Single-Center Experience With Cyclosporine for Treatment of Idiopathic Minimal Change Nephrotic Syndrome in Children

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Introduction. Cyclosporine A is used in the treatment of idiopathic nephrotic syndrome. We conducted this study to evaluate the effect of cyclosporine and its combination with ketoconazole in Egyptian nephrotic children with steroid-resistant and steroid-dependant minimal change.

Materials and Methods. Forty-eight children with minimal change lesions who received cyclosporine with or without ketoconazole were studied. Their mean age was 5.17 ± 1.59 years, and they were 31 boys and 17 girls. The mean duration of the disease was 6.22 ± 3.16 years. Thirty-one of the children were steroid dependent and 17 were steroid resistant. Cyclosporine treatment was commenced after remission was attained and adjusted to a target trough level of 100 ng/mL. The mean cyclosporine therapy at a dose of 2.07 ± 0.91 mg/kg was administered for a mean of 25.75 ± 1.95 months. Thirty-three patients received adjunctive ketoconazole therapy.

Results. Thirty-eight patients (79.2%) responded well to cyclosporine. Steroid therapy could be discontinued in 43 patients (89.6%), but 9 experienced relapse. Ten patients (20.8%) were resistant to cyclosporine therapy. Fifteen patients received cyclosporine alone, while 33 received concomitant cyclosporine and ketoconazole. The response to cyclosporine was significantly better in those on ketoconazole. The economic effect of ketoconazole therapy was a reduction in the costs of cyclosporine treatment by 47.4% at 1 year of treatment.

Conclusions. Cyclosporine treatment in children with minimal change nephrotic syndrome is effective in preventing relapse and decreasing steroid toxicity. Its combination with low-dose ketoconazole is safe, reduces treatment costs, and improves the response to cyclosporine.

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INTRODUCTION

Minimal change nephrotic syndrome (MCNS) remains the most common pattern of idiopathic nephrotic syndrome (NS) in children. Among children with idiopathic NS, about 90% have MCNS, and most of whom will show an excellent response to steroid therapy.[1] However, management of idiopathic NS presents many therapeutic problems. Steroid-dependent NS comprises more than 30% of the cases of idiopathic NS in children. The disease, however, can relapse as soon as the therapy is reduced or withdrawn.[2] On the other hand, repeated use of corticosteroids results in serious adverse effects, such as growth retardation, cataracts, and osteoporosis.[3] Other patients can be steroid resistant, requiring cytotoxic drugs.[4]

Cyclosporine A is indicated in patients with resistance to steroids and cytotoxic agents, steroid-

dependent patients with multiple relapses, those with serious toxic side effects, and patients with contraindications for steroids and cytotoxic drugs.[5] Nevertheless, cyclosporine is expensive, which makes it unaffordable to a large proportion of patients from developing countries. Concurrent administration of ketoconazole and cyclosporine permits a reduction in the cyclosporine dose of approximately 80%. In addition of reduction of the costs of immunosuppressive therapy, some clinicians believe that ketoconazole may reduce cyclosporine nephrotoxicity.[6] In a recent study, we documented that long-term use of low-dose ketoconazole in cyclosporine-treated kidney transplant recipients is safe and cost-saving and may induce better graft function.[7]

The concomitant use of cyclosporine and ketoconazole in children with MCNS, however, is a novel subject, as it has not been widely reported in the literature.[8-10] The potential benefits of this combination may be capable of being extrapolated from its results in transplant patients. Furthermore, ketoconazole may inhibit T cell function.[11] Thus, its use may be attractive in MCNS; a condition characterized by altered cellular immunity and abnormal T-cell response.[12] The objective of this study was to investigate the effect of cyclosporine therapy and to evaluate the cost-savings and safety of concurrent administration of ketoconazole in both steroid-resistant and steroid-dependent children with MCNS.

