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Intensive pulse therapies for focal glomerulosclerosis in South African children

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Abstract. Seven children with steroid-resistant focal segmental glomerulosclerosis (SR-FGS) were placed on a therapeutic protocol of methylprednisolone (MP), oral prednisone (pred) and oral cyclophosphamide (CYC) given over 16 months (regimen A). Another 5 children with SR-FGS were treated with a shorter course of intravenous CYC (monthly doses over 6 months), intravenous MP (3 consecutive daily doses) and oral pred 2 mg/kg (alternate days) (regimen B). With regimen A, 1 child had a short remission, and in the others, oedema subsided, the urine protein/creatinine ratio decreased, haematuria disappeared and the estimated glomerular filtration rate (GFR) increased. The observation period was 21–42 months and the drugs were well tolerated. With regimen B, 2 patients went into complete remission, 1 had partial remission, 1 failed to respond and another died because of severe concurrent infections. In the responding children, oedema cleared, the urine protein/creatinine ratio decreased, haematuria disappeared and the GFR rose. The follow-up was between 3 and 34 months. Minor side effects were alopecia and transient hypertension. Both regimens improved the quality of life of most children. Compared with regimen A, regimen B is six times less costly with a quarter of the number of hospital visits. These observations may be of value in designing appropriate multicentre controlled trials, which have been advocated recently, for the rational and optimum management of SR-FGS.

Key words: Focal segmental glomerulosclerosis – Pulse cyclophosphamide – Methylprednisolone – Oral prednisone

Introduction

In most paediatric nephrology centres, the management of childhood nephrotic syndrome is relatively simple because about 80% [1] of such children have minimal change disease which responds favourably to steroids and has an excellent long-term prognosis. The treatment of the next largest histological group, focal glomerulosclerosis (FGS), which constitutes 9.1%–15.2% [2–4], is however difficult and the outcome often unsatisfactory. Although roughly 15%–23% of patients with FGS are initially steroid responsive, the prospects of retaining normal renal function are generally poor, with the majority going into renal failure within 10 years of onset [5, 6].

These problems are accentuated in parts of sub-saharan Africa, where FGS is the dominant histological group among children with nephrotic syndrome and nearly all are steroid resistant (SR) ab initio [2, 7]. A prolonged and intensive course of therapy with steroids and alkylating agents has been used in the United States for FGS and the results are promising [8–10]. In developing countries, however, this is not an easy option given the predictable problems of irregular follow-up and maintenance of treatment, and the exposure to serious infections.

Recent experience of other treatment designs, in particular the use of intermittent intravenous cyclophosphamide (CYC), appear to be rewarding in SR minimal change nephrotic syndrome [11] and in systemic lupus erythematosus with severe renal involvement [12, 13]. We now report on a selected group of patients with SR-FGS given either the prolonged (18 months) intensive therapy of pulse methyl prednisolone (MP), oral prednisone (pred) and cycles of oral CYC, recommended by Mendoza et al. [8], or a shorter course (6 months) based on pulses of CYC and MP together with oral alternate-day pred.

Patients and methods

Patients

Patients were selected from the renal clinic at King Edward VIII Hospital, Durban, South Africa. Patients were allocated to receive either regimen A (MP, pred, oral CYC for 18 months) or regimen B (intravenous CYC monthly for 6 months, MP for 3 consecutive daily

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doses, alternate-day oral pred for 6 months). The decision for selecting patients for either regimen was based on discussion with the parents, which included aspects of travelling distance from the hospital and the number of school days affected. Informed consent for inclusion in the proposed plan of management was obtained from all parents or guardians.

