

Specific management of IgA nephropathy: role of steroid therapy

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GUIDELINES

Steroid therapy may protect against progressive renal damage in patients with IgA nephropathy with persistent proteinuria at risk of progressive renal failure. (Level I evidence, consistent effects)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

Who to treat?

Patients with persistent and heavy proteinuria, renal impairment and/or hypertension at presentation are more likely to develop progressive renal impairment and seem to warrant intervention. It should be noted that large randomised controlled trials (RCTs) have included only those patients at risk for developing progressive renal disease and who are likely to respond to therapy (proteinuria, mild histopathological changes, etc).

At this time, there is no evidence to suggest patients with IgA nephropathy and established renal impairment (< 60mL/min) benefit from steroid therapy (Level III evidence). In addition, steroids do not prevent recurrent disease in transplant patients, and do not prevent progression in these patients.

Many patients with IgA nephropathy do not progress to renal impairment and do not require treatment. Patients with recurrent macroscopic haematuria in association with infection episodes tend to have a more benign course and can be managed expectantly in the absence of poor prognostic features. (Level III evidence)

A threshold for treatment?

The threshold for initiating steroid treatment is controversial. Some believe that greater than 1 g/d is a reasonable threshold for concern, while others would accept greater than 2 g/d. There is universal consensus that proteinuria greater than 3 g/d is associated with a very high likelihood of a subsequent progressive decline in renal function. (Level III evidence, consistent findings)

Histological features such as glomerular sclerosis, tubulo-interstitial atrophy or fibrosis and scarring also presage a poor outcome. (Level III evidence)

Patients with trivial (< 1.0 g/d) or no proteinuria, normal renal function, normal or easily-controlled hypertension who have only minor histological changes on biopsy are at low risk of progression. There is currently no data supporting the treatment of these patients. (Level III evidence)

However, even the evaluation of standard prognostic markers sometimes fails to correctly predict outcome, probably because of the heterogeneity of the disease and the discontinuous activity of some injuring mechanisms during its course. Even in the absence of specific therapeutic intervention, patients with IgA nephropathy should therefore continue to be monitored. Patients who subsequently develop markers of progressive renal disease should then be considered for intervention. (Level IV evidence)

What dose of steroid? What duration?

Optimal dosing and duration of therapy remain to be established. The RCTs that have shown benefit from steroid therapy have treated with an initial dose of approximately 1 mg/kg/day with a gradual tapering over the duration of treatment.

A reduction in proteinuria after 6 months of treatment, or at the very least no increase in proteinuria during follow-up appear to presage a more favourable outcome. (Level III evidence)

Alternate day therapy may limit toxicity. (Level III evidence)

All the studies that have shown benefit from steroid therapy have treated for more than 4 months. (Level III evidence)

There are no studies comparing longer courses to continuous therapy *ad infinitum*.

Background

IgA nephropathy is the most common glomerular disease in Australia and New Zealand (ANZDATA Registry Report 1999). Although the natural history of IgA nephropathy is variable, many patients develop progressive loss of renal function over many years. End-stage kidney disease (ESKD) is said to develop in 20% of cases after 10 years and in 30% after 20 years, whereas another 30% show some decline in renal function (Rekola et al 1991). In addition to non-specific renal interventions (control of hypertension, ACE inhibition, etc), there is evidence that interventions to specifically treat IgA nephropathy may also slow the progression to ESKD. The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of steroid therapy on renal functional decline in chronic IgA nephropathy. While proliferative or crescentic IgA nephropathy also causes renal impairment and ESKD, these guidelines only refer to chronic progressive IgA nephropathy

Search strategy

Databases searched: MeSH terms and text words for IgA nephropathy were combined with MeSH terms and text words for steroid therapy. The search was carried out in Medline (1966 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of searches: 17 September 2004.

What is the evidence?

Corticosteroids, given on a daily or alternate day basis, have been shown to produce remission of proteinuria and slow the progression to ESKD in adults with IgA nephropathy in some studies (Locatelli et al 1999).

There have been a number of RCTs in which steroids have been tested against no treatment:

- Lai et al (1986) studied 34 patients with IgA nephropathy with mild glomerular histopathological changes and nephrotic syndrome. Seventeen patients were randomised to receive daily oral steroids for 4 months and compared with 17 controls who received supportive care alone. Corticosteroid treatment resulted in a remission of nephrotic syndrome in 80% of patients, but side-effects were experienced in over 40% of patients. Some of these patients may also have had minimal change in disease on a background of IgA. No significant difference in creatinine clearance was demonstrated between the two groups during the mean study period of 38 months.
- In a longer and larger study by Pozzi et al (1999), 86 patients with biopsy-proven IgA nephropathy, urine protein excretion of 1.0–3.5 g daily, and plasma creatinine concentrations of 133 mmol/L or less were randomly assigned either supportive care or steroid treatment. Treatment consisted of intravenous methylprednisolone 1 g per day for 3 consecutive days at the beginning of months 1, 3, and 5, plus oral prednisone 0.5 mg/kg on alternate days for 6 months). Nine of 43 patients in the steroid group and 14 of 43 in the control group had a 50% increase in plasma creatinine by year 5 of follow-up ($P < 0.048$).

