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Immunosuppressive therapy in the nephrotic syndrome in children

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Abstract. The high incidence of remission and prevention of relapse of minimal change nephrotic syndrome (MCNS) in children, produced by corticosteroids is reviewed. With the introduction of corticosteroids over 30 years ago and the increased expertise in their use, the mortality rate has been reduced to less than 5%. There is no justification for a clinical trial to test the effect of corticosteroids in inducing remission, but the need remains to evaluate methods of administration in order to achieve therapeutic benefit with minimum toxicity. Children with frequently relapsing, steroid-dependent MCNS will usually enter remission following treatment with an alkylating agent such as cyclophosphamide. In about 50% no further relapse in experienced. The results of recent experience using cyclosporin A immunosuppression suggest a beneficial effect associated with steroid responsiveness. Approximately 30% of children with focal segmental glomerulosclerosis enter remission following treatment with corticosteroids. Some 30% require dialysis and transplantation within 5 years of diagnosis and immunosuppressive therapy to prevent deterioration of renal function is probably justified.

Key words: Immunosuppression – Minimal change nephrotic syndrome – Focal segmental glomerulosclerosis – Corticosteroids – Cyclophosphamide – Cyclosporin A

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Introduction

Data from the the prospective international Study of Kidney Disease in Children (ISKDC) study have confirmed the general experience that minimal change is the most common histological form of nephrotic syndrome in childhood, accounting for 80% of cases [1, 2]. The majority of children with this condition respond to corticosteroid therapy, whereas corticosteroid resistance is usual with other histological appearances. The term minimal change nephrotic syndrome (MCNS) has become synonymous with "steroid-responsive nephrotic syndrome"; the latter has the merit of focussing on the most important objective characteristic of the condition but has the disadvantage of excluding a few otherwise similar cases that do not respond to conventional corticosteroid regimens. Nevertheless it is somewhat illogical to define this condition by a negative histological feature that, in the majority of cases, remains a presumption inferred from the steroid response.

Among the histological patterns associated with corticosteroid resistance, the most prominent are mesangial proliferation and focal segmental glomerulosclerosis (FSGS), but with both appearances it is difficult, both practically and conceptually, to define a clear boundary from MCNS. The purpose of this article is to review immunosuppressive therapies used in the treatment of MCNS and FSGS. For completeness alternative forms of treatment will be also be discussed briefly.

Minimal change nephrotic syndrome

Corticosteroids

Corticosteroids were first used for the treatment of nephrotic syndrome in childhood over 30 years

ago, and there is general agreement that they are effective in inducing remission in the majority of cases of MCNS [3]. Corticosteroid drugs have a wide variety of effects, both anti-inflammatory and immunosuppressive, and it is not clear which of these is relevant to the therapeutic response. Although there is general consensus on the effect of corticosteroid drugs in MCNS, adequate prospective controlled studies in children have to date not been undertaken. It was not until 1970 that the results of a controlled trial in adults with the nephrotic syndrome were published [4]. This study employed a relatively low dose of steroids (prednisolone 26 mg/day), continued for 6 months in all patients, and the trend to a higher mortality in the prednisolone-treated group compared with controls was noted. In those with minimal change histology the disappearance of proteinuria was much more rapid on treatment; however, in the controls the proteinuria had fallen to less than 1 g/24 h in more than half the patients at 2 years after the entry into the trial. The same tendency to natural recovery was seen in nephrotic children before the advent of corticosteroids. The risks of the nephrotic state nowadays are such that it would not be justified to withhold corticosteroids for any significant length of time from a nephrotic child, and that the effect of corticosteroid treatment in inducing remission is obvious enough for a controlled trial not to be necessary or appropriate. There is, however, a need for controlled trials designed to evaluate different methods of administration of corticosteroids. In comparing the results of different series it is important to note that in addition to differences in dosage schedules, the criteria for responsiveness, dependency and resistance have not been uniform.

