Management and Outcome of Steroid-Resistant Nephrotic Syndrome in Children

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Original Paper

Introduction. Steroid-resistant nephrotic syndrome (SRNS) is uncommon in children, but often leads to ESRD. We report our experience with SRNS and its treatments and outcomes.
Materials and Methods. We assessed 73 children with SRNS admitted to Ali Asghar Children Hospital in Tehran, Iran. Their clinical presentations, treatment, and disease courses were reviewed. The mean follow-up duration was 6.0 ± 4.2 years. Moreover, survival times were calculated and the Cox regression method was used to determine variables able to predict survival of the kidneys.
Results. Age at the onset of the disease, sex, and hematuria were not predictive of the response to treatment with immunosuppressive drugs in the children with SRNS. The type of resistance (early or late) was associated with the responsiveness to immunosuppressives. Response to any of the immunosuppressive drugs determined the responsiveness to other immunosuppressive drugs. Cyclosporine was more effective than cyclophosphamide as initial therapy. The mean kidney survival time was 11.62 years. Kidney survival rates were 94.6%, 70.0%, 56.0%, and 34.0% at 1, 5, 10, and 15 years, respectively, in patients with initial resistance to steroid, while these were 100%, 100%, 83.0%, and 83.0% in those with late resistance, respectively (P = .03).
Conclusions. We showed that patients with late steroid resistance had better response to immunosuprressive drugs than patients with early resistance. We also showed that resistance to immunosuppressive therapies increased the risk of resistance to other immunosuppressive drugs. Achievement of complete or partial remission with any therapy reduced the risk of ESRD.

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INTRODUCTION

Idiopathic nephrotic syndrome affects about 2 children per 100 000 aged 15 years and younger.[1,2] About 10% to 20% of these children are resistant to steroids.[1] The risk of primary steroid resistance depends on the initial histopathology. Studies by the International Study of Kidney Disease in Children showed that 70%, 44%, and 7% of children with focal segmental glomerulosclerosis (FSGS), mesangial proliferative glomerulonephritis (MPGN), and minimal change disease (MCD) had primary steroid resistance, respectively.[3]

Response to steroids is associated with a good long-term prognosis.[4] Steroid-resistant idiopathic nephrotic syndrome (SRNS) accounts for more than 10% of children who progress to end-stage

renal disease (ESRD).[5] This progression to ESRD has been reported to be different in various races.[6] On the other hand, in all children with SRNS, treatment is problematic. Treatment has been directed against immunological abnormalities in SRNS using immunosuppressive agents. However, there is increasing information indicating a genetic basis for many cases of FSGS and that these would not be expected to respond to immunosuppressive medications. We decided to assess the clinical course, treatment, and outcome of our pediatric patients with SRNS in a single center in Tehran in order to estimate the rate of ESRD our population and evaluate their treatment outcome.

MATERIALS AND METHODS

Patients and Protocols

We reviewed the clinical records of 73 children with SRNS presented to Ali Asghar Children Hospital, in Tehran, Iran, between 1990 and 2007. The charts of these patients were evaluated and the clinical presentations and disease courses were recorded.

Nephrotic syndrome was defined as proteinuria greater than 40 mg/m^2/h along with hypoalbuminemia, hyperlipidemia, and edema. Steroid-resistant idiopathic nephrotic syndrome was defined as the failure to respond to 4-week daily prednisone since the onset of the disease. In patients who responded to steroids, relapses during the protocol were treated by restarting corticosteroids (before they became late non-responders). Children with relapses who did not respond to steroids were included in the group of late nonresponders. In addition, patients with a familial history of nephrotic syndrome were excluded from study. We did not have genetic analysis in our patients.

On admission, blood pressure, serum creatinine concentration, and hematuria were assessed in these children. Glomerular filtration rate (GFR) of the patients was measured using the Shwartz formula at admission. Hypertension was defined as systolic and/or diastolic blood pressure against the 95 percentile for age and sex. Microscopic hematuria was defined as 1+ more positive by dipstick, or 5 or more erythrocytes per high-power field.