The following definitions were used: (1) nephrotic syndrome – heavy proteinuria (>40 mg/m^2 per hour), oedema and hypoalbuminaemia (serum albumin <25 g/l); (2) steroid-responsive nephrotic syndrome – patients who respond to conventional doses and duration of steroid therapy (pred 2 mg/kg per day for 1 month followed by decreasing doses over the next 2 months); response was defined as absence of oedema and clearing of proteinuria for at least 1 week; (3) SR nephrotic syndrome – persistence of the features of nephrotic syndrome despite single or multiple courses of steroids as given above; (4) relapse – the presence of the three diagnostic features of the nephrotic syndrome and a protein/creatinine ratio >2.0; (5) complete remission – no oedema, serum protein ≥ 3 g/l, urinary protein/creatinine ratio <0.2; (6) partial remission – no oedema, serum albumin ≥ 2.5 g/l and urinary protein/creatinine ratio of 0.2–1.9, (7) FGS localised or segmental areas of sclerosis in some of the glomerular tufts, unaffected glomeruli appear normal by light microscopy and sclerotic areas often contain rounded eosinophilic areas situated in the capillary loop (hyalinosis) [14]. Estimated glomerular filtration rate (GFR) was derived from body length and plasma creatinine [15].

Inclusion criteria were an age range of 1–15 years; diagnosis of FGS on renal biopsy in all patients, steroid resistance and/or resistance to oral CYC therapy and impaired renal function, as evidenced by a rising urea and creatinine (corrected for age), GFR $<$ two-thirds normal corrected for body surface area, as well as unremitting relapses. The details of each patient at entry into the programme are given in Tables 1 and 2. Exclusion criteria included the following: acute or chronic infections, end-stage renal disease (ESRD) (GFR $<$ 10ml/m^2 per min) and refused parental consent. Fluid overload was managed using standard therapy (diuretics in combination with intravenous albumin or plasma).

Drug dosages

The standard therapy prescribed was pred 2 mg/kg per day for 1 month followed by decreasing doses over the next 2 months and/or CYC 3 mg/kg per day for an 8-week period.

Regimen A. MP (30 mg/kg per dose intravenously) was given on alternate days for 6 doses, followed by weekly intravenous injections for 8 weeks, biweekly for 8 weeks then monthly for 12 months. Oral pred (2 mg/kg on alternate days) was prescribed from the 3rd week of treatment. CYC (3 mg/kg per day for 8 weeks) was commenced if the patient failed to respond to 10 weeks of treatment.

Regimen B. Patients were commenced on three daily pulse doses of MP (30 mg/kg per dose) followed by monthly pulse CYC at a dose of 0.5 g/m^2 per dose for six doses and oral pred (2 mg/kg given on alternate days).

If the response to either treatment was slow, treatment was not discontinued but the course was completed, as a late response might be anticipated [8]. Monitoring for the side effects of steroids included ophthalmological examination for cataracts and radiological examination for bone changes, before commencing treatment and every 6 months thereafter. The clinical signs of CYC toxicity were checked for at each visit and included alopecia, pallor, blue discoloration of the nails and cystitis. The full blood count, urea, electrolytes and creatinine were measured before each dose of CYC. Height and weight measurements were documented at each visit.

The drug costs of the two regimens were calculated. The cost of drugs for regimen A is six times that of regimen B [$ 687 (R2610.80) compared with $ 108.9 (R414.14)]. Furthermore the minimum number of hospital visits for regimen A is 34 compared with 8 for regimen B. Besides the cost of the hospital outpatient visits (free for those under 6 years), transport charges have to be considered.

Evaluation of therapy

Clinical criteria for the response to therapy included the loss of oedema and ascites, a decrease in body weight and the absence of constitutional symptoms and urinary sediment. Laboratory criteria included a decrease in the protein/creatinine ratio [16], a decrease in the blood urea and creatinine, a rise in serum albumin and an improved GFR. Patient response was categorised as: complete remission, partial remission or unremitting relapse.

Laboratory investigations

Baseline and 3-monthly laboratory investigations included a full blood count, blood urea, electrolytes and creatinine and serum albumin. The urine was tested for the presence of blood, protein, glucose and the protein/creatinine ratio assessed at each monthly visit. SDS PAGE for fine urinary protein analysis was performed as a confirmatory test. These tests were repeated 2 weeks after each dose of CYC. The GFR was monitored every 6 months using the modified Schwartz formula [18].