In a subsequent follow-up of this study, 10-year renal survival was significantly better in steroid-treated patients than in the control group (97% vs 53%; $P = 0.0003$). Steroids also significantly reduced proteinuria and protected against renal function deterioration.

- Julian & Barker (1993) prospectively reviewed 18 adults with moderate disease treated with steroids for 2 years. A non-statistically significant trend towards improved renal function was seen in the treated group at 2 years, but no beneficial effects on proteinuria were observed.
- Kobayashi et al (1989) reported an uncontrolled retrospective study of 29 patients with proteinuria over 2 g/day who were given daily prednisone for 12–36 months. Steroids stabilized kidney function in the subgroup with preserved initial creatinine clearance (> 70 mL/min). They later published a prospective

controlled study in which a subgroup of the original study was compared with an untreated group. After long-term follow-up of 10 years or more, patients in this study with initially well-preserved renal function (creatinine clearance > 70 mL/min) tended to have stable renal function or progressed more slowly when treated with glucocorticoids, whereas untreated patients continued to progress. However, patients with initial impaired renal function (creatinine clearance < 70 mL/min) did poorly with or without glucocorticoid therapy.

- Welch et al (1992) followed 20 children and adolescents with IgA nephropathy. Each received 12 weeks of prednisolone therapy and 12 weeks of placebo dosing. At the end of the short study period, there was no evidence that corticosteroid therapy was effective in reducing proteinuria or preserving renal function.
- Katafuchi et al (2003) conducted a prospective RCT of low-dose prednisolone therapy in 90 patients with IgA nephropathy. Although baseline proteinuria was significantly greater in the steroid group than in controls, steroids resulted in a greater reduction in albumin creatinine ratio compared to untreated controls (steroid group, -0.84 ± 1.78 ; controls, 0.26 ± 1.65 ; $P = 0.0034$). However, kidney survival was similar in both groups possibly because this study was too short to see differences in this outcome and insufficient doses of prednisolone were given.

There have been two meta-analyses:

- Schena et al (1990) analysed eight small RCTs prior to 1990 involving 196 patients with IgA nephropathy and moderate to heavy proteinuria. Only those patients with heavy proteinuria (> 3g/d), whether or not associated with the nephrotic syndrome appeared to benefit from therapy. In contrast, no beneficial effect was observed in IgA nephropathy patients with moderate proteinuria (1–2 g/d).
- In the most recent meta-analysis (Samuels et al 2003), there was a lower risk of reaching ESKD in the steroid-treated group compared with the no treatment or placebo group (six trials, 341 patients: RR 0.44, 95%CI: 0.25–0.80). Although this analysis was dominated by the Kobayashi et al (1989) study, there was no significant heterogeneity between these trials.

Steroids vs antiplatelet therapy

- Shoji et al (2000) studied 21 adults with diffuse IgA nephropathy with proteinuria less than 1.5 g/d of protein, and serum creatinine level less than 1.5 mg/dL. Patients were randomly assigned to the corticosteroid or antiplatelet group. After 1 year of treatment, proteinuria was significantly decreased in the corticosteroid group, associated with improved histological findings on repeat biopsy.

Chronic IgA nephropathy in children

In contrast to adult nephropathy, there have only been a few small RCTs with chronic IgA nephropathy in children, each reporting variable success with steroids. Many of these studies have included patients with crescentic nephropathy, which is not

specifically considered here and is certainly steroid-responsive in some cases. In addition, children with IgA nephropathy and pathological changes of minimal change disease (with diffuse foot process fusion and nephrotic range proteinuria) readily respond to steroid therapy, in the manner of patients with minimal change alone.

- Waldo et al (1993) reported their experience in non-randomised concurrent cohort comparison, of alternate-morning dose of prednisone for 2–4 years compared to historical control (untreated). The treated patients had a significant improvement in urinalysis ($P < 0.00001$) and preservation of normal glomerular filtration rate (GFR) [$P = 0.03$].
- Welch et al (1992) followed 20 children and adolescents with IgA nephropathy. Each received 12 weeks of prednisolone therapy and 12 weeks of placebo dosing. At the end of the short study period, there was no evidence that corticosteroid therapy was effective in reducing proteinuria or preserving renal function.

Summary of the evidence

The use of glucocorticoids for high-risk patients with IgA nephropathy is associated with a slower rate of progression to ESKD, lower risk of doubling of serum creatinine and a significant reduction in urinary protein excretion. GFR is also better preserved with steroids compared with placebo/ other treatment.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: Patients with proteinuria over 3 g/day, mild glomerular changes only, and preserved renal function (creatinine clearance over 70 mL/min) should be treated with steroids.

