Membranous nephropathy – role of steroids

Date written: July 2005
Final submission: September 2005
Author: Merlin Thomas

GUIDELINES

There is currently no data to support the use of short-term courses of steroids as the sole therapy to prevent progressive kidney disease in patients with membranous glomerulonephritics (MGN). (Level I evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on level III and IV evidence)

- **This guideline refers to the use of steroids as sole therapy for patients with membranous glomerulonephropathy. Most studies that have successfully used alkylating agents or cyclosporine to induce remission have used them in combination with steroids delivered either as 2-monthly pulses of methylprednisolone, oral prednisone 0.5 mg/kg per 48 h, or sequential combinations therein. The optimal route remains to be established in clinical studies.**

Background

Idiopathic MGN runs a variable course. Most patients do well, with 10-year renal survival of 70%–90% (Schieppati et al 1993). Spontaneous remissions occur in up to 65% of patients (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 patients 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 steroid therapy on renal functional decline in MGN with poor prognostic features.

Search strategy

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

Date of searches: 9 September 2004.

What is the evidence?

There have been three large, prospective, randomised, placebo-controlled clinical trials (n = 333) using corticosteroid as sole therapy for MGN.

- The U.S. Collaborative Study of Adult Idiopathic Nephrotic Syndrome (AINS1979), reported in a controlled trial of 72 adult patients with MGN, randomised to receive 8 weeks of alternate-day prednisone (100–150 mg) or placebo. Patients receiving steroids had less proteinuria and a reduction in the rate of progression to renal failure. Deterioration of glomerular filtration rate was significantly more rapid in placebo-treated than in prednisone-treated patients, and ultimately 10 of 38 given placebo but only one of 34 given prednisone were in kidney failure (defined by a creatinine > 440 µmol/L). However, patients in the placebo group had a relatively short follow-up and their outcome was substantially worse than non-treated patients in other studies, leading many to criticize this study.

- The British Medical Research Trial (Cameron et al 1990) used a similar protocol, except that the study also included patients with impaired renal function (< 30 mL/min). Prednisone was also abruptly discontinued at 8 weeks rather than tapered (as in the US trial). A 107 adult patients who had not previously received immunosuppressive treatment were followed for a longer period of at least 3 years from treatment. An additional 160 patients, excluded from the trial, but with membranous nephropathy were identified, followed and assessed retrospectively at the end of the trial as a comparison group. Although there was a modest early beneficial effect on urinary protein excretion and serum albumin noted at 3 to 6 months, they were unable to demonstrate significant benefit in creatinine clearance from steroid treatment.

- The Toronto Glomerulonephritis Study Group (Cattran et al, 1990) assigned patients to receive either a 6 month course of prednisone (45 mg/m^2) (n = 81) or no specific treatment (n = 77). After a median follow-up of 48 months, like the British study, renal outcomes were similar in the two groups with respect to progression to kidney disease.

Two meta-analyses of these randomised trials confirmed both a lack of beneficial effect on total mortality or end-stage kidney disease (ESKD) in patients treated with glucocorticoids (RR 0.88, 95%CI: 0.39–1.97, P = 0.75) (Hogan et al 1995, Schieppati et al 2004). In addition, glucocorticoids had no effect on partial or complete remission.

Each of the three studies that make up the bulk of patients in the meta-analysis used a relatively brief course of steroids to treat a disease with a slow and indolent course. This has led some to question the conclusions based on short-term interventions.

- A recent small trial has looked specifically at the outcome of long-term steroid treatment. Polenakovik et al (1999) studied patients with stage II to III membranous nephropathy with proteinuria more than 2.5 g/d, without hypertension and kidney failure. Ten patients were not treated, 13 were treated with only steroids, 13 with alternate-day steroids and chlorambucil. The follow-up period was 5–10 years. A significant decrease in proteinuria was

noted both in patients treated with steroids alone and in patients treated with steroids and chlorambucil. Compared with patients treated with steroids (15. 3%) and patients treated with steroids and chlorambucil (15.3%), untreated patients had a high frequency of chronic kidney failure after 5 years of follow-up (70%) and had a significant increase in mean serum creatinine.

This data remains to be reproduced in larger trials. Prolonged treatment also carries the risk of significant toxicity, including change in appearance, weight gain, diabetes and bone loss, even when delivered as alternate-day therapy.

Summary of the evidence

There is no data to support the short-term use of steroids on their own for the treatment of patients with nephrotic syndrome and idiopathic membranous MGN.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: There is no benefit of either a short or prolonged course of oral, alternate-day steroids for either inducing remission of nephrotic syndrome or preserving renal function in patients with membranous nephropathy. Corticosteroids should not be used as sole therapy (Muirhead 1999).

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

Implementation and audit

No recommendation.

Suggestions for future research

No recommendation.

References

AINS Collaborative. A controlled study of short-term prednisone treatment in adults with membranous nephropathy. Collaborative Study of the Adult Idiopathic Nephrotic Syndrome. N Engl J Med 1979; 301: 1301–6.