MATERIALS AND METHODS

Children

Data were collected retrospectively from both outpatient and inpatient records of the Urology and Nephrology Center of Mansoura University, in Mansoura, Egypt. Records of all children in whom MCNS had been diagnosed from 1995 to 2005 and received cyclosporine (Neoral, Novartis, Basel, Switzerland) therapy were reviewed. All patients were subjected to ultrasonography-guided biopsy of the kidneys prior to initiation of cyclosporine specimens and examination by light and immunofluorescence microscopy. Forty-eight children (31 boys and 17 girls) met the criteria and were included in this study. The exclusion criteria for cyclosporine therapy were age below 2 years, serum creatinine levels (corrected for age) higher than normal, moderate to severe tubular atrophy and/or interstitial fibrosis on tissue examination, hepatic impairment, and hypertension. None of our studied patient had been receiving diltiazem, verapamil, or felodipine, as these agents might have interacted with cyclosporine.

Collected Data

We revised our medical records thoroughly for clinical and laboratory parameters. Clinical parameters included: age at the disease onset, age at the start of cyclosporine treatment, gender, response to steroid therapy, disease duration, number of steroid courses, history of cyclophosphamide therapy and its effect prior to cyclosporine treatment, time interval between kidney biopsy and initiation of cyclosporine therapy, mean value of maintenance cyclosporine dose and blood level, response to corticosteroid withdrawal while on cyclosporine, duration of cyclosporine treatment, response to cyclosporine therapy, cyclosporine discontinuation, and side effects of cyclosporine. Laboratory parameters included assessment of proteinuria, serum albumin, serum creatinine, liver function indicators, and serum cholesterol levels; presence of hypertension; and use of adjunctive therapy with angiotensin-converting enzyme inhibitors.

Previous Drug History

All patients had initially received a full steroid therapy course (prednisolone, 2 mg/kg/d, maximum 80 mg, for at least 4 weeks) followed by gradual reduction of the dose. Seventeen patients (35.4%) were steroid resistant and 31 (64.6%) were steroid dependent. The definition of steroid-dependence, steroid-resistance, and frequent relapses of NS were made according to the International Study of Kidney Disease in Children.[13] Twenty-seven children (56.3%) had been previously treated with cyclophosphamide; 23 were resistant to the treatment and 4 were sensitive, but had relapse after discontinuation of cyclophosphamide. Cyclophosphamide had been discontinued at least 6 months before starting cyclosporine therapy.

Cyclosporine Therapy

In Children older than 6 years, the initial dosage of cyclosporine was 4 mg/kg/d to 5 mg/kg/d, in 2 divided oral doses 12 hours apart. In children

whose age was 6 years or less, the initial dosage was 5 mg/kg/d to 6 mg/kg/d, in 3 divided doses. Trough levels of cyclosporine were monitored by fluorescence polarization immunoassay using the TDX auto-analyzer and kits produced by Abbott Diagnostics (Chicago, Illinois, USA). It was assessed on weekly basis during the first month of treatment, and monthly thereafter. The target cyclosporine whole blood trough level was 100 ng/mL to150 ng/mL during the first 2 months, and 50 ng/mL to 100 ng/mL thereafter. In patients who had a cyclosporine-induced remission with no evident side effects for 6 months, cyclosporine was administered in the dose that achieved the lowest possible level that maintained remission. In other words, a level of 30 ng/mL to 40 ng/mL was acceptable as long as it maintained the remission.

After 4 months of cyclosporine therapy, the patients were classified according to cyclosporine response as complete responder (proteinuria < 4 mg/h/m^2 body surface area), partial responder (proteinuria between 4.1 mg/h/m^2 and 40 mg/h/m^2), and resistant (proteinuria > 40 mg/h/m^2).[14] Kidney dysfunction was defined as loss of 50% of kidney function as measured by doubling of baseline serum creatinine or halving of creatinine clearance.

Concomitant Steroid Therapy

Oral prednisone was given concomitantly with cyclosporine (0.5 mg/kg/d) in steroid-resistant patients and doubled the dependant dose (below which the patient tends to relapse) in steroid-dependent patients. All children received the combined therapy while in relapse. Steroid resistance was defined as no response during the initial 8 weeks of steroid treatment, while steroid dependence was defined as steroid response (protein-free urine on at least 3 consecutive days within 7 days) that was followed by relapse while receiving or within 2 weeks after discontinuing steroid treatment.[10]

In children who maintained their partial or complete response to cyclosporine monotherapy for 2 months, the drug was given in a dose that achieved the lowest possible trough level that maintained such response. Relapse while on cyclosporine monotherapy was treated by increasing cyclosporine dose to achieve a level of 100 ng/mL to 120 ng/mL, if the level was below 80 ng/mL at the time of relapse. A lack of response to increasing cyclosporine dose or the presence of an acceptable level at the time of relapse was an indication to resume prednisone at a dose of 0.5 mg/kg/d to 1 mg/kg/d for 4 weeks followed by gradual withdrawal.

