Focal segmental glomerulosclerosis: use of cyclosporin A

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GUIDELINES

Cyclosporin may be effective in preserving filtration function in patients with steroid-resistant focal segmental glomerulosclerosis (FSGS), in those with steroid dependence or in those who frequently relapse on conventional therapy. (Level II evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

A number of open studies have shown that cyclosporin is able to induce complete and partial remission in both adults and children with steroid-resistant FSGS and steroid-dependent FSGS (Meyrier et al 1994, Niaudet 1994). Partial or complete remission is most likely in steroid-dependent FSGS, while the response rate in steroid-resistant FSGS is variable, ranging between 20 and 70% in most studies.

Cyclosporin is also associated with significant toxicity, which means that use of this agent should be reasonably restricted to patients at high risk of end-stage kidney disease (ESRD), or in whom toxicity from steroid-dependence confers a greater danger than chronic cyclosporin therapy.

What dose should be used?

Optimal dosing and monitoring of cyclosporin has not been fully clarified. Most studies have used doses of approximately 5 mg/kg/day with a blood level of 100–200 mg/mL. (Level III evidence)

Should steroids also be used?

Most studies have also continued a low dose of steroids while using cyclosporin. There is anecdotal evidence that this approach may be more effective in achieving remission in children than cyclosporin alone (Meyrier et al 1992).

Optimal duration of therapy

A minimum effective dose of cyclosporin should be continued for at least 2 years. (Level IV evidence) Relapse is common after tapering or discontinuing the drug. Patients who are in complete remission for more than 1 year on cyclosporin appear to be more likely to remain in remission if the cyclosporin

is gradually tapered and discontinued, rather than stopped suddenly. (Level IV evidence, anecdotal reports)

Background

FSGS is one of the most common primary glomerular diseases that result in renal impairment and ultimately ESKD, and 40–80% of patients do not respond to corticosteroids. These patients are at high risk for progressive renal disease and ESKD. In these patients, the induction of a complete or partial remission by other agents may improve or stabilize their renal function (Troyanov et al 2005). The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of cyclosporin A on renal functional decline in patients with idiopathic FSGS.

Search strategy

Databases searched: MeSH terms and text words for focal segmental glomerulosclerosis were combined with MeSH terms and text words for cyclosporin A therapy. This search was carried out in Medline (1996 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also searched for trials in focal segmental glomerulosclerosis not indexed in Medline.

Date of searches: 17 September 2004.

What is the evidence?

There have been a number of small randomized studies of adults with idiopathic FSGS and nephrotic syndrome:

- Heering et al (2004) randomly assigned 57 patients with idiopathic FSGS to receive steroids and cyclosporin (n = 34) or steroids and chlorambucil (n = 23) for 6 months. There were no differences in mean serum creatinine or proteinuria between the groups. In addition, switching patients receiving chlorambucil to cyclosporin failed to improve remission rates. Interpretation of this study is made difficult by the responsiveness to steroids alone (see guideline titled “FSGS: treatment with steroids”) in both groups biasing the improvement in renal parameters.

- Cattran et al (1999) studied 49 patients with steroid-resistant FSGS, comparing 26 weeks of cyclosporin treatment plus low-dose prednisone to placebo plus prednisone. Seventy per cent of the cyclosporin group had a partial (9%) or complete remission (61%) of their proteinuria by 26 weeks compared with 4% of the placebo group (P < 0. 001). However, 60% of responders subsequently relapsed by week 78. Nonetheless, there was a decrease of 50% in baseline creatinine clearance in 25% of the cyclosporine-treated group compared with 52% of controls, independent of other baseline demographic and laboratory variables.

- Garin et al (1988) conducted a small randomized trial of cyclosporin that included 4 patients with FSGS. Patients were randomly allocated to a

cyclosporin (5 mg/kg/d) or a control group. After 8 weeks of therapy and 1 month without cyclosporin therapy, patients in the control group were given cyclosporin for 8 weeks and those in the cyclosporin group became controls. Proteinuria remained unchanged with cyclosporin treatment, while there was a significant increase in proteinuria in the control group. Renal progression could not be tested in this brief study format or the disease-specific impact of therapy.

- Ponticelli et al (1993) reported a prospective trial that comprised 19 patients including adults and children with probable FSGS, of whom 10 received cyclosporin, and 9 were in the control group. A biopsy diagnosis of FSGS was made if one glomerulus with segmental hyalinosis was seen. Patients were classified as steroid-resistant if they had no response after only 6 weeks of prednisone therapy. The cyclosporin dose was 5 mg/kg per day in adults and 6 mg/kg per day in children. Treatment was stopped at 6 months in non-responders. For responders, the dose was reduced by 25% every 2 months so that the drug was ultimately stopped after 12 months. Three cyclosporine-treated patients attained complete remission, and 4 had partial remissions. Three patients in the control group had partial remissions, but their diagnoses were not itemized in the report.

In addition, there has been one trial in children with FSGS:

- Tejani et al (1991) randomised 28 children with nephrotic syndrome to receive either cyclosporin and low-dose prednisone or high-dose prednisone alone. Thirteen of 14 children receiving combined therapy underwent remission versus only 8 of 14 children receiving prednisone alone ($P < 0.05$). However, there was no difference between the two groups as regards the duration of remission after discontinuation of therapy. It also was not clear how many of these patients had idiopathic FSGS.

Summary of the evidence

Small RCTs suggest that remission can be induced in some steroid-resistant patients and deterioration of renal function can be slowed.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology:

- The use of cyclosporin at doses of approximately 5 mg/kg/day may be effective in reducing urinary protein excretion. (Grade B)

- Relapse after reducing the dose or stopping cyclosporin is very common (Grade B).