Cameron JS, Healy MJ, Adu D. The Medical Research Council trial of short-term high-dose alternate day prednisolone in idiopathic membranous nephropathy with nephrotic syndrome in adults. The MRC Glomerulonephritis Working Party. Q J Med 1990; 74: 133–56.

Cattran DC, Delmore T, Roscoe J et al. A randomized controlled trial of prednisone in patients with idiopathic membranous nephropathy. N Engl J Med 1989; 320: 210–5.

Geddes CC, Cattran DC. The treatment of idiopathic membranous nephropathy. Semin Nephrol 2000; 20: 299–308.

Hogan SL, Muller KE, Jennette JC et al. A review of therapeutic studies of idiopathic membranous glomerulopathy. Am J Kidney Dis 1995; 25: 862–875.

Muirhead N. Management of idiopathic membranous nephropathy: evidence based recommendations. Kidney Int Suppl 1999; 70: S47–55.

Polenakovik MH, Grcevska L. Treatment and long-term follow-up of patients with stage II to III idiopathic membranous nephropathy. Am J Kidney Dis 1999; 34: 911–7.

Schieppati A, Perna A, Zamora J et al. Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. The Cochrane Database 2004 of Systematic Reviews, Issue 4.

Schieppati A, Mosconi L, Perna A et al. Prognosis of untreated patients with idiopathic membranous nephropathy. N Engl J Med 1993; 329: 85–9.

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
AINS Collaborative 1979	72	Randomised controlled clinical trial	Multicentre, US	72 adults with nephrotic syndrome without renal insufficiency with membranous type of renal histology on biopsy	Alternate-day prednisolone	Placebo	23	
Cameron et al, 1990	103	Randomised controlled clinical trial	Multicentre, UL	103 adults with histological diagnosis of membranous nephropathy	High-dose, alternate-day prednisolone	Placebo	36	
Cattran et al, 1989	158	Randomised controlled clinical trial	Multicentre, Canada	158 patients with biopsy-confirmed idiopathic membranous nephropathy	Alternate-day prednisolone	No treatment	48	

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)		
AINS Collaborative, 1979	Central	Yes	Yes	Yes	No	6.9 %
Cameron et al, 1990	Central	Yes	Yes	Not stated	Yes	6.8%
Cattran et al, 1989	Random numbers	No	No	Not stated	Yes	17.1 %

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Cameron et al, 1990	Serum Cr (µmol/L) at 36 mo	251 (165.83)	203 (163.94)	48.00 (95%CI:-21.30, 117.30)
	Serum Cr (µmol/L) including those on dialysis as 1000 µmol/l plasma creatinine	317 (263.27)	297 (169.56)	20.00 (95%CI:-69.15, 109.15)
	Cr clearance (mL/min) at 36 mo	75 (41.31)	67 (43.28)	8.00 (95%CI: -9.88, 25.88)
	24-h urine protein (g/24 hr)	5.6 (4.59)	5.6 (4.59)	1.10 (95%CI:-0.84, 3.04)
	Serum albumin (g/L)	34 (8.52)	35 (5.90)	-1.00 (95%CI:-4.10, 2.10)

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]
AINS Collaborative, 1979	Complete/partial remission	22/34	11/38	2.24 (95%CI: 1.28, 3.90)	0.36 (95%CI: 0.14, 0.57)
	Complete remission	4/34	4/38	1.12 (95%CI:0.30, 4.13)	0.01 (95%CI:-0.13, 0.16)
	Partial remission	8/34	3/38	0.01 (95%CI:-0.13, 0.16)	2.98 (95%CI:0.86, 10.34)
	No response	22/34	31/38	0.16 (95%CI:-0.01, 0.32)	0.79 (95%CI:0.59, 1.06)
Cameron et al, 1990	Mortality	1/52	4/51	0.25 (95%CI: 0.03, 2.12)	-0.06 (95%CI: -0.14, 0.02)
	In remission at 36 mo	7/52	4/51	1.72 (95%CI: 0.53, 5.51)	0.06 (95%CI:-0.06, 0.17)
	Proteinuria at 36 mo	30/52	33/51	0.89 (95%CI: 0.65, 1.21)	-0.07 (95%CI: -0.26, 0.12)
	Renal failure at 36 mo	6/52	7/51	0.84 (95%CI:0.30, 2.33)	-0.02 (95%CI:-0.15, 0.11)
Cattran et al, 1989	Progression to renal failure	3/77	4/81	-0.17 (95%CI:-0.37, 0.03)	-0.01 (95%CI:-0.07, 0.05)
	Mortality	3/77	1/81	3.16 (95%CI:0.34, 29.69)	0.03 (95%CI:-0.02, 0.08)
	Complete remission	16/77	19/81	0.89 (95%CI:0.49, 1.59)	-0.03 (95%CI:-0.16, 0.10)