Treatment of Membranous Nephropathy in Children

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Membranous nephropathy (MN) is not a common pediatric glomerular disease and not a common cause of idiopathic nephrotic syndrome (NS) in children. Because of the rarity of the disease, there is only a limited amount of uncontrolled data and no controlled data available in children regarding the treatment of MN. Older uncontrolled data indicate that nearly a quarter of children with NS, whether untreated or treated with various immunosuppressive agents, develop chronic renal failure. Current recommendations for treatment both for children presenting with or without NS therefore are based on controlled data obtained in adults with MN. All children should receive angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs). Children with NS may be treated initially with corticosteroids. If a satisfactory response is not obtained with corticosteroids, then treatment with cyclosporine or chlorambucil can be tried. The protocols of treatment with these drugs are described in this article.

IDIOPATHIC MEMBRANOUS nephropathy (MN), also known as membranous glomerulonephritis or membranous glomerulonephropathy, is not a common pediatric glomerular disease and not a common cause of idiopathic nephrotic syndrome (NS) in children. In the international study of kidney disease in children, idiopathic MN accounted for only 4 of 400 children presenting with idiopathic NS.[1] The rarity of idiopathic MN as an underlying cause of idiopathic NS in children is supported by my own experience and that of others who have found that only 2% to 6% of those children who are studied by a renal biopsy examination for the evaluation of idiopathic NS have idiopathic MN.[2-6] Idiopathic MN, however, may be detected first during the evaluation of asymptomatic proteinuria.[2,7,8] Because all children with asymptomatic proteinuria do not come to the attention of physicians and because renal biopsy examinations seldom are performed on children with asymptomatic proteinuria or even those with idiopathic NS, it is possible that the prevalence of MN in children is higher than has been appreciated from the earlier reports.

TREATMENT

Existing Data

All of the existing data in the literature on the treatment and natural history of idiopathic MN in children is uncontrolled[3,4,9-11] and has been reviewed recently.[12] In these uncontrolled data there is insufficient information regarding uniformity of the definition of remission; the number of patients receiving treatment; dose, schedule, and duration of therapy with corticosteroids or other immunosuppressive agents used (azathioprine, cyclophosphamide, and chlorambucil); side effects of these drugs both in the near and long term; duration of follow-up; and the incidence of spontaneous remission. Therefore, it is not possible to make a recommendation regarding treatment from this data. The uncontrolled data, however, do show that chronic renal failure develops only in patients who have NS and not in those with asymptomatic proteinuria, and that treated or untreated, about 25% of patients with NS develop chronic renal failure after a variable follow-up of 1 to 17 years. These data are summarized in Table 1.

As in adults with idiopathic MN, the treatment of MN in children is evolving and is a study in progress. The progress in children is, however, even slower because the number of cases available for study is much smaller. For discussion purposes, the treatment of MN in children may be divided into 2 categories depending on the clinical presentation of the child.

Children With Asymptomatic Proteinuria

Children with idiopathic MN who only have asymptomatic proteinuria and without NS, hypertension, or renal failure, should be treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blocker (ARB) agents for their beneficial effect on reduction of proteinuria

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Table 1. Clinical Features, Natural History, and Treatment of Idiopathic MN in Children

	Number	%
Onset		
Total Number	166	
Males	100	60
Females	66	40
Asymptomatic proteinuria	46/165	28
NS	119/165	72
Hypertension	37/166	22
Macroscopic hematuria	3/166	2
Microscopic hematuria	114/162	70
Renal failure	2/76	3
Duration of follow-up (y)	1–17	
Treatment		
No treatment	43/166	26
Treated with immunosuppressive agents	123/166	74
Outcome with or without treatment		
Remission	63/162	39
Active disease	43/112	38
Chronic renal failure	29/156	19

and renoprotection effects. Both ACE inhibitors and ARB agents reduce intraglomerular pressure and have been shown to reduce proteinuria and progression of renal disease in a variety of chronic renal diseases (see article by Remuzzi in this issue).