Most patients with no response to steroids were treated with oral cyclophosphamide, 2 mg/kg/d to 3 mg/kg/d for 8 to 12 weeks. If this protocol produced no response or if the patient suffered more than 2 relapse episodes during the treatment, cyclosporine was added to the treatment protocol. However, some patients received cyclosporine after failure of steroid therapy and did not receive cyclophosphamide. We tackled cyclosporine dependence or resistance by substituting it with mycophenolate mofetil. However, azathioprine had been administering instead of mycophenolate mofetil before1997.

Outcome Classification

Complete remission was considered in case of achieving a normal GFR ($\geq$ 80 mL/min/1.73 m^2) and no urinary abnormalities (no hematuria and no proteinuria) with or without concurrent treatment. Partial remission was defined as a decline by 50% or more of proteinuria after the treatment. Relapse was considered as proteinuria reappeared in the nephrotic range for more than 3 consecutive days with less than 25 g/L of serum albumin. Persistence of nephrotic syndrome for more than 3 months was recognized as persistent resistance. Patients who underwent or needed dialysis or transplantation were considered to suffer from ESRD. Finally, death secondary to the complications of nephrotic syndrome were recorded.

Statistical Analyses

Simple descriptive statistics were used for describing the demographic and baseline data and conditions of the patients. Mean values reported as mean ± standard deviation, missing data were not included in frequencies and percents unless it is mentioned. In bivariate analyses, the chi-square test, Fisher exact test, and Student *t* test were used. Moreover, survival times were calculated using the Kaplan-Meier method, and the Breslow test were used to examine the equality of the survival distributions for the different levels of the factors. The Cox regression method was also used to determine variables able to predict the survival of the kidneys. All statistical procedures were performed using the SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc, Chicago, Ill, USA), and level of significance was considered as a *P* value less than .05.

RESULTS

Patients

Seventy-three children suffering from SRNS (35

girls and 38 boys) were assessed in this study. The mean GFR on admission was 110.70 ± 19.56 mL/min/1.73 m^2 (range, 60 mL/min/1.73 m^2 to 150 mL/min/1.73 m^2). Kidney biopsy was performed in 70 children. The specimens were taken for light microscopy and immunofluorescence assays. Histological findings included MCD, FSGS, diffuse MPGN, and global sclerosis in 19 (27.1%), 26 (37.1%), 21 (30.0%), and 4 (5.7%) of the patients, respectively. Primary SRNS was seen in 59 children (80.8%), whereas late SRNS was seen in 14 (19.2%). Table 1 shows the characteristics of the children with primary and late SRNS.

Table 1. Characteristics of Children With Primary and Late Steroid-Resistant Nephrotic Syndrome*

	Steroid-Resistant Nephrotic Syndrome	
Characteristic	**Primary**	**Late**
Number of patients	59	14
Age, y	6.2 ± 3.7	4.9 ± 3.0
GFR, mL/min/m^2	109.7 ± 20.4	113.68 ± 15.9
Hypertension	39 (66.1)	9 (64.3)
Hematuria		
Gross	4 (6.8)	2 (14.3)
Microscopic	20 (33.9)	4 (28.6)
Histopathology		
MCD	14 (23.7)	5 (35.7)
FSGS	24 (40.7)	2 (14.3)
MPGN	16 (27.1)	5 (35.7)
global sclerosis	4 (6.8)	0
Not defined	1 (1.7)	2 (14.3)

*GFR indicates glomerular filtration rate; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; and MPGN, mesangial proliferative glomerulonephritis.

Follow-up

Treatment of the patients is demonstrated in Figure 1. The mean follow-up duration was 6.0 ± 4.2 years (range, 6 months to 16 years). Two patients, who had global sclerosis, progressed rapidly to ESRD, and thus, did not receive any substitute treatment for corticosteroid.

Factors which could possibly affect response to treatment with the administered immunosuppressives were assessed. Age at disease onset, sex, presence of hematuria on admission, and histology results of kidney biopsies were not able to predict the possibility of response to treatment with these drugs. In contrast, the type of resistance to steroid (primary or late) was associated with the responsiveness to these immunosuppressive drugs; patients with late SRNS were significantly more frequently responsive to the immunosuppressive drugs (P = .02). Also resistance to any of the immunosuppressives was associated significantly with resistance to other immunosuppressive drugs; 84% of the patients who were resistant to cyclosporine were also resistant to cyclophosphamide, and 93.3% of the patients who were resistant to mycophenolate mofetil were resistant to cyclophosphamide, too (P < .001). Similarly, 79.0% of the patients who were resistant to mycophenolate mofetil were also resistant to cyclosporine (P < .001). Response to mycophenolate mofetil and cyclosporine were the same in the patients.