For the induction of remission, a high-dose regimen of prednisolone, i.e. 2 mg/kg ideal weight for height (the 50th centile weight for height age) [5] per 24 h (maximum dosage 80 mg/24 h), has become almost universal. This dose is best prescribed once daily in the morning until proteinuria has disappeared for at least 2 days, followed by stepwise withdrawal over 6 weeks. This is probably an acceptable regimen remission having been induced. Currently there are no data to suggest that remission induction is enhanced if the steroid dose is prescribed in a divided dose, twice daily. Administration of the maximum dose for 4 weeks is reasonable prior to performing a renal biopsy, provided that side-effects of the treatment are minimal. The same regimen should be used for the treatment of relapses as for the initial episode. Once the decision has been taken to treat a relapse, it is preferable to use such a high dosage, since a lower dosage often results in the child being symptomatic longer than is necessary. Common errors in corticosteroid therapy are to use too low a dosage or to start reducing the dosage before remission has been achieved.

The median time of response is towards the end of the 2nd week of therapy and only a small minority of patients respond after 4 weeks' treatment. Steroid resistance may, therefore, be defined as continued proteinuria after 4 weeks of prednisolone at a dosage of 2 mg/kg body weight per 24 h. The precise definition of steroid resistance is, however, somewhat arbitrary. The ISKDC treatment regimen, for example, consists of prednisolone 60 mg/m^2 per 24 h (maximum dosage 80 mg/24 h) in divided doses for 4 weeks followed by 40 mg/m^2 per 24 h, 3 days weekly for a further 4 weeks [6]. Persisting proteinuria after such a course defines the non-responders.

It is an acceptable objective that following the first two or even three relapses corticosteroids should be tapered off completely. However, if there have been three or more relapses during the previous 6 months, the child may be designated as a frequent relapser and will be considered steroid-dependent if he or she relapses during the phase of corticosteroid reduction.

Approximately 40% of children with MCNS do not relapse after an initial response to therapy; 20% have infrequent relapses and generally respond quickly to each short course of corticosteroids; and about 40% who respond to therapy experience frequent relapses [7]. According to the ISKDC data, the best prediction of a difficult course is the number of relapses that occur during the first 6 months following initial response to prednisolone [8]. Three or more relapses during this initial period were associated with a pattern of up to ten or more relapses over the subsequent 18 months.

Several controlled trials of therapy in frequently relapsing children have been published. Leisti et al. [9] reported that steroid dependency and frequency of relapse are predicted by adrenocortical suppression and subnormal response to adrenocorticotropic hormone stimulation. The ISKDC reported that prolongation of daily steroid therapy given for early relapse did not have lasting influence on the relapse rate [10]. Remissions of MCNS have also been reported following the administration of short courses of high-dose intravenous pulse methyl prednisolone [11]. Although the duration of remission does not appear to differ significantly from that achieved with oral

prednisolone therapy, [12, 13] the side-effects may be less. Similarly, low-dosage oral hydrocortisone has been demonstrated to reduce the frequency of relapse compared with prednisolone, with an improvement in the speed of growth, and in the short term no obvious side-effects followed 6 months of this treatment [14].

For the steroid-dependent child the most helpful assessment is the steroid threshold, i.e. the highest corticosteroid dosage at which relapses have occurred; this is not to be confused with the corticosteroid dosage used to treat the relapse. Many frequently relapsing or steroid-dependent cases can be satisfactorily maintained on alternate-day prednisolone therapy (35 mg/m^2 per 48 h) [15], which has been shown to be a more effective form of maintenance therapy in preventing relapse than an intermittent schedule (40 mg/m^2 on 3 consecutive days). Up to 0.5 mg/kg body weight on alternate days as a single morning dose can be used without significant toxicity in children aged 5 years and older and an even higher dosage can be used in younger children. The maintenance dosage should just exceed the steroid threshold and should be continued for a minimum of 6 months. The principal complications result from prolonged steroid therapy during daily induction therapy in a child who turns out to be steroid-resistant and has had 4 weeks or more of treatment. In addition the frequent relapser in whom multiple courses of treatment have been prescribed may not be spared unacceptable side-effects even if steroids are given on alternate days.