Concomitant Administration of Ketoconazole

Thirty-three of our patients received adjunctive daily ketoconazole (Nizoral, Janssen-Cilag, Breese, Belgium) in a dosage of 50 mg/d with concomitant reduction of the cyclosporine dose by one-third, while 15 patients received cyclosporine alone. Accordingly, the patients divided were into these two groups in data analyses. In the group with ketoconazole, the drug was added at the same time with to or soon after (within 1 month) the start of cyclosporine. The major reason for administration of ketoconazole was economic (in patients whom insurance does not cover cyclosporine cost). Also, in small children who received cyclosporine doses as low as a capsule of 25 mg twice per day with maintained acceptable trough level, ketoconazole was started. Neither kidney pathology examination results nor previous steroid or cyclophosphamide response had an impact on deciding on ketoconazole administration.

Follow-up

All children were followed up once weekly in the first month, every 2 weeks in the second month, and every month thereafter. At each visit, they were thoroughly evaluated clinically and subjected to full laboratory assessment including 24-hour urine collection for assessment of proteinuria (corrected as mg/h/m^2 of body surface area) and serum cyclosporine level. Kidney impairment was diagnosed when serum creatinine increased by 30% or more above its baseline value, even if it was still in the normal range for age. Cyclosporine level was rechecked with dose reduction if its level was higher than 120 ng/mL. When serum creatinine levels remained elevated or continued to rise, cyclosporine was immediately stopped. Of other indications to discontinue cyclosporine were resistance to cyclosporine after 4 months of treatment, persistent kidney dysfunction, decision of the child's parents to stop treatment, noncompliance, and new-onset hypertension requiring more than 1 drug for treatment.

Statistical Analyses

Qualitative data were displayed in cross tabulation, and quantitative data were described in terms of mean ± standard deviation. Bivariate techniques were used for initial evaluation of contrasts. Thus, the chi-square test and Fisher exact test were used for comparisons of frequencies of qualitative variables, and the t test was used for comparisons of means of two quantitative variables. P values less than .05 were considered significant. The SPSS software (Statistical Package for the Social Sciences, version 11.0, SPSS Inc, Chicago, Ill, USA) was used for these analyses.

RESULTS

Treatment Outcomes

A total of 48 children (31 boys and 17 girls) with idiopathic MCNS received cyclosporine during the study period (Table 1). They received a mean cyclosporine dosage of 2.07 ± 0.91 mg/kg/d. Ten patients (20.8%) were resistant to cyclosporine and 38 (79.2%) were responders, 32 of whom were on cyclosporine monotherapy (Table 2). Steroid therapy could be discontinued in 43 patients (89.6%), but 9 experienced relapse.

The laboratory studies showed reduction of 24-hour proteinuria (from 5.84 g/d to 0.76 g/d; $P < .001$), elevation of serum albumin level (from 1.38 mg/dL to 3.54 mg/dL; $P < .001$), decrease in serum cholesterol level (from 448.52 mg/dL to 201.88 mg/dL; $P < .001$), and insignificant increase in serum creatinine level (from 0.51 mg/dL to 0.68 mg/dL). Comparisons between patients sensitive and patients resistant to steroid therapy are outlined in Table 1.

