Cyclosporine for Nephrotic Syndrome—Isn’t It Time for a Collaborative Trial?

The incidence of nephrotic syndrome in childhood is estimated to be 2 to 7 per 100,000 children. In Erie County, New York, an average of 2 per 100,000 children under 16 develop nephrotic syndrome each year, leading to a cumulative prevalence of 15.7 per 100,000 children (1). When the children are under age 5 or 6, some 90 to 95% have minimal change disease and the majority are steroid responsive. Nonetheless, two-thirds of these patients have relapses, and particularly when the children are young and have not yet established resistance to many typical upper respiratory viruses, frequent relapses are common. Growth inhibition is a common result of the need to give corticosteroids for such long periods. The remaining 5 to 10% of patients are steroid resistant. This condition leads to renal biopsy, which shows a variety of processes, most frequently focal segmental glomerulosclerosis in this young age group.

Historical information tells us that many children with nephrotic syndrome died before the advent, particularly, of antibiotics, and, to a lesser extent, corticosteroids. Infections were frequent, and short stature was a major complication of urinary protein losses. Horror stories of children maintained for months in hospitals in those days still circulate in most pediatric facilities. Currently, children with minimal change disease seldom require hospitalization beyond an initial short one for evaluation, and families learn to handle the disease at home. Yet, the child who needs almost constant corticosteroid to remain free of proteinuria, and worse yet, the child who is steroid resistant present frustrating treatment dilemmas. The search for additional more efficacious treatments has led to pharmacologic intervention with alkylating agents, such as cyclophosphamide and chlorambucil, and cyclosporine.

Approximately 11% of children with nephrotic syndrome have focal sclerosis. Up to 25% of these children also respond to corticosteroids (2), but the remainder lead lives fraught with frustrating attempts to control edema, to survey for infections, and to provide adequate nutrition for growth. Because the majority of these children develop renal failure in 2 to 10 yr, several regimens have been proposed to stop the process. Among them are alkylating agents, cyclosporine, and high-dose pulse methylprednisolone plus alkylating agents (3). Whether any of these potentially dangerous regimens is efficacious is really unknown, and attempts to study the pulse methylprednisolone protocol in a multicenter collaborative trial have been thwarted by lack of funding on at least three occasions.

This issue of JASN contains a detailed review of the reports of the experience of cyclosporine treatment in both steroid-responsive and steroid-dependent nephrotic syndrome as well as in steroid-resistant disease (4). The category "focal sclerosis" includes those with focal segmental glomerulosclerosis, mesangial hypercellularity, and immunoglobulin M nephropathy. Cyclosporine induced complete remissions in 84.5% of 129 children and 76% of 33 adults with steroid-dependent idiopathic nephrosis from 12 centers. Most of these patients relapsed when either prednisone or cyclosporine was discontinued. In those with steroid-resistant disease, 22% of 50 children and 15% of 49 adults from 11 centers achieved complete remission with cyclosporine.

This review provokes some thought. Our own experience with cyclosporine in steroid-dependent patients echoes what is reported—it is steroid sparing, but when patients stop the drug, relapses follow. The authors of the review note that when cyclosporine is discontinued, subsequent relapses were more difficult to treat successfully with the reapplication of cyclosporine. When, then, should we consider using cyclosporine? It seems reasonable to consider it when steroid side effects are severe—glucose intolerance, hypertension, and short stature are three such effects. In our hospital pharmacy, a bottle of cyclosporine containing 5 g costs the buyer $274. If a child weighs 10 kg and receives 5 mg/kg per day, a 4-month supply would cost $247; the cost would be $741 for a 30-kg child. The 4-month duration is arbitrary. Those with frequent relapses may well be placed on the drug for many more months. We must determine when this cost is justified.

The experience in focal sclerosis that is reviewed is intriguing. The individual reports include small numbers of patients (4 to 11 children; 4 to 32 adults). The individual reports made one skeptical that cyclosporine could be helpful in the steroid-resistant patient at all. With this accumulation of all of the available information, however, there is a hint at least that it might benefit some. Eleven of 50 children and 6 of 49 adults achieved complete remission, a state that is likely to be associated with an improved prognosis. Yet, the authors state that, in their experience, only about 50% of all patients with focal sclerosis develop renal failure. Has the cyclosporine merely identified those who might have achieved long-lasting remission anyway?

The question of nephrotoxicity also remains. The authors of the review were able to compare posttreatment with pretreatment biopsies from 42 patients
with idiopathic nephrosis who had received cyclosporine for a period ranging from 4 to 63 months. Atrophic tubules and interstitial fibrosis were seen in 26 of these patients, even though laboratory estimates of renal function were normal. Because the underlying lesion of the nine patients with the most severe tubulo-interstitial changes was not focal sclerosis, cyclosporine is implicated as the offending agent.

The bottom line is that we are left with a number of reports that summarize the effects of cyclosporine in steroid-dependent and steroid-resistant idiopathic nephrosis in only a few patients, with different treatment strategies and with information that some develop significant nephrotoxicity that is not obvious by noninvasive blood tests. How can we move from this anecdotal reporting that leaves us unable to draw conclusions to firm knowledge of how to treat our patients effectively?

Multicenter collaborative trials have been achieved in other disciplines. The Pediatric Oncology Group was started in 1956 because pediatric oncologists were very frustrated with the mortality rate in childhood cancer and the National Cancer Institute believed that chemotherapeutic regimens should be tested prospectively. The multicenter system was conceived because there were too few such children in any one center for such testing (T. Vietti, personal communication). That system has been in operation since that time, and all those in pediatric centers are aware of the marked decrease in mortality rates in childhood cancer. The pediatric oncologists now have an infrastructure for the rapid implementation of studies of newly developed drugs and other therapeutic regimens. Apparently, the reimbursement is insufficient to cover costs completely so that institutions must supplement them, but operation continues full force.

There have also been some multicenter collaborative trials in nephrology. The Southwest Pediatric Nephrology Study Group has studied a number of short-term issues, but recent years have brought greater difficulty in achieving funding. Donadio and Glassock (5) reviewed the treatment of lupus nephritis and noted that, despite a national collaborative trial by the National Institutes of Health, there were too few patients and too short an observation period to know the efficacy of the more recent treatment regimens for lupus nephropathy. There have been a number of other collaborative trials, but none has been sustained for long observation periods in the way the Pediatric Oncology Group has.

How are we going to assure that we accumulate more data of clinical relevance in the next decades? Isn’t it time we insisted on the development of an infrastructure that will allow the timely entry of patients into appropriate protocols that can assure long observation? The Modification of Diet in Renal Disease Study may serve as a prototype. We learned from that study, costly though it was, that low-protein diets do not slow the progression of renal failure as we had hoped. Can we not learn how to structure and fund such studies more efficiently? Multicenter collaborative trials will never be inexpensive, but neither are dialysis and transplantation. It is up to us to insist on reliable data on which to base our patients’ therapy.

I was a pediatric renal fellow in 1970 to 1972. We were using alkylating agents for steroid-dependent or steroid-resistant nephrotic syndrome then. We still use them. Despite a lack of clear data on its efficacy and long-term toxicity, we have added cyclosporine to our regimen. I will retire in the year 2006. My strong suspicion is that we will still be using both alkylating agents and cyclosporine then and that the basis will be the same kind of reports that have been summarized in this review. We must create a structure that can be assured of funding and good management through which we can determine appropriate treatments and/or cures for our patients.

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REFERENCES