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

Implementation and audit

No recommendation.

Suggestions for future research

No recommendation.

References

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Appendices

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Julian et al, 1993	35	Randomised controlled clinical trial	Multicentre, Switzerland	35 patients 15-62 yrs with CrCl>25 ml/min/1.73m ²	Alternate day prednisone 60 mg x 3 mo, subsequent tapering	No treatment	6-24	
Kobayashi et al, 1996	46	Randomised controlled clinical trial	University hospital, Japan	46 patients 23-43 yrs, proteinuria 1- 2 g/d. CrCl >70 mL/min/1.73m ²	Prednisolone 40 mg/d then tapering over 7 mo total treatment	No treatment	120	
Lai et al, 1986	34	Randomised controlled clinical trial	University hospital, Hong Kong	34 Chinese patients 14-42 yrs	Prednisolone 40-60 mg/d x 2 mo, then ½ dose for 2 mo	No treatment	38	
Pozzi et al, 1999	86	Randomised controlled clinical trial	7 renal units, Italy	86 patients 15-69 yrs, SCr <1.5mg/dL, urinary protein excretion 1-3.5 g/d	Methylprednisolone 1g x 3d and prednisone 0.5 mg/kg/d x 6 mo	No treatment	60	
Welch et al, 1992	20	Crossover, randomised controlled clinical trial	University hospital, Ohio	20 patients, mean age 13 yrs, SCr >1.6 mg/dL	Prednisolone 2 mg/kg/d for 2 wks, then qod for 10 wks	Placebo	3	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Julian et al, 1993	Not specified	No	No	No	No	5.7
Kobayashi et al, 1996	Inadequate	No	No	No	No	49
Lai et al, 1986	Not specified	No	No	No	No	0.0
Pozzi et al, 1999	Not specified	No	No	No	Yes	3.5
Welch et al, 1992	Not specified	Yes	Yes	No	Unclear	15.0

Table 3. Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Julian et al, 1993	Urinary protein excretion (g/24) at end of treatment	1.30 (1.24)	1.80 (2.97)	-0.50 (95%CI: -1.99, 0.99)
	Serum creatinine (µmol/L) at end of treatment	95.00 (11.00)	157.00 (41.00)	-62.00 (95%CI: -82.14, -41.86)
Kobayashi et al, 1996	Urinary protein excretion (g/24) at end of treatment	0.80 (0.50)	1.50 (1.30)	-0.70 (95%CI: -1.25, -0.15)
	GFR (any measure) at end of treatment	54.00 (35.00)	20.00 (29.00)	34.00 (95%CI: 15.04, 52.96)
Lai et al, 1986	Urinary protein excretion (g/24) at end of treatment	2.30 (2.20)	3.30 (2.10)	-1.00 (95%CI: -2.45, 0.45)
	Serum creatinine (µmol/L) at end of treatment	126.90 (77.70)	130.70 (55.00)	-3.80 (95%CI: -49.05, 41.45)
	GFR (any measure) at end of treatment	74.10 (24.10)	64.60 (20.90)	9.50 (95%CI: -5.66, 24.66)
Pozzi et al, 1999	Urinary protein excretion (g/24) at end of treatment	0.70 (0.53)	1.80 (2.30)	-1.10 (95%CI: -2.14, -0.06)
	Serum creatinine (µmol/L) at end of treatment	105.60 (45.76)	154.00 (55.44)	-48.40 (95%CI: -80.24, -16.56)
	GFR (any measure) at end of treatment	95.60 (28.20)	71.60 (21.70)	24.00 (95%CI: 8.15, 9.85)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Julian et al, 1993	ESRD	1/18	2/17	0.47 (95%CI: 0.05, 4.74)	-0.06 (95%CI: -0.25, 0.12)
	Doubling of serum creatinine	1/18	2/17	0.47 (95%CI: 0.05, 4.74)	-0.06 (95%CI: -0.25, 0.12)
Kobayashi et al, 1996	ESRD	7/28	31/49	0.40 (95%CI: 0.20, 0.78)	-0.24 (95%CI: -0.51, 0.02)
	Doubling of serum creatinine	7/28	31/49	0.40 (95%CI: 0.20, 0.78)	-0.24 (95%CI: -0.51, 0.02)
Lai et al, 1986	ESRD	0/17	0/17	Not estimable	0.00 (95%CI: -0.11, 0.11)
	Doubling of serum creatinine	0/17	0/17	Not estimable	0.00 (95%CI: -0.11, 0.11)
	Remission of proteinuria	7/17	0/17	15.00 (95%CI: 0.92, 243.52)	0.41 (95%CI: 0.17, 0.65)
Pozzi et al, 1999	ESRD	0/43	3/43	0.14 (95%CI: 0.01, 2.68)	-0.07 (95%CI: -0.16, 0.02)
	Doubling of serum creatinine	10/43	23/43	0.43 (95%CI: 0.24, 0.80)	-0.30 (95%CI: -0.50, -0.11)