Although there have been no reported studies in children with MN, there is sufficient data in adults with MN[13] (see article by Remuzzi in this issue) that it seems reasonable to use these agents in such children with MN. Many ACE inhibitors are available and some, as discussed elsewhere in this issue, have been studied for their beneficial effects on proteinuria in adults. Two commonly used ACE inhibitors are enalapril and lisinopril. The dosages of these 2 drugs in children are not known, but both generally can be started at a dose of 0.08 mg/kg/d. The generic form of enalapril recently has become available and is quite inexpensive. Most of my experience has been with enalapril, and I generally start most children on a dose of 2.5 to 5 mg/d depending on the weight of the child. The dose can be increased gradually at 2- to 4-week intervals as tolerated until a maximum effect on reduction of proteinuria is achieved. Most children have tolerated the drug well and chronic cough has not been a common occurrence. Dosages up 20 to 30 mg/d, either as a single dose or in 2 divided doses, have been well tolerated. Children not tolerating ACE inhibitors instead can be treated with one of the ARB agents. These agents, as discussed elsewhere in this issue with regard to adults, also can be used with ACE inhibitors as an adjunctive therapy. Once again, there are no data on their use in children with idiopathic MN, and the dosages in children are not established. My own limited experience indicates that losartan at a dose of 25 to 100 mg/d, depending on the weight of the child, can be used.

Whether these patients also could benefit from treatment with corticosteroids or other immunosuppressive agents is not known, but given the uncertainty of their proven value to induce remission of proteinuria, potential for serious side effects, and the fact that at least some of these patients may go into remission on their own, it is my view that these patients should not be treated with immunosuppressive agents, particularly the noncorticosteroids type of immunosuppressive drugs. However, one could ague that the stage of asymptomatic proteinuria is the time when this disease, which most likely is an autoimmune disease, would be more amenable to treatment, and because most children tolerate a short (1-2 mo) course of corticosteroids without serious side effects, it might be reasonable to use such a short course of steroids.

Children With NS

There are no controlled trials in children with NS who have been treated with corticosteroids or other immunosuppressive drugs. The uncontrolled data, as pointed out earlier, is also quite limited. How to treat a child with NS with idiopathic MN, therefore, remains a difficult decision at present.

It is unlikely that a sufficient number of cases can be collected to conduct a prospective, randomized, controlled study because of the low prevalence of the disease in children. In the absence of such possible future information, the decisions have to be based on opinions formulated from experience from small, uncontrolled studies and the information available from controlled studies performed in adult patients. The results of these controlled trials in adults with MN and the recommendations for their treatment have been discussed in detail in other articles in this issue. They are reviewed here briefly and their possible use in children both in terms of their potential benefits and risks as they relate to children are discussed.

Corticosteroids

Alternate-day corticosteroids alone have been used in adults in 3 controlled trials producing conflicting results.[14-16] Two of these trials used alternate-day prednisone at a dose of 100 to 150 mg for 8 weeks, and the third trial used a dose of 45 mg/mol/L^2 body surface area for 6 months. In the 2 trials using 100 to 150 mg alternate-day dosing of prednisone for 8 weeks, the study from the United States[14] found the treatment to be beneficial (deterioration of renal function was more rapid in untreated than in treated patients ($P < .02$). The other study, from the United Kingdom,[15] found no significant difference ($P > .05$) between the untreated and treated groups in plasma creatinine concentration, creatinine clearance, or 24-hour protein excretion. The third study, from Canada,[16] using the smaller doses for a longer duration (45 mg/mol/L^2 body surface area for 6 mo), concluded that the therapy was of no benefit ($P < .2$).

There are no controlled trials with the earlier-listed dosages or any other dosages of corticosteroids in children. It is not known whether a longer duration of therapy or a different dose of prednisone than what was used in the earlier-listed trials in adults would be beneficial in children as has been found in adults in some uncontrolled studies.[17] As stated earlier, even the uncontrolled data in children are limited and incomplete, and no conclusions can be drawn from those data. Therefore, the answer to the question of whether children should be treated with corticosteroids, and if treated with what dosages and for how long, is unknown at present. My own bias, based on experience in 9 children, is that corticosteroids can be helpful. Seven of these 9 children achieved partial remission (resolution of edema, decrease in proteinuria) or complete remission (resolution of proteinuria) on the following schedule of prednisone. Prednisone (2 mg/kg/d, maximum 60 mg/d) was given daily for 4 to 8 weeks and then switched to an alternate-day schedule (60 mg/M^2 body surface area to a maximum of 80 mg/dose). Depending on the response, the dosages were reduced gradually as the patient improved to as low as 10 to 30 mg on the alternate-day schedule and eventually discontinued. The duration of therapy varied from 6 months to 5 years. A sample case seen recently is described later.