Overall, 19 patients (26.0%) reached ESRD. Total improvement of nephrotic syndrome was achieved

Table 2. Comparison of Children Steroid-Resistant Nephrotic Syndrome With and Without End-Stage Renal Disease*

Variable	**No ESRD**	**ESRD**	***P***
Number of patients	54	19	…
Age at Diagnosis, y	6.0 ± 3.6	5.7 ± 3.6	.78
Female gender	21 (40.4)	7 (38.3)	.86
Hematuria	27 (50.0)	7 (38.3)	.80
Hypertension	27 (50.0)	15 (81.0)	.02
The interval from disease onset to cyclosporine initiation, mo	22.4 ± 4.7	20.0 ± 9.9	.84
Resistance to cyclophosphamide	26 (48.4)	19 (100)	< .001
Resistance to cyclosporine	21 (38.6)	18 (94.7)	< .001
Resistance to mycophenolate mofetil	31 (58.0)	19 (100)	.02
Histopathology			
MCD	16 (29.6)	3 (15.7)	
FSGS	20 (37.0)	6 (31.5)	
Diffuse MPGN	15 (27.8)	6 (31.5)	
Global sclerosis	0	4 (21.0)	.16
Initial glomerular filtration, mL/min/m^2	115.8 ± 27.8	110.2 ± 17.5	.60

*ESRD indicates end-stage renal disease; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; and MPGN, mesangial proliferative glomerulonephritis.