Side effects of therapy

All immunosuppressive therapy was discontinued if patients developed severe sepsis, bone marrow suppression (haemoglobin <10 g/dl, white cell count $<3{,}000$/mm3, platelets $<$ 100,000/mm3) or uncontrolled hypertension. Antimicrobial therapy was instituted and appropriate investigations undertaken. Infection was managed using aggressive antibiotic therapy. Hypertension was managed using conventional antihypertensive drugs and patients were monitored for bone marrow suppression until blood counts returned to normal.

Results

Regimen A (Table 1)

Patients. Seven children (5 males, 2 females) aged 3–8 years were treated; 4 were Indian and 3 were black.

Course of disease before treatment. The duration of the disease varied from 6 months to 15 years before treatment with regimen A. All the children had been given a standard course of pred, and 7 had a standard course of oral CYC. Two children (nos. 2, 6) responded initially to steroids but thereafter developed steroid resistance. One child responded to oral CYC but subsequently relapsed (Table 1). The periods of remission following these drugs were 3 months, 3 years and 8 years, respectively before the onset of unremitting relapses and/or deteriorating renal function.

Response to treatment. The period of follow-up ranged from 21 to 42 months with a mean of 38.1 (SD 8.8) months. One of the patients (Indian) achieved complete remission, this followed a second course of therapy. However, he subsequently relapsed and remains in relapse. The protein/creatinine ratio decreased from the nephrotic range to the mild-to-moderate range in 7 children. All patients lost their

Table 1. Details of children treated with pulse methylprednisolone, oral cyclophosphamide and oral prednisone (regimen A)

Patient no.	Age (years) Gender	Duration of illness (months)	Follow-up (months)	Serum creatinine (mmol/l)		GFR (ml/min per 1.73 m^2)		Urinary P/C ratio		Treatment duration (months)	Side effects	Clinical outcome
				B	A	B	A	B	A			
1[a, c]	7 F	15	42	261	97	27	73	1.87	0.21	18	Cataract Hyper-tension	Partial remission
2[b, d]	3 F	12	36	277	56	27	132	0.47 0.47		18	Nil	Partial remission
3[a, c]	3 M	7	24	244	78	28	123	3.3	1.59	12	Hyper-tension	Partial remission
4[c, e]	7 M	5	42	92	27	50	212	2.9	0.39	18	Frequent infections	Relapse
5[c, e]	8 M	2	36	35	24	170	275	4.2	0.48	18	Nil	Partial remission
6[b, e]	7 M	2.5	24	83	56	72	116	2.57	0.59	18	Osteopenia	Partial remission
7[a, c]	5 M	2	24	25	50	68	155	3.1	0.79	18	Frequent infections	Partial remission

B, Before treatment; A, after treatment; P/C, protein/creatinine ratio; GFR, glomerular filtration rate
[a] Black
[b] Secondary steroid resistance
[c] Primary steroid resistance
[d] Response to oral cyclophosphamide
[e] Indian

oedema within 2–6 weeks of treatment. Haematuria decreased and disappeared after 6–12 weeks of treatment in all patients. One of the Indian children had glycosuria during the course of her disease which gradually decreased over the first 4 months of treatment. The GFR improved in all patients except for the child who progressed to ESRD.

Side effects of treatment. Hypertension developed in 2 children and the regimen was discontinued for this reason in 1 child. The other developed hypertension at the end of the course and despite discontinuing steroids, the patient remained hypertensive and was subsequently controlled on antihypertensive therapy.

One child had pre-existing subcapsular cataracts of unknown aetiology at the onset of treatment and a second developed mild osteopenia during the course of treatment. Another experienced a number of infections during the course of treatment. Eight months into the course of therapy this child developed viral meningitis and treatment was stopped. He subsequently went into remission for 8 months but then relapsed following episodes of severe infection – herpes stomatitis, *Escherichia coli* septicaemia. Following his recovery, a second course of treatment was commenced. He remitted after 6 months and remained in remission for 15 months, but thereafter relapsed following development of a urinary tract infection.