A 12-year-old girl evaluated for sudden onset of edema was diagnosed after a renal biopsy examination to have NS secondary to idiopathic MN. At presentation she was normotensive (blood pressure 126/76 mm Hg), had normal renal function (serum creatinine level of 0.6 mg/dL), and had overt NS (24-hr urine protein of 9,338 mg, protein/creatinine ratio of 8.4, serum albumin level of 1 g/dL, and serum cholesterol level of 537 mg/dL). She was offered treatment with corticosteroids but declined—an understandable response for a teenage girl. She was started on 2.5 mg of enalapril and 81 mg of aspirin per day, and enalapril was increased gradually to 7.5 mg/d over 7 weeks. After 3 months of observation, although her proteinuria improved a bit (protein/creatinine ratio, 7.3), she remained severely nephrotic (serum albumin level of 0.8 to 1 g/dL and serum cholesterol level of 489 to 553 mg/dL). At this time she agreed to treatment with corticosteroids. Prednisone was started at a dose of 20 mg 3 times/d (0.85 mg/kg/d). There was a progressive resolution of all features of her NS with time. The serum albumin level (mg/dL) after starting prednisone was 1.3 on day 12, 1.7 on day 28, 1.9 on day 42, and 2.3 on day 78, when she was switched to 80 mg prednisone on the alternate-day schedule. She continued to improve and at 9 months after the beginning of prednisone treatment she had a negative urine culture for protein with a protein/creatinine ratio of 0.06, serum albumin level of 3.7 g/dL, and a serum cholesterol level of 174 mg/dL. Her dose of alternate-day prednisone was reduced gradually to her current dose of 20 mg every other day. On this dose, 4 years after onset, she remains in complete remission with normal blood pressure, normal urinalysis, normal serum creatinine (0.7 mg/dL), serum albumin (3.7 g/dL), and serum cholesterol (184 mg/dL). Throughout this time she also has been receiving enalapril 10 mg/d.

Although it cannot be proven that the remission in this child resulted from therapy with prednisone, the persistence of NS for 3 months in the absence of prednisone, the progressive improvement noted within days of starting prednisone, and the maintenance of remission for 4 years while receiving prednisone suggest that prednisone was beneficial to this patient. At this time she has no side effects of corticosteroids and as far as the effect of prednisone on growth is concerned, it has been minimal. She was at the 95th percentile for height at

onset and is currently at the 90th percentile for height. Her menstrual periods have been normal.

Side Effects of Corticosteroids

The side effects of corticosteroids are well known and are similar in children and adults. However, the psychosocial effects of Cushingoid features, development of striae, and impairment of linear growth are of particular concern to children. Cushingoid features develop in all children who are treated with daily doses of 2 mg/kg of prednisone (maximum, 60 mg/d) for greater than 3 to 4 weeks. The Cushingoid features are troublesome to older children and particularly to teenage girls and may lead to serious difficulties in social interactions with peers, decreased performance in school, and even noncompliance with corticosteroids. Fortunately, the Cushingoid features are reversible and resolve within a few weeks once the corticosteroids are discontinued. However, the striae that develop in some patients are not reversible, but they do fade to a pale color after discontinuation of corticosteroids. Patients who are started on alternate-day prednisone treatment at the dose of 1 to 2 mg/kg (maximum, 80 mg) usually have minimal or no Cushingoid effect, and usually do not develop psychosocial problems. Poor linear growth is always a concern in growing children treated with corticosteroids. The degree of growth retardation is dependent on the dose, schedule of dosing (daily versus alternate days), and duration of treatment. In general, growth is impaired severely for the duration of therapy with daily doses of 1 to 2 mg/d of prednisone, less impaired with doses of 0.2 to 0.4 mg/d, and, in my experience, even less impaired with an alternate-day schedule even with doses of 60 mg/M^2 (maximum, 80 mg/d). Most children continue to grow on dosages of 0.2 to 0.5 mg/kg given on an alternate-day schedule. Once corticosteroids are discontinued, catch-up growth often follows.

Cytotoxic Agents

Data of controlled trials in adults with chlorambucil and cyclophosphamide in combination with corticosteroids have been reviewed by Ponticelli. The most impressive results encompassing 10 years of follow-up were obtained using alternating courses of daily prednisone and chlorambucil.[18] In this protocol, methyl prednisolone was given intravenously at a dose of 1 g/d for 3 consecutive days, followed by daily oral prednisone at a dose of 0.5 mg/kg for 27 days. Prednisone then was discontinued and substituted by chlorambucil at a dose of 0.2 mg/kg/d for 1 month. These alternating courses of prednisone and chlorambucil were continued for 6 months. At 5 years of follow-up there were significantly more remissions in the treated than in the untreated group ($P = .026$), and a significant deterioration of renal function from baseline in the untreated group ($P = .0002$) but not in the treated group (P = not significant). At 10 years of follow-up these benefits were maintained.[19]

