Membranous nephropathy – role of cyclosporine therapy

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GUIDELINES

a. **The use of cyclosporine therapy alone to prevent progressive renal injury in idiopathic membranous glomerulonephritis (MGN) is not supported by current data. (Level I evidence)**

b. **Cyclosporine therapy in combination with steroids may be more effective than steroids alone for the induction of remission in patients with idiopathic MGN. (Level II evidence, One RCT)**

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on level III and IV evidence)

What dose should be used?

- **Most studies using cyclosporin have used a dose of 4–6 mg/kg/day in divided doses, aimed at achieving a trough level of 150 ng/mL.**

How long should therapy be continued?

- **The antiproteinuric response of cyclosporine is typically seen within 2 to 4 weeks, if therapy is going to be effective. (Level III evidence) Generally, if no response is seen in a patient with adequate drug levels by 3 months, therapy can be considered ineffective and discontinued.**
- **If remission is induced, most studies have continued treatment for at least 12 months, although the optimal duration of therapy remains to be established.**
- **In general, within 2 years of discontinuing cyclosporine, a relapse rate between 30 and 40% is observed. This may be responsive to reintroduction of the cyclosporine treatment or a cytotoxic/corticosteroid.**
- **It has been suggested that more prolonged therapy or long-term lower dose maintenance may be considered for patients who achieve a partial remission with cyclosporine, who are at high risk of relapse or progressive renal impairment. (Level IV, anecdotal reports). However, this practice remains to be tested in any clinical studies.**

Background

Idiopathic MGN is the most common form of nephrotic syndrome in adults. Although many patients have a benign course or undergo spontaneous complete or partial remission, 30–40% of patients progress toward nd-stage kidney disease (ESKD) within 5–15 years (Schieppati et al 1993; Geddes et al 2000), sometimes months or years after the onset of nephrotic syndrome and a substantial percentage of patients never progress to kidney failure. To avoid possibly unnecessary treatments, most clinical studies have focused on individuals who are thought to be at greater risk for progressive disease. The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of cyclosporine on renal functional decline in MGN with poor prognostic features, such as heavy proteinuria (> 3 g/24 h), impaired renal function at presentation, deteriorating renal function and/orreduced response to therapy.

Search strategy

Databases searched: MeSH terms and text words for Membranous Nephropathy were combined with MeSH terms and text words for cyclosporine therapy. This search was carried out in Medline (1966 to September Week 1 2004). The Cochrane Renal Group Trials Register was also searched for trials in membranous nephropathy not indexed in Medline.

Date of searches: 9 September 2004.

What is the evidence?

There have been three randomised controlled trials (RCTs) comparing cyclosporine vs. placebo or no treatment and one of these included adding cyclosporine to a therapy based on steroids.

- Guasch et al (1995*)* identified 17 patients with MGN and persistent nephrotic range proteinuria, a rate of decline in creatinine clearance in excess of 8 mL/min/year and baseline renal impairment (creatinine clearance ~ 50 mL/min/1.73 m^2). These patients were randomised to cyclosporine (n=9) or placebo. After 12 months of cyclosporine therapy, there was significant slowing of loss of glomerular filtration rate (GFR) in patients on cyclosporine compared to that of the placebo-treated patients. This improvement was maintained in 6 of 8 patients over a mean follow-up of 21 months after cyclosporine was discontinued.

- Braun et al (1995) randomised 105 patients with MGN and persistent nephrotic range to cyclosporine and prednisone, methyl-prednisolone/chlorambucil or symptomatic treatment (control group). There was no difference in rates of remission and doubling of serum creatinine was found in approximately 20% of patients, irrespective of treatment modality.

- Pisoni and colleagues (2000) examined cyclosporine vs. conservative therapy in 21 patients with idiopathic MGN and deteriorating renal function and

followed them for 12 months. In this study, there was no significant difference in any of the study outcomes.

- Cattran et al (1995) randomised 51 patients with biopsy-proven idiopathic MGN and nephrotic-range proteinuria to 26 weeks of cyclosporine treatment plus low-dose prednisone to placebo plus prednisone. Seventy five per cent of the treatment group vs. 22% of the control group (P < 0.001) had a partial or complete remission of their proteinuria by 26 weeks. Relapse occurred in 43% (N = 9) of the cyclosporine remission group and 40% (n = 2) of the placebo group by week 52. Form this time until the end of the study at 78 weeks, the fraction of the total population in remission remained unchanged (cyclosporine 39%, placebo 13%, P = 0.007). Renal insufficiency, defined as doubling of baseline creatinine, was seen in 2 patients in each group.

In a recent meta-analysis of placebo-controlled trials of cyclosporine/prednisolone, involving 104 randomised patients, no clinically relevant beneficial effect was observed (Schieppati et al 2004). Nonetheless, partial remissions were more frequent in cyclosporine-treated patients than in those treated with alkylating agents (partial remission RR 1.68, 95%CI: 1.06–2.65, P = 0.03)

While some authors have suggested that cyclosporine/prednisolone treatment can be considered an alternative to therapy with alkylating agents, this assertion remains to be adequately tested.