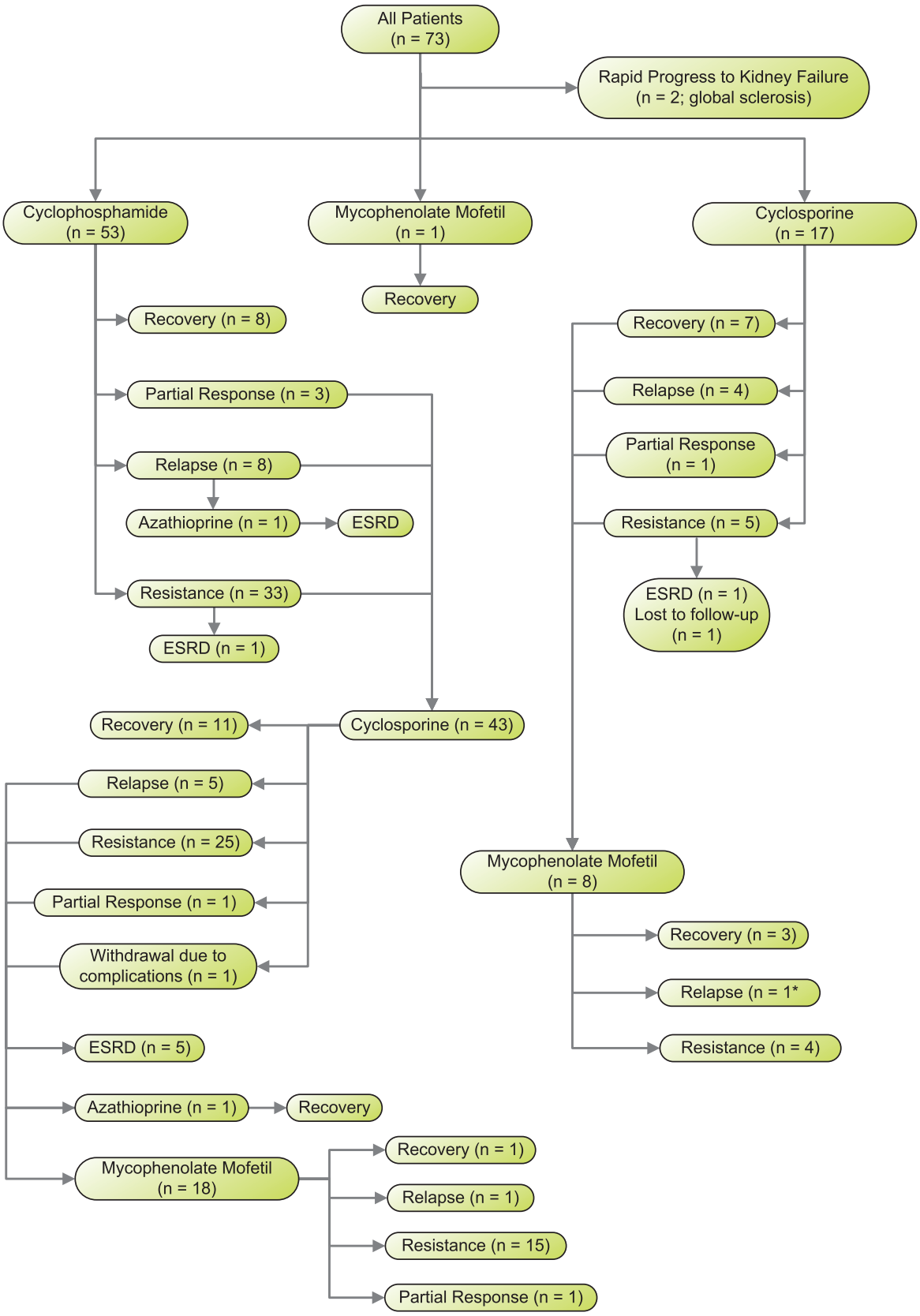

Figure 1. The pattern of resistance to immunosuppressive drugs and outcome of children with steroid-resistant nephrotic syndrome. ESRD indicates end-stage renal disease.

in 33 patients (45.2%). Fifteen of 32 children who were nonresponsive to cyclophosphamide (46.9%) ended up with ESRD; however, none of the patients with either complete response or partial response or relapse with cyclophosphamide reached ESRD during the follow-up period ($P < .001$). Also, 46.6% of the children (14 of 30) who were nonresponsive to cyclosporine reached ESRD; however, none of the patients with complete or partial response reached ESRD during the follow-up period ($P = .003$). Concerning Mycophenolate mofetil, 8 of 19 children who were nonresponsive (40.0%) reached ESRD, while none of those with either complete response or relapse did reach ESRD during the follow-up ($P = .05$).

Table 2 outlines comparisons of the frequency and mean of the possible risk factors in patients with and without ESRD. As shown, hypertension and resistance to immunosuppressive drugs were associated significantly with ESRD in the future. In contrast, histopathologies were not associated with the progression of ESRD in the patients ($P = .16$).

Kidney Survival

The mean kidney survival time was 11.62 years (95% confidence interval, 10.01 to 13.23). The mean time to reach ESRD was 4.9 ± 3.7 years (range, 3 months to 13 years). The mean kidney survival time in the patients with high and normal blood pressure on admission were 12.14 years and 10.84 years, respectively (Breslow test, $P = .09$).

Kidney survival rates were 96.7%, 61.0%, 43.0%, and 21.0% at 1, 5, 10, and 15 years, respectively, after the onset of the disease in children who did not respond to cyclophosphamide. In contrast, kidney survival rate was 100% at all these times in children who responded partially or totally or had one or more relapses on cyclophosphamide protocol ($P = .01$; Figure 2). Concerning children with cyclosporine, kidney survival rates were 96.5%, 63.0%, 41.0%, and 15.0% at 1, 5, 10, and 15 years, respectively, in those who did not respond

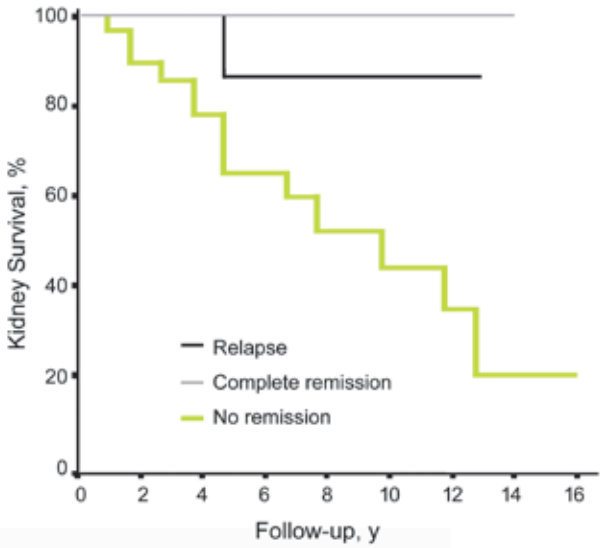

Figure 3. Kidney survival rate in children with and without response to cyclosporine.