Cyclosporine in Steroid-Dependent Nephrotic Syndrome

In 31 children with steroid-dependent NS (22 boys and 9 girls), cyclosporine was continued for 28.6 ± 14.36 months, with a mean maintenance dose of 1.8 ± 0.7 mg/kg/d. Twenty-eight children (90.3%) attained complete remission in response to combined therapy with cyclosporine and prednisolone, while 3 children were resistant (9.7%). Discontinuation of prednisone, while in remission, was carried out in all the 28 children who exhibited a complete or partial response to combined therapy, which resulted in relapse, either while tapering prednisone or within a month of its discontinuation in 6 patients (21.4%). Nine children had cyclosporine monotherapy discontinued while in remission. In this group, relapse occurred in 6, and resumption of cyclosporine monotherapy was followed by

Table 1. Characteristics for 48 Children With Minimal Change Nephrotic Syndrome*

Characteristics	Steroid-Dependent (n = 31)	Steroid-Resistant (n = 17)
Age at diagnosis, y	5.07 ± 4.77	4.21 ± 4.21
Sex		
Male	22 (71.0)	9 (52.9)
Female	9 (29.0)	8 (47.1)
Disease duration, y	6.22 ± 3.16	1.53 ± 0.51
Number of steroid courses	3.71 ± 1.64	3.06 ± 2.14
History of cyclophosphamide administration	14 (45.2)	13 (76.5)
Response to cyclophosphamide	2 (6.5)	2 (11.8)
24-hour proteinuria, g/d		
Pretreatment	5.76 ± 2.05	5.99 ± 1.77
Posttreatment	0.26 ± 0.53	1.69 ± 2.23
Serum albumin, mg/dL		
Pretreatment	1.43 ± 0.54	1.28 ± 0.63
Posttreatment	3.70 ± 0.54	3.24 ± 0.14
Serum Cholesterol, mg/dL		
Pretreatment	455.87 ± 146.21	435.18 ± 106.37
Posttreatment	184.58 ± 92.55	233.41 ± 110.10
Serum creatinine, mg/dL		
Pretreatment	0.55 ± 0.18	0.51 ± 0.14
Posttreatment	0.57 ± 0.28	0.88 ± 0.82

*Values in parentheses are percents.

Table 2. Characteristics of 48 Children With Minimal Change Nephrotic Syndrome According to Their Response to Cyclosporine Therapy

Characteristics	Cyclosporine-Sensitive (n = 38)	Cyclosporine-Resistant (n = 10)	*P*
Age at cyclosporine initiation, y	11.76 ± 5.81	9.95 ± 4.11	.36
Sex			
Male	25 (65.8)	6 (60.0)	
Female	13 (34.2)	4 (40.0)	.70
Disease duration			
< 5 years	16 (42.1)	3 (30.0)	
≥ 5 years	22 (57.9)	7 (70.0)	.70
Ketoconazole administration	28 (73.7)	5 (50.0)	.20
Number of steroid courses	1.39 ± 0.49	1.50 ± 0.53	.56
Resistance to steroid	10 (26.3)	7 (70.0)	.02
Resistance to cyclophosphamide	18 (47.4)	5 (50.0)	.20
Pretreatment biochemistry			
Serum albumin, mg/dL	1.37 ± 0.58	1.44 ± 0.56	.71
Serum cholesterol, mg/dL	451.26 ± 100.81	438.10 ± 101.83	.80
24-hour urinary protein, g/d	5.87 ± 1.99	5.72 ± 1.81	.82
Serum creatinine, mg/dL	0.49 ± 0.11	0.54 ± 0.21	.40

*Values in parentheses are percents.

remission in 5. The pretreatment and posttreatment characteristics are listed in Table 1.

Cyclosporine in Steroid-Resistant Nephrotic Syndrome

In 17 patients (9 boys and 8 girls) with steroid-resistant NS, cyclosporine was maintained for 21.5 ± 1 0.9 months, with a mean maintenance dose of was 2.46 ± 1.10 mg/kg/d. Ten patients (58.8%) attained complete remission in response to combined therapy with cyclosporine and prednisone and 7 patients (41.2%) were resistant to cyclosporine therapy. Withdrawal and discontinuation of prednisone, while in remission, was decided in 12 children (those who exhibited a complete or partial response to combined therapy), which resulted in relapse in 3 children, while 9 patients remained in remission. Eleven patients with steroid-resistant NS had cyclosporine monotherapy discontinued while in remission; relapse occurred in 4 (36.4%) and resumption of cyclosporine monotherapy was followed by remission in 3 (Table 1).

