

## Focal segmental glomerulosclerosis: cytotoxic therapy

Date written: July 2005

Final submission: September 2005

Author: Merlin Thomas

### GUIDELINES

No recommendations can be made due to conflicting Level I and Level II evidence.

### SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

#### *Cytotoxic therapy in children with focal segmental glomerulosclerosis (FSGS)*

Cytotoxic therapy with cyclophosphamide can induce remission in children with steroid-dependent nephrotic syndrome due to FSGS, or those with FSGS with steroid-related side-effects. (Level I–II evidence, conflicting)

A number of uncontrolled studies of cytotoxic therapy in children with FSGS have reported complete remission in between 32% and 65% of cases.

- Hari et al (2001) prospectively treated 65 children with idiopathic steroid-resistant nephrotic syndrome and FSGS with intravenous pulses of corticosteroids and oral cyclophosphamide. Dexamethasone (5 mg/kg) or methylprednisolone (30 mg/kg) were administered intravenously, initially as 6 pulses on alternate days, followed by 4 fortnightly and 8 monthly pulses. Oral cyclophosphamide therapy was given for 12 weeks and tapering doses of prednisolone were administered for 52 weeks. Of 59 patients who completed the initial alternate-day therapy, 17 experienced complete remission with a further 8 having partial remission. Thirty-four (57.6%) patients did not respond to treatment. The outcome in patients receiving intravenous dexamethasone (n = 48) or methylprednisolone (n = 11) was similar.
- Geary et al (1984) described the response to cyclophosphamide in 29 steroid-resistant patients with idiopathic FSGS. Twenty of the patients were nephrotic when cyclophosphamide was started. Three of the nephrotic patients had a sustained remission of disease following treatment with cyclophosphamide. Nine nephrotic patients had partial responses. Of those responding, only one (1/9) progressed to end-stage kidney disease (ESKD). By contrast, 7 of the 8 non-responders had reached ESKD at the study completion.
- Tufro-McReddie et al (1992) described the response to cyclophosphamide in 26 children presenting with idiopathic focal

glomerulosclerosis, 22 of whom were steroid-resistant. Ten of these patients responded to cyclophosphamide within 16 weeks of starting therapy. Seven patients relapsed after a cyclophosphamide-induced remission, however, remission could be induced with steroid therapy in five of them, despite the fact that they were previously steroid-resistant.

- Tune et al (1995) found progression to renal failure to be less frequent in children treated with cyclophosphamide.
- Tune and colleagues (1996) reported a good response in treating steroid-resistant children with chlorambucil 0.15–0.2 mg/kg/day. Of 32 children treated with chlorambucil, 66% had a complete remission of proteinuria.
- Banfi et al (1991) retrospectively reviewed the management of 59 patients of FSGS with nephrotic syndrome treated with corticosteroids and/or immunosuppressive drugs as primary therapy. Twenty-seven patients were initially treated with corticosteroids alone for 9.3 months; 19 patients received corticosteroids and immunosuppressive agents associated or every other month for 5.5 months; 13 patients received either azathioprine or cyclophosphamide alone for 25 months. Remission numbers were no different from that seen in those treated with steroid alone, although fewer relapses and more sustained remissions were noted with combination therapy.

#### *Cytotoxic therapy in adults with FSGS*

Cytotoxic therapy with cyclophosphamide can induce remission in adults with steroid-dependent nephrotic syndrome due to FSGS, or those with steroid-related side-effects. (Level III-IV evidence, conflicting)

The potential role of cytotoxic therapy in the treatment of FSGS is controversial. Overall, there have been a number of small studies that suggest the addition of cytotoxics to prednisolone results in only an extra 10% of those who do not respond to prednisolone alone (Passerini et al 2001). Although one study has suggested that a remission induced by prednisolone and cyclophosphamide lasts longer than one induced by prednisolone alone (Ponticelli et al 1999). (Level III– IV evidence, conflicting results)

In adults who frequently relapse after steroid therapy has been discontinued or require continuous steroid therapy to sustain the remission, cytotoxic agents can induce remission. (Level III– IV evidence, conflicting results)

- Ponticelli et al (1999) reviewed 80 nephrotic adults with FSGS and plasma creatinine lower than 3 mg/dL. Patients were given corticosteroids (53 patients) or immunosuppressive agents (27 patients) as primary therapy for a median of 16 and 75 weeks, respectively. Forty-two patients responded with complete remission (29 patients, 36%) or partial remission (13 patients, 16%). There were no differences between steroid and cytotoxic groups.

- In a clinical series, Korbet et al (1994) reported that cyclophosphamide given at a dose of 2 mg/kg/day resulted in complete or partial remission in approximately 75% of cases. However, in cases of steroid-resistance, cyclophosphamide was much less effective, with less than 25% deriving sustained benefit from an 8 to 12 week course of therapy. Similar results for treating FSGS with chlorambucil were also reported.

*What dose should be used?*

Where cytotoxics are to be used, therapy should be limited to a brief course only (3–4 months) because of the risk of significant toxicity, even if reduction in proteinuria is achieved. Most of the studies of cytotoxic therapy in primary FSGS have used 8 weeks of therapy. (Level IV evidence, anecdotal evidence)

*Which agent, cyclophosphamide or chlorambucil?*

In the absence of trials comparing cyclophosphamide with chlorambucil in patients with FSGS, experience with either agent and patient characteristics should be taken into consideration when choosing which cytotoxic agent to use. (Level IV evidence, conflicting evidence)

## **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 increased 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 (Trojanov et al 2005). Those patients not receiving any treatment, or failing to respond to treatment, have a high risk of developing chronic renal failure (Burgess 1999). The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of cytotoxic therapy used in combination with prednisone 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 cyclophosphamide and antineoplastic agents. This search was carried out in Medline (1966 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also searched for reflux nephropathy trials not indexed in Medline.