Cyclophosphamide

It is a paradox that the major role of immunosuppressive drugs in the treatment of the nephrotic syndrome is in that group of children with the least convincing evidence of immuno-pathogenesis, namely patients with MCNS who are either sensitive or resistant to steroids. The first report of the successful use of cyclophosphamide in children appeared 25 years ago [16] and it is now well established that this drug can prevent relapse in steroid-responsive nephrotic syndrome (SRNS). In well-controlled prospective studies less than 50% of patients treated with cyclophosphamide relapsed compared with 90% of controls treated only with steroids [17, 18].

An 8-week course of cyclophosphamide at a dosage of 3 mg/kg body weight per 24 h results in about 75% of cases remaining in remission for 1 year and 50% for 5 year [19]. Results are better in older children, possibly reflecting the spontaneous decline in susceptibility with age; and in the frequent relapser rather than the steroid-dependent. There is no benefit to be gained from higher dosages and shorter courses are less effective [20–22]. Longer courses, 2 mg/kg per 24 h for 12 weeks in conjunction with maintenance prednisolone may be associated with prolonged remission when prescribed for the previously steroid-dependent, frequent relapser [23]. Although the cumulative dose remains identical to that for an 8-week course at 3 mg/kg per 24 h (168 mg/kg), it is likely that the "critical" dose varies between individual patients. However, cyclophosphamide is less effective in children in whom relapses occur while they are on maintenance steroid therapy [24, 25]. It is, therefore, reasonable to reserve such treatment for those who relapse frequently and seem to be in danger of serious steroid toxicity developing. The drug is, therefore, best administered as a single daily dose of 3 mg/kg oedema-free weight during a steroid-induced remission. It is of interest that cyclophosphamide is effective even after the induction of a remission with steroids. This suggests that the susceptibility to the disease continues during a steroid-maintained remission but is modified by cyclophosphamide, although the patient remains in remission throughout [26].

Chlorambucil and nitrogen mustard

Chlorambucil, a derivative of mechlorethamine (nitrogen mustard), has been successfully used since 1966 in steroid-dependent, steroid-resistant, and frequently relapsing nephrotic children but does not appear to be superior to cyclophosphamide [25]. Although its use has been more limited than cyclophosphamide, dosages of chlorambucil rising to 0.3 mg/kg appear to be as effective in inducing substained remission [27]. Although short-term toxicity may be less with this drug than with other alkylating agents, especially when given in a low-dosage regimen, the long-term effects such as acute leukaemia and renal carcinoma suggest that exposure to chlorambucil can only be justified in those children with serious steroid toxicity.

In 1958, West [28] reported that in children with pure lipoid nephrosis (MCNS) the addition of nitrogen mustard at the end of a course of corticosteroids resulted in remission of greater duration than those observed following steroid therapy alone. This drug may be more effective and less toxic than cyclophosphamide. Schoeneman et al. [29] reported a 46% sustained remission 27 months following treatment with a single course

of nitrogen mustard therapy (0.1 mg/kg for 4 days) in 12 children, all of whom were steroid responsive and had received multiple courses of other immunosuppressive drugs.

Azathioprine

Azathioprine is an antimetabolite that is rapidly broken down to 6-mercaptopurine after ingestion. Controlled clinical trials have failed to show a therapeutic effect in preventing relapse of MCNS [30, 31] and its use is, therefore, unwarranted.

Levamisole

The use of levamisole, a known action of which is to stimulate T-lymphocyte function, in SRNS was first described by Tanphaichitr et al. [32] in an uncontrolled study. This group noted a response characterised by remission off steroids whilst receiving levamisole. Subsequently there has been a small number of uncontrolled trials using a variety of treatment regimens reporting a variable response. To date, however, there are insufficient data on the frequency of relapse following discontinuation of therapy [33, 34].

Cyclosporin A

The role of cyclosporin A (CyA) having been well established in transplant immunosuppression, it was only a short time before its use was suggested in the management of the nephrotic patient. Early reports by Meyrier et al. [35] in adults and Brodehl and Hoyer [36] in children pointed to a beneficial effect in frequently relapsing, minimal change disease. Subsequently, several prospective studies have treated a heterogeneous group of both steroid responsive and resistant cases with varying histopathology using different regimens. The majority of these children were previously treated with cyclophosphamide, chlorambucil or nitrogen mustard.

