

## **Specific Management of IgA Nephropathy: role of Cyclosporin and Other Therapies**

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**Author:** Merlin Thomas

### **GUIDELINES**

**There is currently insufficient data to support the use of cyclosporin to slow the progression of IgA nephropathy. (Level I evidence)**

### **SUGGESTIONS FOR CLINICAL CARE**

(Suggestions are based on level III and IV evidence)

- **In patients with IgA nephropathy and nephrotic syndrome that have proved resistant to conventional treatment, clinical remission in selected patients has been reported following the use of cyclosporin (Chabova et al 1997), azathioprine (Goumenos et al 1995), mycophenolate (Briggs et al 1998, Briggs et al 2003) and intravenous immunoglobulin (Rostoker et al 1994), ketoconazole (Walser et al 1997) and mizobine (Tornino 1997). These anecdotal reports do not provide conclusive evidence of their efficacy in preventing disease progression in IgA nephropathy and further studies are needed before these treatments can be recommended. (Level III evidence - anecdotal reports, uncontrolled and retrospective reviews).**
- **Although their utility in preventing progressive renal impairment remains to be established, fluvastatin appears to have antiproteinuric effects in patients with IgA nephropathy. In the presence of dyslipidemia, which complicates many cases of IgA nephropathy, it seems reasonable to consider a statin as a first-line therapy.**
- **Similarly, while the clinical utility of vitamin E therapy in preventing progressive renal impairment remains to be established, its good side-effect profile means that some patients will wish to consider vitamin E supplementation in addition to other relevant supportive strategies.**

### **Background**

IgA nephropathy is the most common glomerular disease in Australia and New Zealand. 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 summarize evidence for the utility of these agents in patients with IgA nephropathy.

## **Search strategy**

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

**Date of searches:** 17 September 2004.

## **What is the evidence?**

### **Cyclosporin A**

There is no current evidence that treatment with cyclosporin either prevents the occurrence of IgA nephropathy (as it recurs in transplants) or retards the long term progression of IgA nephropathy, although long-term studies have not been performed. There are only a few small studies available using cyclosporin for the treatment of IgA nephropathy.

There has been only one small short-term randomised controlled study:

- Lai et al (1987) randomised 19 patients with IgA nephropathy and proteinuria (greater than 1.5 g/day) to receive oral cyclosporin (5 mg/kg/day) for 12 weeks (n = 9) and placebo (n = 10). Although there was a significant fall in protein excretion, this was accompanied by a rise in serum creatinine in cyclosporin-treated patients. This was despite the plasma cyclosporin concentrations being maintained within a narrow therapeutic range. However, both proteinuria and renal function returned to pre-treatment levels after cessation of treatment.

In another small non-randomised open label study (Chabova et al 1997), 6 patients with IgA nephropathy, nephrotic-range proteinuria resistant to corticosteroids administered for 3 months and serum creatinine less than 200 mmol/L were given cyclosporin (5 mg/kg/day) titrated to a serum concentration of 70–150 ng/mg and alternate day prednisolone for 1 year tapered to discontinuation in 9 months. Cyclosporin treatment reduced proteinuria. Overall, glomerular filtration rate (GFR) decreased after 1 year of treatment, although after 2 years it was not significantly different from baseline. The variable natural history of this disease makes such uncontrolled observations difficult to interpret.

A recent meta-analysis concluded that there was no significant difference in the risk of ESKD or rate of decline of GFR between patients treated with cyclosporin and patients treated with placebo (Samuels et al 2004).

## **Vitamin E**

Oxidative stress is believed to be an important mediator of renal injury in IgA nephropathy. There has been one randomised controlled trial of vitamin E therapy in children with IgA nephropathy.

- Chan et al (2003) randomised 55 children with IgA nephropathy to received vitamin E (400–800 IU /day) (n = 27) or placebo (n = 28). Proteinuria was significantly reduced in those receiving vitamin E compared to placebo. However, there were no significant changes in the prevalence of hematuria. As these patients did not have progressive renal impairment, the effect of vitamin E in preserving renal function could not be assessed.

## **Mycophenolate**

Humoral immunity is believed to play a role in the pathogenesis of IgA nephropathy. There have been two prospective placebo-controlled randomised studies in patients with IgA nephropathy using mycophenolate mofetil (MMF).

- Maes et al (2004) randomised 34 patients at risk for progressive disease, to receive ACE inhibition and MMF (2 g per day, n = 21) or placebo (n = 13) for 3 years of treatment. No significant effect of MMF could be demonstrated on renal function/outcome or proteinuria.
- Chen et al (2002) randomised 62 patients with severe IgA nephropathy and proteinuria to receive MMF or oral prednisolone. After 6, 12 and 18 months, proteinuria was reduced in both groups, although the effect was larger in patients receiving MMF. In addition, lipid parameters were significantly improved in patients receiving MMF compared with those receiving prednisolone alone.

## **Fluvastatin**

Fluvastatin may have an anti-proteinuric effect in IgA nephropathy, independent of its lipid-lowering activities (Buemi et al 2000). There has been one prospective controlled trial of fluvastatin in patients with IgA nephropathy.

- Kano et al (2003) randomised 30 patients with IgA nephropathy and moderate proteinuria to receive 20 mg of fluvastatin and 5 mg/kg of dipyridamole or dipyridamole alone. After 1 year, proteinuria and hematuria and creatine clearance increased in patients treated with fluvastatin compared to patients receiving dipyridamole alone.