Growth. Height measurements (NCHS percentiles) were within normal percentiles in 6 of the 7 children. One was stunted before institution of treatment. Another child who developed ESRD had normal height during the course of treatment and has now received a transplant; she now has severe stunting.

Regimen B (Table 2)

Patients. Five children, 2 Indian (males) and 3 black (2 males), were studied. The onset of the nephrotic syndrome was between 2.5 and 9 years of age.

Diagnosis of FGS. This was made on renal biopsy in all 5 children.

Course of disease before treatment. The duration of illness before the course of therapy ranged from 6 months to 2 years. Both Indian children had been given standard pred and oral CYC therapy with no response (Table 2). The black children had one course of standard pred therapy and were resistant. These children remained severely oedematous, had rising serum creatinines and falling GFRs.

Response to treatment. The period of follow-up (from the commencement of treatment) in the 4 surviving children was 3–34 months, with a mean of 14.6 (SD 11.7) months. Of the 5 children, 2 black remitted, following the third and fifth doses of intravenous CYC, respectively. One black child went into partial remission following the last dose of CYC. In 1 patient (Indian) there was no response to therapy

Table 2. Details of children treated with pulse methylprednisolone, pulse cyclophosphamide and oral prednisone (regimen B)[d]

Patient no.	Age (years) Gender	Duration of illness (months)	Follow-up (months)	Serum creatinine (mmol/l)		GFR (ml/min per 1.73 m^2)		Urinary P/C ratio		Treatment duration (months)	Side effects	Clinical outcome
				B	A	B	A	B	A			
8[a]	9 M	24	15	58	32	70	204	2.1	0.12	6	Frequent infection Hypertension/ alopecia	Complete remission
9[a]	3 M	12	9	87	40	50	110	8.12	0.86	6	Alopecia	Complete remission
10[a]	4 M	18	12	33	83	57	144		0.67	4	Alopecia	Partical remission
11[b, c]	9 M	6	34	27	30	212	200	0.39	0.26	6	Recurrent infections	Relapse
12[b, c]	2.5 M	6	3	36	45	–	–	3.7	–	2	Severe infections	Died

[a] Black
[b] Resistant to oral cyclophosphamide
[c] Indian
[d] All patients had primary steroid resistance

and he died following overwhelming sepsis; the second Indian child remains in relapse.

Oedema settled in 4 weeks and the proteinuria, protein/creatinine ratios and haematuria decreased and the GFRs improved over 1–3 months in all the 4 survivors. Two had severe recurrent infections. One of these children, (an Indian child) did not respond at all, developed severe infections and died following 3 months of therapy. Another child had frequent infections which necessitated discontinuation of the CYC and oral pred, he recovered from the infection and now has moderate proteinuria (protein/creatinine ratio 0.67).

Side effects of treatment. Infections were the major side effects. The death of the 1 child was due to severe Gram-negative septicaemia and systemic candidiasis occurring 2 weeks after the second dose of intravenous CYC. The full blood count was normal in all patients except for the child who died, in whom severe leucopenia was documented. Most children experienced varying degrees of alopecia and 3 children developed blue discoloration of their nails. These side effects remitted following completion of therapy.

Growth. In the child with recurrent infections there was evidence of growth retardation. All the remaining patients, except for the 1 who died early in the course of treatment, maintained linear growth within 1 SD of their initial height.

Discussion

We have recorded our experience in the management of children with SR-FGS using two intensive therapeutic regimens under sub-optimal conditions of health service delivery in South Africa, which parallels those existing in many developing countries. The results appear to be promising, notwithstanding the side effects of such therapy. The major benefits gained were that children were treated on an outpatient basis and maintained relatively symptom free. The latter was primarily due to an improvement in renal function, as shown by the reduction in proteinuria and serum creatinine, an improvement in the estimated GFR and excretion of less ‘active’ urine. Intractable oedema, hypertension and the metabolic derangements due to renal impairment, which are the most frequent indications for inpatient admission, were prevented or infrequent with the treatment regimens employed in most of these patients.

