Efficacy and safety of glucocorticoids therapy for IgA nephropathy: a meta-analysis of randomized controlled trials

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CRD summary
The authors' concluded that glucocorticoids had significant effects on protecting renal function and reducing proteinuria in patients with immunoglobulin A nephropathy, but with a risk of gastrointestinal tract reactions. This was generally a well conducted review but, as the authors acknowledged, the conclusions should be interpreted with some caution due to the poor quality and heterogeneous nature of the studies.

Authors' objectives
To determine the efficacy and safety of glucocorticoids agents for immunoglobulin A nephropathy (IgAN).

Searching
MEDLINE (from 1966), EMBASE (from 1988) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to 2008. Search terms were reported. Reference lists of identified studies were screened.

Study selection
Randomised controlled trials (RCTs) that compared glucocorticoid agents with placebo, no treatment or other non-immunosuppressive agents for treating IgAN were eligible for inclusion. Cross-over studies were eligible for inclusion, but only the first period was included.

The primary outcome was renal survival (defined by impairment of renal function reaching doubling of serum creatinine or/and reaching end stage renal disease that required dialysis therapy or transplantation at any time during treatment). Secondary outcomes were daily proteinuria (g/24 hours) at the end of treatment and adverse events of treatment. Interventions in the treatment group consisted of prednisone, prednisolone and methylprednisolone followed by prednisone at various doses. Control interventions consisted of cilazapril, dipyridamole, supportive therapy, placebo and no treatment. Age ranged from 11 to 69 years. Duration of follow-up ranged from six to 65 months.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
Two reviewers independently assessed methodological quality using the Jadad scale (randomisation, double blinding, withdrawals/drop-outs). Studies were assigned a score out of 5 according to the number of items fulfilled. The following items were also assessed: allocation concealment; intention-to-treat analysis; blinding of investigators, participants and outcome assessors; and completeness of follow-up.

Data extraction
Two reviewers independently extracted data. Dichotomous data were extracted as relative risks (RR) together with 95% confidence intervals (CI). For continuous outcomes, mean differences at the end of treatment were extracted together with 95% CIs. For the outcome of renal survival, data were extracted as hazard ratios (HR); when these were not reported in the original papers they were estimated from the observed numbers of events and the log-rank statistics for the difference between Kaplan-Meier survival curves using the methods of Parmar.

Methods of synthesis
Heterogeneity was assessed using the $X^2$ test. In the absence of heterogeneity ($p>0.05$) data were pooled using the Mantel-Haenszel fixed-effect model, otherwise the DerSimonian and Laird random-effects model was used. Publication bias was assessed using funnel plots and Begg's test. Sensitivity analysis was conducted by excluding studies judged to be of poor quality (Jadad score <3).

Results of the review
Seven RCTs reported in nine publications were included (n=386). Jadad scores ranged from 0 to 5. Participants and investigators were blinded in one RCT, sufficient details of drop-outs and withdrawals were reported in six RCTs, six studies used appropriate methods of randomisation, two studies used an intention-to-treat analysis and allocation concealment was adequate in three RCTs.

Glucocorticoid treatment reduced the risk of deterioration in renal function (HR 0.20, 95% CI 0.20 to 0.39; four RCTs) and induced a greater reduction in proteinuria (SMD -0.51, 95% CI -0.73 to -0.29; six RCTs) compared to control. There was no evidence of heterogeneity (p>0.44). There were no significant differences between treatment and controls in terms of age (nine studies, p=0.91), creatinine clearance at baseline (four studies, p=0.65), mean systolic blood pressure at baseline (four studies p=0.47) and after treatment (four studies, p=0.15).

Adverse events were generally similar between treatment groups with no significant differences in terms of type 2 diabetes mellitus (five RCTs, p=0.68), hypertension (five RCTs, p=0.38), insomnia/perspiration (five RCTs, p=0.48), cushingoid (five RCTs, p=0.19) and withdrawals (six RCTs, p=0.26). The risk of gastrointestinal tract symptoms (such as heartburn and bleeding) was significantly greater in the glucocorticoid treatment groups compared to controls (RR 2.91, 95% CI 1.25 to 6.77; five RCTs). There was no significant heterogeneity for any of the adverse events.

Restriction of the analysis to studies that scored 3 or more on the Jadad scale did not alter the results. There was no evidence of publication bias (p=0.29).

**Authors' conclusions**

Glucocorticoids had statistically significant effects on protecting renal function and reducing proteinuria in patients with IgAN, but there was a risk of gastrointestinal tract reaction.

**CRD commentary**

The review addressed a focused question supported by clearly defined inclusion criteria. The literature search was adequate for published studies. But, no specific attempts were made to locate unpublished studies and it was unclear whether any language restrictions were applied, so there was a possibility of language and publication bias (assessed in the review). Appropriate steps were taken to minimise bias and errors at all stages of the review process. Study quality was assessed using appropriate criteria and the results were clearly presented and considered in the analysis. Relevant study details were summarised in tables and the results of the meta-analyses were presented clearly using forest plots. This was generally a well-conducted review and the authors' conclusions are likely to be reliable. But, as the authors acknowledged, the conclusions should be interpreted with some caution due to the poor quality and heterogeneous nature of the included studies.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that glucocorticoid agents should be investigated further for the treatment of IgAN.

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