Cyclophosphamide

Twenty-seven patients who showed evidence of steroid toxicity received oral cyclophosphamide therapy, 2 mg/kg/d), for 12 weeks, of whom only 4 were responsive, while 23 were resistant.

Side Effects of Cyclosporine

Hypertrichosis and gum hyperplasia and were the most frequent side effects of cyclosporine that were observed in 28 patients (58.3%; 16 steroid-resistant versus 12 steroid-dependent patients, $P = .08$) and 15 patients (31.2%; 10 steroid-resistant versus 5 steroid-dependent patients, $P = .07$), respectively. Hypertension occurred in 9 (18.7%) and kidney dysfunction in 5 (10.4%) children. Hypertension occurred in 4 steroid-resistant children, compared with in 5 steroid-resistant ones ($P = .70$). None of the patients were treated with an angiotensin-converting enzyme inhibitor for their hypertension.

Ketoconazole

Fifteen patients received cyclosporine alone, while 33 received concomitant cyclosporine and ketoconazole. The mean duration of cyclosporine treatment was 25.7 ± 13.7 months. Characteristics of these two groups were comparable (Table 3). Response to cyclosporine, duration of treatment, and response to cyclosporine withdrawal were also comparable between the two groups (Table 4). The economic effect of ketoconazole therapy was a reduction in the cost of providing cyclosporine by 37.5% (from 224 to 140 Egyptian £/patient/mo) after 1 month and 47.4% (from 190 to 100 Egyptian £/patient/mo) at 1 year. When the cost of the ketoconazole (25.5 Egyptian £/patient/mo) was included, the net cost savings were about 34% (774 Egyptian £/patient/mo).

Ketoconazole was generally well tolerated.

Table 3. Characteristics of Children With and Without Ketoconazole in Treatment of Minimal Change Nephrotic Syndrome*

Characteristics	Ketoconazole (n = 33)	No Ketoconazole (n = 15)	*P*
Age, y	5.49 ± 2.51	5.43 ± 1.30	.90
Sex			
Male	17 (51.5)	6 (40.0)	
Female	16 (48.5)	9 (60.0)	.34
Disease duration, y	1.51 ± 0.50	1.29 ± 0.46	.27
Number of steroid courses			
≤ 3	17 (51.5)	10 (66.7)	
> 3	16 (48.5)	5 (33.3)	.26
Resistance to steroid	23 (70.0)	9 (60.0)	.34
Resistance to cyclophosphamide	2 (11.1)	3 (25.0)	.36
Baseline creatinine clearance, mL/min/ 1.73 m^2	133.0 ± 8.0	136.0 ± 9.0	.25
Baseline 24-Hour urinary protein, g/d	6.21 ± 2.34	6.32 ± 2.42	.50
ACE inhibitors administration	6 (19.3)	5 (33.3)	.24

*Values in parentheses are percents. ACE indicates angiotensin-converting enzyme.

Table 4. Cyclosporine Therapy in Children With and Without Ketoconazole*

Characteristics	Ketoconazole (n = 33)	No Ketoconazole (n = 15)	*P*
Disease duration before cyclosporine therapy, mo	15.3 ± 7.2	13.5 ± 7.9	.45
Resistance to cyclosporine	3 (9.0)	6 (40.0)	.02
Treatment duration, mo	27.32 ± 14.37	22.33 ± 11.84	.36
Response to stop cyclosporine			
Maintained remission	5 (71.4)	3 (75.0)	
Relapse	2 (28.6)	1 (25.2)	.67
Response to stop steroid			
Maintained remission	25 (86.2)	8 (66.7)	
Relapse	5 (13.8)	5 (33.3)	.16
24-hour urinary protein at last follow-up, g/d	1.21 ± 1.31	2.35 ± 2.12	.001
Serum alanine transferase, U/L	29 ± 12	25 ± 10	.98
Serum bilirubin, mg/dL	1.1 ± 0.2	1.0 ± 0.1	.89
Cost of cyclosporine at month 12, Egyptian £/patient/mo	100.51	190.87	.001

*Values in parentheses are percents.