Capodicasa et al. [37] reported 10 children; 6 frequently relapsing and 4 steroid-resistant, who received a 6-month course of CyA (150 mg/m^2 per day), in combination with prednisolone. All 6 children with MCNS entered remission, the longest period of follow-up being 14 months. Niaudet et al. [38] treated 35 children in whom steroid toxicity and/or resistance were prominent. Prior to CyA all children received at least 3 months of a standard, tapering course of prednisolone in addition to pulse intravenous methyl prednisolone (1 g/1.73 m^2 × 3 doses), in order to stratify patients into steroid responders, partial responders and non-responders. CyA was prescribed for 8 months, the dose varying between 6 and 15 mg/kg per day in order to achieve therapeutic plasma levels. Of 20 children with MCNS, 17 children i.e. steroid responders) entered remission for up to 9 months. Side-effects included impairment of renal function in 8 of 35; although this was demonstrated in only one patient with biopsy-proven MCNS. Tejani et al. [39] reported on 20 steroid-resistant or steroid-dependent, relapsers who received only 8 weeks of CyA (maximum dose 7 mg/kg per day). Complete remissions were observed in 14 patient including 6 FSGS. 6 "IgM nephropathy" and 2 MCNS. No significant changes in renal function were observed post-treatment. Although Tejani et al. [39] correlated response to histopathology, the consensus experience is for remission to occur in patients with MCNS, the majority of whom have been historical steroid responders. There are as yet insufficient data on the superiority of CyA and its ability to induce a remission compared with conventional immunosuppression and on the stability of long-term remission following a short course of treatment.

Focal segmental glomerulosclerosis

Corticosteroids

FSGS is the histopathological lesion observed in approximately 10% of all children with idiopathic nephrotic syndrome [1]. Hayslett et al. [40] recognised the concept of evolution of what would not be termed minimal changes into focal sclerosing lesions as well as the progression of the nephrotic syndrome to renal failure. Early observations of corticosteroid resistance and haematuria as presenting features of FSGS in children were followed by reports, summarised by Cameron [41], of uniformly poor results of corticosteroid and immunosuppressive therapy. However, some patients did appear to be either completely or partially responsive to corticosteroids and appeared to benefit from immunosuppression. The results of nine series in which the response of nephrotic children with FSGS to treatment with corticosteroids have been previously reported [42]. The heterogeneity of FSGS is reflected in the varied manifestations at onset of the illness, the variable histopathology and unpredicatable natural history and response to treatment. Individual practice will vary from centre to centre and different regimens for the administration of corticosteroids make analysis of these data difficult when advising on the preferred form of treatment. Furthermore, it would now be unusual for any child pre-

Table 1. Response of steroid-resistant nephrotic children with focal segmental glomerulosclerosis (FSGS) to treatment with immunosuppression

Author	Year		*n*	Responded	%
Newman et al.	1976	Azathioprine and cyclophosphamide	6	1	7
Gubler et al.	1978	Chlorambucil and nitrogen mustard	23	2	4
ISKDC	1980	Cyclophosphamide	23	9	39
Mongeau et al.	1981	Cyclophosphamide	11	0	0
Trompeter et al.	1984	Cyclophosphamide	43	10	23
Total			106	22	20

Table 2. Response of patients with biopsy-proven FSGS to treatment with cyclosporin A

Author	Year	*n*	*n* Remission
Adikhari	1985	2	0
Brodehl and Hoyer	1985	2	0
Meyrier et al.	1986	3	0
Capodicasa et al.	1986	2	0
Niaudet et al.	1987	7	2
Tejani et al.	1988	10	5
Total		26	7 (27%)

senting with nephrotic syndrome not to have received a single therapeutic course of treatment with corticosteroids in order either to achieve remission or to define steroid resistance. These data are, therefore, retrospective and lack the accuracy of controlled trials but suggest a response rate, i.e. the induction of remission in 112 of 389 cases, of approximately 30%. It is now generally accepted that FSGS in remission has a good prognosis and that the treatment directed to this aim is justified to improve patient survival and to prevent potential complications of the nephrotic state. Progressive renal damage is observed in patients in whom FSGS was present at or near the onset of a nephrotic syndrome. Such children are usually resistant to treatment with corticosteroids, have microscopic haematuria and develop chronic renal insufficiency and hypertension in a high proportion of cases. Actuarial analyses of children with FSGS suggest that renal survival is probably between 45% and 65% at 15–20 years respectively.