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

## **What is the evidence?**

There are no randomized controlled studies of cytotoxic therapy alone as primary therapy in FSGS in children. There have been two studies in children with steroid-resistant nephrotic syndrome including a variable number of children with FSGS.

- In the International Study of Kidney Disease in Children (Tarshish et al 1996), 60 children with biopsy-diagnosed FSGS and with resistant nephrotic syndrome, were randomly allocated in a clinical trial comparing prednisone 40 mg/m<sup>2</sup> on alternate days for a period of 12 months (control group), with the same prednisone regimen plus a 90-day course of daily cyclophosphamide, 2.5 mg/kg in a single morning dose (experimental group). One-quarter of the children in each group had complete resolution of proteinuria. The proportions of children with increased, unchanged, and decreased proteinuria by the end of the study were similar in both groups. In addition, there was no significant difference between treatments in between the control and experimental groups.
- The French Society of Pediatric Nephrology (Niaudet 1992) conducted a randomized controlled trial (RCT) comparing the efficacy of chlorambucil (8 mg/kg) vs. a 3-month course of cyclosporin (6 mg/kg) in inducing sustained remission in 40 children with steroid-dependent idiopathic nephrotic syndrome and signs of steroid toxicity. Only one of the 20 patients treated with cyclosporin remained in remission 16 months after the end of treatment; in comparison, six of 20 receiving chlorambucil were still in remission at 27–49 months after the drug was stopped.

Two meta-analyses of children with steroid-resistant nephrotic syndrome have been performed (again including a variable percentage of patients with FSGS).

- Habashy et al (2004) found insufficient evidence to comment on the possible effect of cytotoxic agents, although a marginal beneficial effect of oral cyclophosphamide could not be completely excluded.
- Latta et al (2001) reviewed the effects of cyclophosphamide and chlorambucil in children with relapsing steroid-sensitive nephrotic syndrome, evaluating 38 studies comprising 1,504 children and 1,573 courses of cytotoxic drug therapy. They concluded that there was an overall increased rate of relapse-free survival with increasing doses of either alkylating agent, particularly in children with frequently relapsing nephrotic syndrome compared with steroid-dependent patients. In this study, chlorambucil appeared to have higher rates of severe side-effects than cyclophosphamide.

The utility of cyclophosphamide and chlorambucil has not been tested in an RCT in adults.

## **Summary of the evidence**

Cytotoxic therapy may be useful for inducing or maintaining remission in steroid-resistant patients or children with steroid dependence or frequent relapse. However, the data is conflicting with one large RCT demonstrating no effect. Moreover, any

potential benefits must be balanced against the significant risk of toxicity when using alkylating agents in children.

There is no Level I or II data on the efficacy of cytotoxic therapy in adults with FSGS.

### **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 cytotoxic therapy (cyclophosphamide and chlorambucil) may be considered as second-line therapy but the evidence is not conclusive.

**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
Niaudet, 1992	40	Randomised controlled clinical trial	Hospital, France	40 children with steroid-dependent idiopathic nephrotic syndrome and signs of steroid toxicity	Cyclosporin 6 mg/kg body wt per day over 3 mo, tapered dose	Chlorambucil at cumulative dose of 8 mg/kg body wt	24	
Tarshish et al, 1996	60	Randomised controlled clinical trial	Multicentre, US	60 children with biopsy-diagnosed FSGS	Prednisone 40 mg/m <sup>2</sup> on alternate days and 90-day course of daily cyclophosphamide 2.5 mg/kg	Prednisone 40 mg/m <sup>2</sup> on alternate days	42	

**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)		
Niaudet, 1992	Not stated	No	No	Not stated	Unclear	0.0
Tarshish et al, 1996	Central	No	No	Yes	Unclear	12.0

**Table 3** 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]
Niaudet et al, 1992	Withdrawal of prednisone	18/20	16/20	1.13 (95%CI: 0.86, 1.46)	0.10 (95%CI: -0.12, 0.32)
	Minimal change in disease (renal biopsy)	17/20	19/20	0.89 (95%CI: 0.73, 1.10)	-0.10 (95%CI: -0.28, 0.08)
	FSGS	3/20	0/20	7.00 (95%CI: 0.38, 127.32)	0.15 (95%CI: -0.02, 0.32)
	Diffuse mesangial proliferation	0/20	1/20	0.33 (95%CI: 0.01, 7.72)	-0.05 (95%CI: -0.18, 0.08)
	Hypertension	1/20	0/20	3.00 (95%CI: 0.13,69.52)	0.05 (95%CI: -0.08, 0.18)
	Hypertrichosis	8/20	0/20	17.00 (95%CI: 1.05, 276.03)	0.40 (95%CI: 0.18, 0.62)
	Gum hypertrophy	5/20	0/20	11.00 (95%CI: 0.65, 186.62)	0.25 (95%CI: 0.05, 0.45)
Tarshish et al, 1996	Mortality	3/35	2/25	1.07 (95%CI: 0.19, 5.95)	0.01 (95%CI: -0.14, 0.15)
	Treatment failure (≥ 30% serum Cr) or renal failure	20/35	9/25	1.59 (95%CI: 0.87, 2.88)	0.21 (95%CI: -0.04, 0.46)
	Complete resolution of proteinuria	8/35	6/25	0.95 (95%CI: 0.38, 2.40)	-0.01 (95%CI: -0.23, 0.21)
	Hypertensive seizure	1/35	1/25	0.71 (95%CI: 0.05, 10.89)	-0.01 (95%CI: -0.11, 0.08)