Summary of the evidence

Cyclosporine may induce remission in patients with idiopathic MGN. Partial remissions may be more common in patients treated with cyclosporine than in those treated with alkylating agents. However, the impact of this finding on long-term, preservation of renal function remains to be established. Moreover, relapse is common when the drug is discontinued.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: Cyclosporine A therapy shows promise as an effective therapy for patients with membranous nephropathy who are at high risk for progressive renal failure. Cyclosporine A of 4 to 6 mg/kg daily for 12 months is the preferred regimen (Muirhead, 1999).

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

Implementation and audit

No recommendation.

Suggestions for future research

The ANZSN should support participation in any multinational clinical trial of cyclopsorine/prednisolone in patients with membranous nephropathy and at high risk of progressive kidney disease.

References

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Guasch A, Suranyi M, Newton L, et al. Short-term responsiveness of membranous glomerulopathy to cyclosporine. Am J Kidney Dis 1992; 20: 472–81.

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Schieppati A, Perna A, Zamora J et al. Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. Cochrane Database Syst Rev 2004; 18: CD004293.

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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
Braun et al, 1995 (abstract)	53	Randomised controlled clinical trial		Patients with idiopathic membranous nephropathy	Alkylating agents	No treatment	60 mo	Cyclosporin
Cattran et al, 1995	17	Randomised controlled clinical trial	Multicentre, Canada	17 patients with biopsy-proven membranous nephropathy with proteinuria	Cyclosporine	Placebo	12 mo	
Pisoni et al, 2000 (abstract)	21	Randomised controlled clinical trial		Patients with idiopathic membranous nephropathy	Cyclosporine	No treatment		

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)		
Braun et al, 1995 (abstract)		No	No	No	No	18.6%
Cattran et al, 1995	Centre stratified	No	Yes	Not stated	Unclear	0.0%
Pisoni et al, 2000 (abstract)		No	No	No	Yes	4.8%

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, 1995	Proteinuria (g/day) at 12 mo	7.2 (7)	11.0 (5)	-3.80 (95%CI: -9.54, 1.94)
	Serum albumin (g/L) at 12 mo	34.8 (4)	34.6 (9)	3.20 (95%CI:-3.23, 9.63)

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]
Braun et al, 1995 (abstract)	ESRD / death (immunosuppressive vs. no treatment)	6/75	2/22	0.88 (95%CI 0.19, 0.46)	-0.01 (95%CI: -0.15, 0.12)
	ESRD / death (alkylating agents vs. placebo/no treatment	2/31	2/22	0.71 (95%CI: 0.11, 4.66)	-0.03 (95%CI:-0.17, 0.12)
	ESRD/death (cyclosporine vs. alkylating agents)	4/44	2/31	1.41 (95%CI: 0.27, 7.22)	0.03 (95%CI:-0.09, 0.15)
	Complete remission (immunosuppressive vs. no treatment)	17/75	4/22	1.25 (95%CI: 0.47, 3.32)	0.04 (95%CI:-0.14, 0.23)
	Complete remission (alkylating agents	7/31	4/22	1.24 (95%CI: 0.41, 3.73)	0.04 (95%CI: -0.17, 0.26)

	vs. placebo/no treatment				
	Complete remission (cyclosporine vs. placebo / no treatment)	10/44	4/22	1.25 (95%CI: 0.44, 3.54)	0.05 (95%CI:-0.16, 0.25)
	Complete remission (cyclosporine vs. alkylating agents)	10/44	7/31	1.01 (95%CI: 0.43, 2.35)	0.00 (95%CI:-0.19, 0.19)
Cattran et al, 1995	GI complaints	2/9	1/8	1.78 (95%CI: 0.20, 16.10)	0.10 (95%CI:-0.26, 0.45)
	Tremor	1/9	1/8	0.89 (95%CI:0.07, 12.00)	-0.01 (95%CI:-0.32, 0.29)
	Hirsutism	1/9	1/8	0.89 (95%CI:0.07, 12.00)	-0.01 (95%CI:-0.32, 0.29)
	Infections	1/9	3/8	0.30 (95%CI: 0.04, 2.31)	-0.26 (95%CI: -0.66, 0.13)
	ESRD	1/8	4/8	0.25 (95%CI: 0.04, 1.77)	-0.38 (95%CI:-0.79, 0.04)
Pisonni et al, 2000 (abstract)	ESRD / death	3/10	1/11	3.30 (95%CI: 0.41, 26.81)	0.21 (95%CI:-0.12, 0.54)
	Complete remission	0/10	1/11	0.36 (95%CI:0.02, 8.03)	-0.09 (95%CI:-0.31, 0.13)
	Stopped treatment due to adverse effects	2/10	0/11	5.45 (95%CI: 0.29, 101.55)	0.20 (95%CI:-0.07, 0.47)