Serum bilirubin and alanine aminotransferase levels usually remained within the reference range, and the overall rate of infection was the same in both groups. The only side effects attributable to ketoconazole therapy were transient visual flashes in 1 patient and gastrointestinal symptoms in 2 patients, both of which resolved spontaneously with no need to stop the therapy.

DISCUSSION

Considerable amount of evidence on the role of T cells in the pathogenesis of MCNS has been recently introduced.[15] Disturbances of T-lymphocyte function in idiopathic NS with excess lymphokine production prompted trials with cyclosporine, a drug that acts selectively on T-helper cells, inhibiting interleukin-2 (IL-2) production.[16] The mechanism by which cyclosporine induces a remission of proteinuria has not been elucidated. It has been hypothesized that the glomerular basement membrane injury leading to proteinuria is cytokine mediated, and the initial attempts to use cyclosporine for NS were based on the IL-2-inhibiting action of cyclosporine.[17] Induction of NS by the administration of IL-2 has been demonstrated in animal model.[18] A study by Zieste and colleagues[19] demonstrated that the administration of cyclosporine significantly improved charge selectivity of the basement membrane. The authors postulated that cytokines such as IL-2 induce a permeability factor which could be blocked by inhibiting IL-2 production by cyclosporine, thus improving the permselectivity.

Since 1980s, several trials have been performed

using cyclosporine in steroid-resistant idiopathic NS, showing its proteinuria-reducing effects in a reasonable number of patients. The exact role of cyclosporine in this disease remains unknown, as well as the appropriate treatment duration by cyclosporine. Because different treatment protocols are advocated by different centers, lack of consensus among centers may present obstacles for multicenter trials. The present study has the advantage of including 48 children with MCNS with a long-term follow-up period in a single centre; thus, circumventing the variability in working protocols and definition of various conditions among different centers. Although our study was designed as a retrospective analysis, the abundance of cases with uniformity of the clinical and pathological presentation and of procedures of diagnosis and treatment empowers the study to highlight the efficacy and limitation of cyclosporine therapy for MCNS. In the present study, cyclosporine therapy was effective in inducing complete remission in 38 patients with MCNS, corresponding to a total complete response of 79.2%.

In agreement with our results, Wyszynska and associates[20] reported 78% response rate in children with MCNS. Patient response to cyclosporine depends on the degree and duration of prior responsiveness to steroid, the histopathology of the underlying lesion (the strength of MCNS diagnosis versus focal segmental glomerulosclerosis), and the age of the patient.[11] Niaudet[21] assigned 40 children with steroid-dependent NS to receive either cyclosporine for 3 months, with a 6-month tapering schedule, or chlorambucil at a cumulative dose of 8 mg/kg. Although 90% of the cyclosporine-treated patients had a remission, 85% relapsed within 8 months after tapering or discontinuing the therapy. The relapse rate was 95% at 16 months. In our study 90.3% of steroid-dependent patients with NS had remission, similar to what was reported by Niaudet, but with a lower relapse rate.

The response rates to cyclosporine have generally been less favorable in patients who are steroid-resistant. In our study, 58.8% of steroid-resistant children attained complete remission, 36% of whom relapsed after cyclosporine was stopped. In agreement with our study, Niaudet[22] reported a remission rate of 48% in another study of 65 children with steroid-resistant NS, treated for 6 months with cyclosporine (150 mg/m^2/d to 200 mg/m^2/d), many remained in long-term remission, while of those who relapsed after the cyclosporine discontinuation, many became steroid-responsive at that point.

During the past 20 years, cyclosporine has been largely used in NS of different etiologies, in both children and adults, with different remission rates. Lagrue and coworkers[23] were the first who reported the use of cyclosporine in the treatment of idiopathic NS. They described 13 adults with an initial 24-hour proteinuria greater than 6 g and normal kidney function. Cyclosporine was instituted with a starting dose of 3 mg/kg/d and increased to 5 mg/kg/d based on its serum levels. After 3 to 6 weeks, proteinuria had disappeared in 7 patients, all with MCNS, and decreased less than 3 g in 5 (2 with MCNS and 3 with focal segmental glomerulosclerosis). Relapses, however, were observed in all patients after 2 to 6 weeks. Meyrier and colleagues[14] analyzed 2 studies in which cyclosporine was used in 112 patients with MCNS or focal segmental glomerulosclerosis. The response to treatment depended on histology and steroid response. The remission rate was highest in patients with steroid-dependent MCNS (71%) and lowest in patients with steroid-resistant focal segmental glomerulosclerosis (20%). Tejani and coworkers[24] compared cyclosporine use associated with low-dose prednisone and high-dose prednisone alone in children with idiopathic NS and demonstrated that remission occurred most frequently in those receiving the combined therapy. They found no evidence of nephrotoxicity.