## **Other agents**

There are no prospective clinical trials in patients with IgA nephropathy using azathioprine, intravenous immunoglobulin, ketoconazole or mizobine.

## **Summary of the evidence**

At present, there is insufficient evidence to support the use of cyclosporin or, MMF to prevent progression of kidney disease in patients with IgA nephropathy. Although both fluvastatin and vitamin E appear to have antiproteinuric effects, their utility in preventing progressive renal impairment remains to be established.

## **What do the other guidelines say?**

**Kidney Disease Outcomes Quality Initiative:** No recommendation.

**UK Renal Association:** No recommendation.

**Canadian Society of Nephrology:** Cyclosporin A should not be used. No recommendation regarding other therapies (Nolin et al, 1999).

**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
Chan et al, 2003	55	Randomised controlled clinical trial	7 paediatric nephrology programs, US	55 children with biopsy-proven IgA nephropathy	Vitamin E	placebo	12 mo	
Kano et al, 2003	60	Randomised controlled clinical trial	Hospital, Japan	30 children diagnosed with normocholesterolemic IgA nephropathy	30 mg fluvastatin and 5 mg/kg dipyridamole	5 mg/kg dipyridamole	24 mo	
Lai et al, 1987	19	Randomised controlled trial	University hospital, Hong Kong	19 patients with IgA nephropathy	Oral cyclosporin (5 mg/kg/day)	Placebo	3 mo	
Maes et al, 2004	34	Randomised controlled clinical trial	University Hospital, Belgium	34 patients with IgA nephropathy	Salt intake restriction, ACE inhibition, MMF 2g/day	placebo	36 mo	

**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)		
Chan et al, 2003	Not specified	Yes	Yes	Yes	unclear	31.0%
Kano et al, 2003	Not specified	No	No	No	No	50.0%
Lai et al, 1987	Computer-generated numbers	Yes	No	No	Unclear	0.0
Maes et al, 2004	Not specified	Yes	Not stated	Not stated	Yes	20.6%

**Table 3** Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Chan et al, 2003	Cr Clearance (mL/min/1.73m <sup>2</sup> ) end of study	127 (50)	112 (31)	15.00 (95%CI: 2.14, 27.86)
	Urinary protein/Cr (mg/mg)	0.24 (0.38)	0.61 (1.37)	-0.37 (95%CI: -0.88, 0.14)
Kano et al, 2003	UP (g/24h/1.73m <sup>2</sup> ) at 1 yr	0.5 (0.4)	0.8 (0.6)	-0.30 (95%CI:-0.66, 0.06)
	Hematuria in morning urine	1.1 (1.0)	1.3 (1.3)	-0.20 (95%CI:-1.03, 0.63)
	Serum Cr (µmol/L) at 1 yr	41.5 (12.4)	48.6 (10.6)	-7.10 (95%CI:-15.36, 1.16)
	Cr Clearance (mL/min/1.73m <sup>2</sup> ) at 1 yr	133.1 (14.9)	110.5 (15.2)	22.50 (95%CI:11.73, 33.27)
	Serum total protein (g/L) at 1 yr	73 (5)	69 (4)	4.00 (95%CI: 0.76, 7.24)
	Serum albumin (g/L) at 1 yr	46 (2)	42 (3)	4.00 (95%CI:2.18, 5.82)
	Serum total cholesterol mmol/L) at 1 yr	3.57 (0.75)	4.48 (0.67)	-0.91 (95%CI:-1.42, -0.40)
	Serum triglyceride (g/L) at 1 yr	0.72 (0.21)	1.02 (0.25)	-0.30 (95%CI:-0.47, -0.13)
	Serum LDL cholesterol (mmol/L) at 1 yr	2.02 (0.60)	2.90 (0.88)	-0.88 (95%CI: -1.42, -0.34)
Maes et al, 2004	Hematocrit (%) at 36 mo	43 (9.17)	42 (3.61)	1.00 (95%CI:-3.39, 5.39)
	Haemoglobin (g/dL) at 36 mo	14.1 (2.75)	13.9 (2.16)	0.20 (95%CI:-1.46, 1.86)
	IgA (g/L) at 36 mo	2.6 (1.37)	2.8 (1.08)	-0.20 (95%CI:-1.03, 0.63)
	Albumin (g/L) at 36 mo	38.7 (4.58)	39.2 (3.61)	-0.50 (95%CI: -3.27, 2.27)

**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]
Lai et al, 1987	Moderate ankle oedema	2/9	1/10	2.22 (95%CI: 0.24, 20.57)	0.12 (95%CI:-0.21, 0.45)
	Hirsutism, epigastric discomfort	2/9	0/10	5.50 (95%CI: 0.30, 101.28)	0.22 (95%CI:-0.07, 0.52)
	Decrease in serum IgA concentration	7/9	0/10	16.50 (95%CI:1.07, 253.40)	0.78 (95%CI: 0.48, 1.07)
Maes et al, 2004	Mortality	0/21	1/13	0.21 (95%CI:0.01, 4.85)	-0.08, (95%CI:-0.25, 0.10)
	Stopped treatment due to adverse events	1/21	1/13	0.62 (95%CI: 0.04, 9.07)	-0.03 (95%CI:-0.20, 0.14)
	Loss of renal function (decrease >25% in inulin clearance)	7/21	2/12	2.17 (95%CI:0.53, 8.88)	0.18 (95%CI:-0.10, 0.46)
	GI complaints	2/21	0/13	3.18 (95%CI: 0.16, 61.49)	0.10 (95%CI: -0.07, 0.26)