Cyclophosphamide

Table 1 summarises the response of steroid-resistant nephrotic children with FSGS to treatment with cyclophosphamide alone or in combination with other immunosuppressive drugs [43–46]. These data are predominantly retrospective and reflect variations in individual practice. Although the numbers are small, analysis suggests that 20% of this group go into remission, or maintain a plasma albumin concentration greater than 25 g/l in the presence of proteinuria. The concept that from within a population of children with FSGS a subgroup with "malignant FSGS" can be identified has been well documented [42]. The identification of this subgroup is difficult, based solely on clinical and or histopathological criteria. However, the presence of a refractory nephrotic state and/or rapid progression to end-stage renal failure are the hallmarks of such patients, and aggressive immunosuppression may have a therapeutic role in a small minority. This treatment has usually involved more than one course of cyclophosphamide, the second usually in combination with corticosteroids and vincristine. The published results are based on only small numbers of children so treated, lasting remission having been induced in 7 of 21 who received immunosuppression prior to progression to end-stage disease. The decision to prolong renal survival by exposure to multiple courses of cytotoxic therapy may be preferable to dialysis and transplantation; however, the decision must remain individual both to clinician and patient.

Cyclosporin A

The results of treatment of nephrotic syndrome secondary to biopsy-proven FSGS with varying doses of CyA are summarised in Table 2 [35–39, 47]. Of 26 patients, adults and children, details of whose treatment has been published, a response, i.e. remission, was noted in only 7 children reported on from two centres. As mentioned above, Tejani et al. [39] correlate the response to CyA with the histopathological findings rather than with the initial response to steroid therapy. The relatively short time of CyA therapy advocated by Tejani et al. [39] may well explain in part why Niaudet et al. [38] alone have experienced irreversible impairment of renal function in 2 of 4 children with FSGS. These data, therefore, imply no

clear beneficial effect in steroid-resistant patients and that any effect in FSGS may be related to steroid sensitivity rather than to histopathology.

Anti-platelet agents

Therapy with dipyridamole was used together with anticoagulation in a group of children with FSGS also receiving cyclophosphamide and steroids; 7 of 9 went into complete remission, in contrast to 3 of 8 receiving cyclophosphamide and steroids only [48]. A lack of consistent results has limited the usefulness of this form of treatment.

Non-steroid anti-inflammatory drugs

Indomethacin has been used sporadically in the management of torrential proteinuria in FSGS. A lack of consistent effect and reports of interstitial nephritis and acute renal failure have limited its use for this purpose [49, 50].

Conclusion

The treatment of nephrotic syndrome in children remains a challenge, with MCNS in particular remaining an enigma. It is a disorder that is amenable to therapy and has a good outcome. Patient benefit and safety must be the main objectives of treatment; the former is obvious but the latter cannot be assumed. The adverse effects of steroid treatment on growth have been related to both dosage and duration of therapy. Alternate-day steroid therapy has been suggested to minimise growth retardation and unaffect ultimate height attainment. Rees et al. [51] have recently demonstrated that low-dose alternate-day steroid therapy had an adverse effect on the rate of growth through adolescence and that overnight hormone profile analysis revealed a disturbance of the hypothalamic-pituitary-gonadal axis with blunting of the expected nocturnal pulses of growth hormone and gonadotrophins.

Further evaluation of corticosteroid administration is, therefore, necessary in order to minimise the effect on growth suppression and the emotional disturbances that many children experience. It may well be that as yet unrecognised predictors of steroid dependency and prevention of relapse may provide an answer.

Can immunosuppression bring about a cure? Many patients appear to have sustained remission after limited treatment with cyclophosphamide or similar therapy; however, patients treated differently also enter remission. Only randomised trials comparing cyclophosphamide and/or CyA with more benign alternatives would resolve this uncertainty. The design of a proper clinical trial is difficult and indeed it may be unethical to deny treatment of known benefit to the nephrotic child. Careful and designed clinical observation of new treatments in comparision with patients not so treated is likely to provide a worthwhile therapeutic advance.

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