This was not a controlled trial, nor are there any data available from such trials. The number of children with FGS seen at any one centre in most parts of the world is usually fairly small. Accordingly the therapeutic protocols adopted by groups in the United States [8, 17] and in France [18] have been helpful in framing some guidelines and forming the basis for management. Regimen A used in this study is identical to that devised by Mendoza et al. [8]. Waldo et al. [17] tried a similar (but not identical) protocol, and the French group utilised pred and cyclosporin A.

In a recent review of their experience of 32 SR-FGS patients, Mendoza and Tune [19] showed that remission was induced in 66% of children and partial remission in 25%, (proteinuria with normal GFR 9%, proteinuria with reduced GFR 16%), and 9% deteriorated to ESRD. Black children in the cohort treated by Waldo et al. [17] responded particularly poorly, five of the seven developed ESRD and two renal impairment. In our study Indian children did not (as we had expected) have a better outcome than the African children [20]. Ingulli and Tejani [21]

also addressed the issue of racial differences in incidence and outcome of children with FGS; black children in their study also responded less well than Caucasian children.

The results we have obtained in black and Indian children are almost midway between the outcomes of the two recent studies [8, 17]. The assessments are not strictly comparable as our mean period of follow-up is shorter, 31 months compared with 76 months [8]. With regimen A, 1 of the 7 children remitted, but relapsed subsequently, and 1 went into ESRD and has been transplanted. Except for the latter, in all the rest, oedema subsided, proteinuria decreased below the nephrotic range, haematuria disappeared and the GFR increased within 3 months. There was no discernible effect on height and only 1 of the 7 children on regimen A had severe infections. He, however, recovered on treatment. One patient had mild osteopenia and another 2 developed hypertension (it is difficult to ascribe this to the drug therapy as hypertension could be due to the renal disorder). We believe these are acceptable limits of hazard for this therapeutic protocol for a severe type of nephrotic syndrome and compares favourably with the rate of 17%–22% for the side effects (cataracts, hypertension, decreased growth, leucopenia) reported by Mendoza et al. [8].

Regimen B gave less satisfactory results: 2 patients went into remission, 1 improved, treatment had to be discontinued in 1 and 1 who did not respond at all, died. Except for the latter 2, over a period of 1–3 months there was clearing of oedema, decrease in proteinuria to lower than nephrotic levels, disappearance of haematuria and an improvement in GFR in the remaining patients. Frequent infections occurred in 2 of the non-responders and led to the death of 1. Growth retardation was noted in the surviving child who had severe infections. These findings suggest that CYC was not well tolerated and the protocol may have to be modified to increase acceptance. Better results have been obtained recently with pulse CYC in SR minimal change disease [11]. Remission was induced in 4 of 7 patients; 3 relapsed but subsequently became steroid sensitive. In addition there were few side effects.

The protocols employed in this study have met with a similar degree of success as the cyclosporin A and pred used by the French Society of Pediatric Nephrology: in 20 children with FGS they document a 30% remission rate, 10% partial remission and a 30% ESRD rate over a mean period of 38 months.

The general improvement in well-being of the children was quite striking: school attendance and sporting activities were resumed. The improved quality of life in 4 of the patients on regimen B leaves a residue of hope for this protocol. Both regimens are relatively cheap, however regimen B is one-sixth of the cost of regimen A and the number of visits to hospital is a quarter that of regimen A.

The poor socioeconomic circumstances of the majority of our patients, together with the dearth of adequate tertiary facilities for transplantation and long-term dialysis, compel health care workers to seek therapies that delay or prevent the inevitable decline of renal function in children with FGS. These observations may add to the data required to set up controlled clinical trials for the optimal treatment of FGS as recommended recently by Mendoza and Tune [22]. This study emphasises that need once more.

In brief, we have shown that even in countries with severe resource constraints, FGS can be successfully managed, as in industrialised countries, by using intensive and prolonged drug treatment protocols with steroids and alkylating agents. The use of intravenous CYC has to be reviewed as it appears, in this small group of patients, to be attended by an unacceptable risk of severe infections.

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