The use of cyclosporine in idiopathic NS seems to be effective only as long as it is being administered, because relapses are very frequent when the drug is withdrawn. Consequently, patients who remit become cyclosporine dependent.[25] According to Ponticelli and colleagues,[26] for those patients who respond to and tolerate cyclosporine well, the drug can be continued for 1 year and then tapered off after 6 months or so. If NS relapse occurs, cyclosporine can be resumed for another year and discontinued again. It is not known yet if the patients who are still using cyclosporine have become dependent on this drug, and if they will remain asymptomatic after cyclosporine withdrawal.

The long-term treatment of children with cyclosporine is effective, but it also has unfavorable side effects, of which hypertension, nephrotoxicity,

and especially renal insufficiency, both hemodynamic and structural, are the most important.[27] In our study, gum hyperplasia and hypertrichosis were the most frequent side effects of cyclosporine, which were observed in 31.2% and 58.3% of the patients, respectively. Hypertension occurred in 18.7% and kidney dysfunction in 10.4% of all the children. On the other hand, cyclosporine is expensive, which makes it unaffordable to a large proportion of patients from developing countries.[28] Concurrent administration of ketoconazole and cyclosporine permits a reduction in the cyclosporine dosage of approximately 80%. Previously, we have documented that long-term use of low-dose ketoconazole in cyclosporine-treated kidney transplant recipients is safe and cost-saving, and it might induce better graft function.[5] The second aim of this study was to evaluate the cost-saving effect of addition of ketoconazole to cyclosporine therapy .We observed persistence of cyclosporine dose reduction and cost-savings until the last follow-up (48% dose reduction and 38% net cost savings). Other investigators reported greater cyclosporine dose reductions in adults (80% to 88).[29-31] This may be explained by the greater doses of ketoconazole that they used (200 mg/d to 400 mg/d). Also, the pharmacokinetics of this combination might be different in children.

Cyclosporine has shown promising results in inducing remission both in steroid-dependent and in steroid -resistant NS. Wyszynska and colleagues[20] reported 78% response rate in children with MCNS. In our study, cyclosporine response rate was 60% and co-administration of ketoconazole improved the response to 94%. The improvement in response to cyclosporine and the preservation of kidney function in the ketoconazole-added group may be explained by the T-cell function inhibition by ketoconazole, as well.[7] Ketoconazole blocks IL-2-dependent T-cell clone proliferation.[15] It also suppresses IL-4 and IL-5 production in stimulated T cells.[32] The possible link between abnormal T-cell response and glomerular disease was postulated 30 years earlier.[33] Also, using ketoconazole, the parent compound rather than cyclosporine metabolites is the predominant fraction in blood,[34] and the parent cyclosporine is known to be more immunosuppressive and less nephrotoxic than cyclosporine metabolites.[35]

CONCLUSIONS

Treatment with cyclosporine can be a good therapeutic option in both steroid-sensitive and steroid-resistant children with MCNS, which may prevent the toxic effects of long-term large doses of steroids, improve the control of cases, and possibly ameliorate the natural progressive course of the disease. Co-administration of low-dose ketoconazole with cyclosporine in children with idiopathic MCNS is safe. This combination significantly reduces cyclosporine treatment costs, which is a major concern in our developing country. Moreover, ketoconazole may improve the response to cyclosporine and may have a favorable effect on kidney function. The concern of the nephrotoxic effects of cyclosporine may be outweighed by its beneficial effect, provided that the selection of patients and their follow-up are carried out sensibly. However, further double-blind randomized studies on a large number of patients are needed to confirm these findings.

CONFLICT OF INTEREST

None declared.

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