuppressant group. Furthermore, a recent study conducted by Cai et al. [33] showed that of the 369 patients with steroids therapy in IgAN, severe or fatal infection happened in 18 patients (4.9%). Of all the studies, only TESTING and STOP trials mentioned death, in which 2 cases of the steroid group in TESTING (of 136, 1.5%) and 1 in the placebo group (of 126, 0.8%) died. In the STOP study, 1 case of the steroid group died in an accident and no deaths occurred in the placebo group.

These data report a high risk of severe infection or even death in the steroids regimen in IgAN. Whether low-dose steroids may provide less adverse effects in IgAN is still unknown. The ongoing international randomized control trial TESTING study (ClinicalTrials.gov No. 01560052) evaluates the efficacy and safety of lower (methylprednisolone: 0.4 mg/kg/day per day for 2 months, and then tapered) versus full-dosage (methylprednisolone: 0.8 mg/kg/day, maximal 48 mg/day, taper by 8 mg/day each month stopped at 6 months) steroids regimens in patients with IgAN. We hope this trial could answer the question of efficacy and safety of different steroids. The NEFIGAN study indicated one hundred and 33 patients experienced adverse events, comprising 91 patients in the TRF-budesonide group (91%) and 42 patients in the control group (84%). Though the number of side effects was very high, there were no serious infections and death happened in TRF-budesonide treatment. It has a preferable tolerability profile, which may provide another choice of treatment for IgAN patients [34]. This tolerability still needs to be confirmed in larger studies and more patients. Therefore, we still need to be cautious about using steroid, because many side effects can be triggered by the steroid therapy.

Strengths of this meta-analysis are the large volume of data that was able to be included, and the rigorous methodology used. However, our study also has the following limitations: (1) Existence of potential confounding factors could not be excluded. For example, the control group is not homogeneous, as it consists ACEI/ARBs or antiplatelet drugs, so that different agents might not have the same risk-benefit ratio in IgAN patients; (2) the prognosis evaluation index is less or data are incomplete in this paper; (3) Our involved studies have poor quality assessment. The limitations of the current study mean that

large high-quality RCTs are needed to reliably emphasize the efficacy and safety of steroids treatment in IgAN patients.

Conclusion

In conclusion, this study provides clear beneficial effects of steroid therapy on kidney function in patients with IgAN. It also points out the significant adverse events that occur as a consequence of such therapies. These results suggest that future guidelines should balance the risk and benefit of corticosteroid treatment in IgAN.

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Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

Financial Disclosure

The authors declare that they have no other relevant financial interests.

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