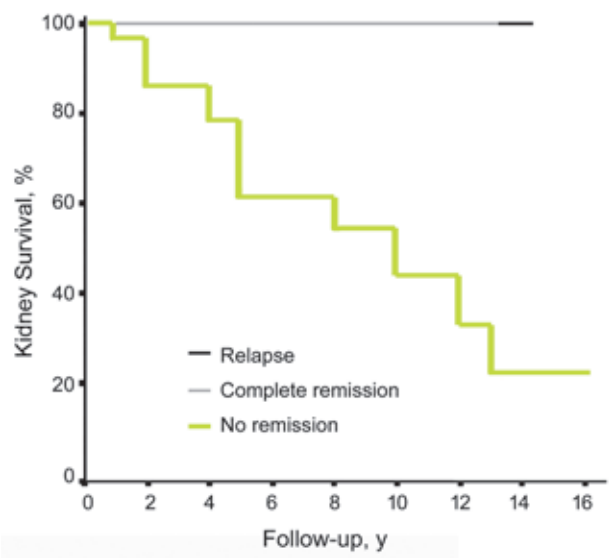

Figure 2. Kidney survival rate in children with and without response to cyclophosphamide.

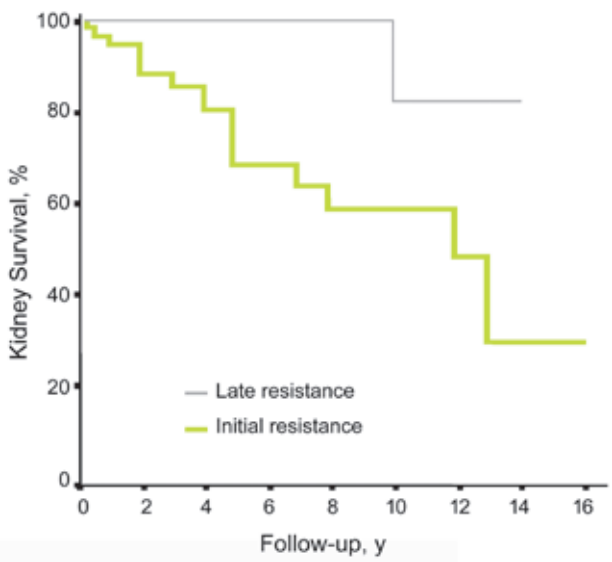

Figure 4. Kidney survival rate in children with initial versus late steroid resistance.

to the drug, whereas these rates were 100% at all these times in those who responded partially or totally. In addition, kidney survival rates were 100%, 86.0%, 86.0%, and 86.0% at 1, 5, 10, and 15 years, respectively, in patients who had relapse on treatment with cyclosporine (P = .002; Figure 3).

Overall, kidney survival rates were 94.6%, 70.0%, 56.0%, and 34.0% at 1, 5, 10, and 15 years, respectively, in patients with initial resistance to steroid, while these were 100%, 100%, 83.0%, and 83.0% in those with late resistance, respectively (P = .03; Figure 4).

DISCUSSION

Steroid-resistant nephrotic syndrome is a relatively uncommon kidney disease in children, comprising approximately 20% of children diagnosed with nephrotic syndrome.[5] Studies by the International Study of Kidney Disease on 55 patients with SRNS showed that 45.5% had MCD, 47.5% had FSGS, and 7% had diffuse MPGN.[3] Macroscopic hematuria is rare, occurring in 3% of these patients while microscopic hematuria is far more common, reported in 32% in a large retrospective review.[7,8]

The best treatment of SRNS in children is not clear. Treatment has been directed against immunological abnormalities in SRNS. Children with MCD or late resistant to steroid respond better to immunosuppressive therapy than children with FSGS or with initial resistant to steroid.[9,10] Children with a partial response to corticosteroids are more likely to respond to cyclophosphamide or cyclosporine and less likely to progress to chronic kidney failure.[11] We found that late resistance to steroid was associated with better response to immunosuppressive agents in contrast to initial resistance to steroid. We did not find any relationship between the type of histopathology and the response to immunosuppressive drugs.