There are no controlled trials with chlorambucil or cyclophosphamide either with a protocol used by Ponticelli or any other protocol in children. Therefore, it is unknown if these agents are effective for idiopathic MN in children. However, intuitively it appears to me that these agents would be as beneficial in children as they are in adults, but greater caution needs to be exercised with their use in children because of their potential for gonadal toxicity and possible risk for future malignancy. Although there is hardly any experience with these agents in idiopathic MN in children, there is considerable experience with their use in children with NS secondary to minimal change disease. My own experience, which stretches over 33 years, has been predominantly with chlorambucil. A dose of 0.15 to 0.2 mg/kg/d appears to be safe and well tolerated.[20,21] This dose, when given along with an alternate-day prednisone dose of 40 to 80 mg for 6 to 8 weeks, usually is not associated with the immediate side effects of bone marrow suppression or increased risk for infections such as herpes zoster, observed sometimes with higher dosages.[20,21] We monitor blood counts weekly and discontinue chlorambucil if the total white blood cell count decreases to 3,000 mm^3 or less, not an uncommon occurrence with higher doses, but rarely seen at the earlier-described dosages. Although we have not seen *Pneumocystis carinii* pneumonia at the earlier-described dosage, it has been observed at higher dosages when used in combination with daily prednisone,[22] and, therefore, we now routinely use trimethoprim-sulphamethoxazole prophylaxis during the duration of treatment with chlorambucil. Chlorambucil also is discontinued if there is development of any infection during the treatment. Alopecia and hemorrhagic cystitis, which are seen

with the use of cyclophosphamide, are not seen with chlorambucil.

The risk for gonadal toxicity with chlorambucil and cyclophosphamide is greater in boys than in girls and is related to the duration and total dose of treatment. The total dosages associated with gonadal toxicity in boys are greater than 200 to 300 mg/kg for cyclophosphamide[23] and 8 to 10 mg/kg for chlorambucil.[24] The corresponding dosages for girls are not known but appear to be higher.[25]

Both primary and secondary malignancies have been noted in patients treated with cyclophosphamide or chlorambucil, and it is feared or believed that these drugs increase the risk for malignancies. Primary malignancies in patients with nonneoplastic disorders have been reported in Wegner's granulomatosis,[26] rheumatoid arthritis,[27,28] systemic lupus erythematosus,[29] and chronic glomerulonephritis.[30] Secondary malignancies in patients with pre-existing malignancy have been reported in Hodgkin's lymphoma,[31] ovarian cancer,[32] breast cancer,[33] and other cancers.[34]

Overall, it appears that although both cyclophosphamide and chlorambucil potentially can induce leukemia and lymphoma, the risk for bladder cancer is seen uniquely with cyclophosphamide.[35] In general, the total dosages used in the earlier situations were much higher than those used by Ponticelli et al[36] for MN or the dosages used in minimal change disease NS. Ponticelli et al,[36] in their 10-year follow-up, did not notice an increased risk for cancer in their patients, amounting to a total time of 662 years. To my knowledge, malignancy has not been reported in children with NS secondary to minimal change disease who were treated with cyclophosphamide or chlorambucil at the dosages described earlier, and I am not aware of any case of malignancy in my experience of over 33 years among over 50 children treated with chlorambucil for NS secondary to minimal change disease or focal segmental glomerulosclerosis.

Cyclosporine

Results of controlled trials with cyclosporine in adults performed by Cattran et al[37,38] have been reviewed in this issue by Cattran, and I briefly summarize them here. In the first trial,[37] 17 selected patients with progressive disease and renal insufficiency were assigned randomly to receive cyclosporine (9 patients) or placebo (8 patients). Cyclosporine was given at a dose of 3.5 mg/kg/d for 1 year. Compared with the placebo, cyclosporine produced a significant reduction in both proteinuria ($P = .02$) and in the decline of renal function ($P < .02$). The improvement in both these parameters was maintained at a mean follow-up period of 21 months after the discontinuation of cyclosporine in 6 of 8 cyclosporine-treated patients, whereas 7 of 8 placebo-treated patients continued to deteriorate.