- Long-term use of cyclosporin may be required to maintain remission (Grade D).

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
Cattran et al, 1999	49	Randomised controlled clinical trial	12 clinical centres in North America	49 patients with steroid-resistant FSGS	Cyclosporine and low-dose prednisolone	Placebo and prednisolone	50	
Garin et al, 1988	8	Randomised controlled clinical cross over trial	University hospital, US	8 patients with idiopathic, steroid-resistant nephrotic syndrome	Cyclosporine 5 mg/kg/s for eight weeks	No intervention	2	
Ponticelli et al, 1993	45	Randomised controlled clinical trial	Multicentre, Italy	45 patients with steroid-resistant idiopathic nephrotic syndrome	Cycloporin (CsA) 5 mg/kg/day for adults, 6 mg/kg/day for children, tapered dose	Supportive therapy	18 – 24	

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)		
Cattran et al, 1999	Central	Yes	No	No	Unclear	0.0
Garin et al, 1988	Not stated	No	No	Not stated	Unclear	0.0
Ponticelli et al, 1993	Sequentially labelled sealed envelopes	No	No	No	Yes	8.9

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Cattran et al, 1999	Mean slope of Cr* clearance (ml/min/yr) over study period	-5.5 (18)	-23 (39)	17.50 (95%CI: 0.12, 34.88)
Garin et al, 1988	Urinary protein excretion at 8 wks	11.7 (8.77)	17.3 (9.90)	-5.60 (95%CI: -14.76, 3.56)
	Cr clearance at 8 wks (ml/s/1.73m^2)	1.12 (0.65)	0.87 (0.62)	0.25 (95%CI: -0.37, 0.87)
	Serum albumin at 8 wks (g/L)	24 (8.49)	18 (8.49)	6.00 (95%CI: -2.32, 14.32)
Ponticelli et al, 1993	Proteinuria at 12 mo (mg/m^2/hg)-(Lg)	136.1 (141.7)	157.8 (102.87)	-21.70 (95%CI: -96.67, 53.27)
	Serum Cr at 12 mo (µmol/L)-(lg)	107.9 (166.4)	95.5 (54.04)	12.40 (95%CI: -61.12, 85.92)
	Cr clearance at 12 mo (ml/min/1.73m^2)-(Lg)	117.8 (57.69)	100.6 (48.38)	17.20 (95%CI: -15.27, 49.67)
	Serum urea at 12 mo (mmol/L)	12.5 (10.32)	13.2 (10.90)	-0.70 (95%CI: -7.23, 5.83)
	Serum protein at 12 mo (g/L)	57.1 (12.20)	51.6 (7.41)	5.50 (95%CI: -0.59, 11.59)
	Serum albumin at 12 mo (g/L)	31.2 (10.79)	27.5 (7.85)	3.70 (95%CI: -2.03, 9.43)
	Plasma cholesterol at 12 mo (mmol/L)	0.076 (0.04)	0.094 (0.41)	-0.01 (95%CI: -0.20, 0.18)

*Cr = creatinine

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]
Cattran et al, 1999	Complete remission	3/26	0/23	6.22 (95%CI: 0.34, 114.42)	0.12 (95%CI: -0.02, 0.25)
	Partial remission	15/26	1/23	13.27 (95%CI: 1.90, 92.79)	0.53 (95%CI: 0.33, 0.74)
	ESRD	4/26	10/23	0.35 (95%CI: 0.13, 0.98)	-0.28 (95%CI: -0.53, -0.04)
Garin et al, 1988	Decrease of more than 20% of their Cr clearance at end of trial	1/8	2/8	0.50 (95%CI: 0.06, 4.47)	-0.13 (95%CI: -0.50, 0.25)
Ponticelli et al, 1993	Remission at 1 yr	13/22	3/19	3.74 (95%CI: 1.25, 11.19)	0.43 (95%CI: 0.17, 0.70)
	Complete remission	7/22	0/19	13.04 (95%CI: 0.79, 214.34)	0.32 (95%CI: 0.11, 0.52)
	Partial remission	6/22	3/19	1.73 (95%CI: 0.50, 5.98)	0.11 (95%CI: -0.13, 0.36)
	Decrease in Cr clearance > 50% at 2 yrs	1/11	3/11	0.33 (95%CI: 0.04, 2.73)	-0.18 (95%CI: -0.50, 0.13)
	Infections	3/22	6/19	0.43 (95%CI: 0.12, 1.50)	-0.18 (95%CI: -0.43, 0.07)

Table 4 Results for dichotomous outcomes Cont.

	Gum hyperplasia	7/22	0/19	13.04 (95%CI: 0.79, 214.34)	0.32 (95%CI: 0.11, 0.52)
	Hypertrichosis	3/22	0/19	6.09 (95%CI: 0.33, 110.84)	0.14 (95%CI: -0.03, 0.30)
	Conjugated bilirubinemia	1/22	1/19	0.86 (95%CI: 0.06, 12.89)	-0.01 (95%CI: -0.14, 0.13)
	Headache	1/22	1/19	0.86 (95%CI: 0.06, 12.89)	-0.01 (95%CI: -0.14, 0.13)
	Bronchospasm	1/22	1/19	0.86 (95%CI: 0.06, 12.89)	-0.01 (95%CI: -0.14, 0.13)
	Parathesia	1/22	0/19	2.61 (95%CI: 0.11, 60.51)	0.05 (95%CI: -0.08, 0.17)
	Extrasystoles or anemia	0/22	1/19	0.29 (95%CI: 0.01, 6.72)	-0.05 (95%CI: -0.18, 0.08)