Most authors believe that alkylating agents have little therapeutic effect in patients with SRNS. The International Study of Kidney Disease in Children concluded in a report of 60 children with steroid-resistant FSGS that there was no beneficial effect of cyclophosphamide in these patients.[12] In contrast, another study group in Canada found that cyclophosphamide resulted in a partial or complete remission in 48% of their children with SRNS. They also found that the risk of chronic kidney disease or ESRD decreased in patients whose SRNS was cyclophosphamide sensitive.[13] We found partial or complete remission in 20.7% of our patients on cyclophosphamide therapy, while 80% of the children were resistant to cyclophosphamide. We also showed that 46.9% of our patients who were resistant to cyclophosphamide ended up with ESRD.

To date, randomized controlled trials have shown some benefits of cyclosporine over placebo or no specific therapy in SRNS.[14] These studies showed an improvement in the outcome of pediatric patients with SRNS treated with cyclosporine. Plank and colleagues performed a controlled multicenter randomized trial to test the efficacy and safety of cyclosporine versus cyclophosphamide pulses as the initial therapy for children with primary SRNS. They showed that cyclosporine is more effective in inducing at least partial remission.[15] Response to cyclosporine correlates more with steroid response than with the underlying histopathology.[16] The predictors for cyclosporine nonresponsiveness are non-MCD pathology and longer duration nephrotic syndrome before administration of cyclosporine, irrespective of the age at the onset of the disease.[17] Cyclosporine-resistant children are at a high risk of significant infections and chronic kidney disease. As shown in Figure 1, 58% of our patients who received cyclosporine after cyclophosphamide were resistant to cyclosporine; in contrast, complete or partial response was seen in 39.5% of these patients. Cyclosporine was also used in the initial therapy of 17 children with newly diagnosed primary SRNS. Recovery more frequently occurred in the patients who received cyclosporine (41%) in comparison to that in the patients who received cyclophosphamide as initial therapy (18.5%). We also showed that 57% of the children who were nonresponsive to cyclosporine reach ESRD.

During a 24-week mycophenolate mofetil therapy, Bayazit and coworkers showed no significant changes in the mean serum creatinine, serum albumin, and proteinuria levels.[18] Cattran and colleagues showed that some patients who failed to respond to alkylating agents or cyclosporine achieved partial remission with mycophenolate mofetil.[19] We showed that all the patients who responded to mycophenolate mofetil had complete or partial responsiveness to cyclosporine, and all who did not respond to cyclosporine were not responder to mycophenolate mofetil, either.

The outcome of children diagnosed with SRNS is worse than that of children who have a steroid-responsive nephrotic syndrome. End-stage renal disease develops in at least 50% of patients with SRNS.[5] However, ESRD is seen in less than 3% of patients with idiopathic nephrotic syndrome who respond to glucocorticoid therapy. It is considered that the achievement of complete or partial remission with any therapy has been assumed to reduce the risk for ESRD.[11,20]

In our study, 26% of the patients developed ESRD, while complete improvement of nephrotic syndrome was achieved in 45% of them. We found that the achievement of complete or partial remission with any immunosuppressive therapy reduced the risk of ESRD. We also showed that patients who were late resistant to steroids had better responsiveness to immunosuppressive drugs and then less frequently ended up with ESRD in comparison with patients with primary steroid resistance. The rate of progression to ESRD was similar in our patients with different histopathologies.

CONCLUSIONS

We found that the resistance to any immunosuppressive therapy increased the risk of resistance to other immunosuppressive therapies. Resistance to immunosuppressive drugs can lead to progression to ESRD. We also concluded that cyclosporine is more effective than cyclophosphamide as the initial therapy for patients with SRNS. We also found that response to mycophenolate mofetil is better in cases of partial response to cyclosporine. Our results about the effect of immunosuppressive agents, especially comparison of cyclosporine and cyclophosphamide, after corticosteroid therapy in SRNS should be confirmed by prospective randomized trials in large specimens.

CONFLICT OF INTEREST

None declared.

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