In a more recent trial,[38] 51 MN patients with NS, who earlier had failed to achieve a remission with an 8-week course of 1 mg/kg/d or greater of prednisone, were assigned randomly to receive prednisone (0.5 mg/kg/d) plus cyclosporine (3.5 mg/kg/d) or prednisone plus placebo for 26 weeks. The dose of cyclosporine was adjusted to maintain a trough blood level of 125 to 225 ng/L measured by monoclonal antibody assay. All patients were followed-up for an average of 78 months. There were 28 patients in the cyclosporine group and 23 in the placebo group. Eight patients in the cyclosporine group and 10 patients in the placebo group had failed an earlier course of 2 to 12 months duration of various cytotoxic agents including 9 with cyclophosphamide, 5 with chlorambucil, and 4 with azathioprine. Which patients in each group had received one of these cytotoxic agents was not specified. At 26 weeks, 75% of cyclosporine-treated and 22% of placebo-treated patients were in partial or complete remission of proteinuria. The corresponding numbers at 78 weeks were 39% versus 13%. At the end of 2 years, the incidence of renal insufficiency was similar in both groups (2 patients in each group). During the period of treatment the number of patients with hypertension was larger, and the severity of hypertension was greater in the cyclosporine-treated versus placebo-treated patients. Although there are no controlled or uncontrolled data in children with cyclosporine it is likely that similar results would be obtained in children.

RECOMMENDATIONS

Immunosuppressive Agents

Before considering the use of corticosteroids and other immunosuppressive agents, a thorough discussion of the current knowledge of the natural course of the disease, current uncertainties about its treatment, the side effects of the drugs, particularly the potential gonadal toxicity and carcino-

genic potential of cytotoxic agents, needs to be communicated to the child (if old enough to understand) and to the parents of the child.

In my experience, most patients and parents initially are hesitant to use a course of cytotoxic agents and generally prefer to wait or select a course of corticosteroids. I generally recommend that they do not wait if the patient, in addition to NS, also has renal insufficiency.

Considering all of the information presented in this article, the following plan of management appears reasonable. Patients first may be given a trial course of corticosteroids alone according to the schedule previously outlined. Prednisone is started at 2 mg/kg/d (maximum, 60 mg) in 3 divided doses and continued for 4 to 8 weeks depending on the response. If and when some response is evident, the patient is switched to an alternate-day schedule at a dose of 40 to 80 mg, which is continued for a variable time and then very gradually reduced and eventually discontinued.

Patients not responding to prednisone are considered for treatment with one of the other immunosuppressive agents. Because the most promising results with 10 years of follow-up were obtained with chlorambucil in the protocol used by Ponticelli et al, this protocol can be tried first.[19] In girls, the risk for infertility is most likely low, and the protocol in its entirety, including 3 months of chlorambucil, may be given. In boys, to avoid the risk for azoospermia, the total dose of chlorambucil should be limited to 8 to 10 mg/kg, which may require a dose of 0.15 mg/kg/d for about 2 months. Although the risk for future malignancy for both sexes is not eliminated, it probably is low at these dosages. Generally, children tolerate prednisone well and are not likely to develop severe side effects on a dose of 0.4 mg/kg/d given 1 month at a time on alternate months for 3 times over a 6-month period. An alternative approach may be to use cyclosporine as outlined by Cattran et al.[37] Although the follow-up is short and the results with this regimen are not as impressive, the side-effect profile of cyclosporine may be more acceptable to some children. Although there are no data with tacrolimus it also can be considered because gum hyperplasia and hirsutism are not seen with tacrolimus, but the risk for developing diabetes mellitus is greater with tacrolimus than cyclosporine.

OTHER THERAPY

Other therapy includes protein restriction, tight control of hypertension, management of edema, use of ACE inhibitors and ARB agents to reduce proteinuria and progression of disease, management of hyperlipidemia, and anticoagulant therapy either as prophylaxis or as treatment of a thrombotic event. These topics, as they pertain to adults, are reviewed in detail elsewhere in this issue. There are no data in children with MN with respect to any of the therapies described earlier, however, the rationale of their use in adults most likely is valid for children as well.

Because of the concern of protein restriction on growth, I do not restrict protein in growing children. Management of edema of NS in MN is similar to other renal diseases producing NS and requires salt restriction and judicious use of various diuretics. Intravenous salt-poor albumin with diuretics rarely has been required in my experience. Adequate control of hypertension is mandatory and is best achieved with ACE inhibitors and ARB agents. Blood pressure is controllable in most patients with these agents and diuretics, but occasionally other antihypertensive agents such as β-blockers and calcium channel blockers may be required. We routinely use hydroxy methylglutaryl co-enzyme A reductase inhibitors (statins) in all patients with hyperlipidemia. Most of my experience is with pravastatin in which doses of 10 to 20 mg/d have proven to be effective. We generally do not use anticoagulants as prophylactic agents for the prevention of thrombosis and reserve their use until a thrombotic event occurs.

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