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Cyclosporine Effectiveness and Adverse Outcomes in Steroid Dependent and Frequent Relapsing Nephrotic Syndrome in Children

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Abstract

Background: Cyclosporine is a calcineurin inhibitor that exhibits a notable steroid-sparing effect in patients with steroid-dependent and frequent relapsing nephrotic syndrome. Despite long-term cyclosporine use, it has been linked to an increased risk of unpleasant side effects, including nephrotoxicity, hypertension, and cosmetic symptoms like hirsutism and gum hypertrophy.

Aim: To assess the effectiveness and side effects of cyclosporine in children diagnosed with steroid-dependent and frequent relapsing nephrotic syndrome at Sohag University Hospital.

Methods: This was a combined prospective and retrospective study which was conducted at Pediatric nephrology clinic, Sohag University Hospital on children diagnosed as steroid-dependent and frequent relapsing nephrotic syndrome who received cyclosporine as a steroid sparing agent.

Results: This study included total 50 nephrotic patients, there mean age was 11.4 ± 3.1 (4-15) years. Male: female ratio was 2.8:1. The median disease duration was 7 years with interquartile range (3.88-9.63) years, and the median cyclosporine use duration was 4 years with interquartile range (1.5-6) years. The average relapse number/patient/year significantly decreased by 82.6% following cyclosporine treatment, and the mean dependent steroid dose decreased by 69.19%.The recorded cyclosporine side effects were: hirsutism in 94%, gum hyperplasia in 38%, gastrointestinal disturbances in 32%, nephrotoxicity in 28% and new onset hypertension in 26% of cases. Histological nephrotoxicity was evident in 14 individuals (35.9%) of biopsied children.

Conclusion: Cyclosporine is deemed both safe and efficacious as a steroid-sparing medication for individuals with steroid-dependent and frequent relapsing nephrotic syndrome. Nonetheless, the safety of cyclosporine is not without exceptions, and various levels of side effects have been documented.

Key words: Calcinurin inhibitor – Nephroptic syndrome – steroid dependency

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Introduction

Nephrotic syndrome (NS) is a prevalent glomerular disorder among children, carrying substantial morbidity and mortality implications. It affects approximately 1 to 3 in every 100,000 children under the age of 16 years.[1,2] Nephrotic syndrome is identified by the occurrence of edema, along with specific indicators such as proteinuria, indicated by a urine protein creatinine ratio (uPCR) equal to or exceeding 200 mg/mmol (2 g/g), or the presence of 3+ protein on a urine dipstick. Additionally, there should be a

characteristic hypoalbuminemia, with albumin level falling below 3 g/dl.[3]

Nephrotic syndrome is divided into two categories based on how it responds to steroids: steroid-sensitive NS (SSNS) and steroid-resistant NS (SRNS). Roughly 90% of cases are steroid sensitive, and a standard treatment protocol of steroids is effective in treating the initial episode in these cases. However, 80% of these patients go on to have more relapses. Fifty percent of them are relapsers who are dependent on steroids. Steroids can be used to treat any relapse, but children may be more susceptible to the side effects of a high cumulative dose, which include obesity, stunted growth, attention issues, behavioral changes, low quality of life, and stress on the family. Many immunosuppressive medications are advised as maintenance therapeutic agents in patients with steroid-dependent NS (SDNS) and frequent relapsing NS (FRNS) in order to reduce steroid toxicity. These include tacrolimus, cyclosporine, mycophenolate mofetil (MMF), levamisole, and rituximab.[4]

More than 75% of patients with SDNS can maintain complete remission after steroid stoppage with the use of cyclosporine, which is a calcineurin inhibitor that is well known for its steroid-sparing effect in SDNS and FRNS. On the other hand, cyclosporine withdrawal too soon may cause relapses, leaving the patient reliant on the drug for years.[5,6]

Long-term use of cyclosporine has been linked to an increased risk of unpleasant side effects, including nephrotoxicity, hypertension, and cosmetic symptoms like hirsutism and gum hypertrophy. As a result, it's critical to closely monitor any cyclosporine side effect and to routinely check kidney function and blood pressure.[7]

Estimating the trough blood levels of cyclosporine is also necessary for patients who exhibit unsatisfactory response, suspected noncompliance, or nephrotoxicity (defined as a 30% or greater increase in serum creatinine from baseline). The goal is to find the lowest possible levels while maintaining remission and avoiding toxicity (target 12-hr trough level of 60-150 ng/ml). If cyclosporine is administered for duration longer than two to three years, kidney biopsy may be part of the long-term cyclosporine protocol to screen for cyclosporine-associated nephropathy. Chronic ischemic insult to the kidneys is the main cause of cyclosporine nephrotoxicity. This insult leads to tubulointerstitial changes, such as striped interstitial fibrosis, tubular vacuolization, and atrophy, as well as arteriolar hyalination.[3,7]

The aim of this study was to assess the effectiveness and adverse outcomes of cyclosporine in children diagnosed with SDNS and FRNS at Sohag University Hospital.

Patients and Methods

This study was carried out at Pediatric nephrology clinic-Sohag University Hospital-Sohag-Egypt during the period from November 2022 to November 2023. It was a combined prospective and retrospective study. It included 50 children and adolescents who were diagnosed as SDNS and FRNS with age at disease onset ranging from 1 to 15 years and were treated with cyclosporine for at least 1 year. The prospective part included follow up of the patients with the inclusion criteria above who started cyclosporine therapy. The Retrospective part included gathering the previous data from the patients' medical files for those who met the aforementioned inclusion criteria above. Patients' demographic data, age at disease onset, disease duration, type of steroid response, age at cyclosporine initiation, doses and duration of cyclosporine treatment, mean values of cyclosporine maintenance doses and their trough blood levels, serum creatinine at regular intervals before and after cyclosporine treatment, and renal biopsy for patients on cyclosporine for longer than 2-3 years are among the data that were gathered. Relapse rate per patient per year and dependent steroid dose before and after cyclosporine use were determined. Various known cyclosporine side effects were searched for and monitored in our studied patients. Blood pressure was evaluated in all patients on regular intervals and the controlling antihypertensive medications types and doses were recorded.

The following definitions were considered for classification of steroid response patterns: [3]

- **Nephrotic range proteinuria:** First morning urine Protein-creatinine ratio (uPCR) ≥ 2 mg/mg (or 200 mg/mmol) or ≥ 3+ dipstick.
- **Nephrotic syndrome:** Presence of nephrotic range proteinuria and either hypoalbuminemia

(serum albumin < 3 g/dl) or edema when albumin level is not available.

- **Complete remission:** First morning uPCR≤ 0.2 mg/mg (or 20 mg/mmol or negative or trace on dipstick) on three or more consecutive occasions.
- **Partial remission:** First morning uPCR > 0.2 mg/mg but < 2 mg/mg (or > 20 and < 200 mg/mmol), and if available, serum albumin ≥ 3 g/dl.
- **Relapse:** Recurrence of nephrotic-range proteinuria. In children, relapse is commonly assessed by urine dipstick and is defined as ≥ 3+ for 3 consecutive days.
- **Steroid-sensitive nephrotic syndrome:** Complete remission achieved after 4 weeks of standard-dose prednisone or prednisolone.
- **Infrequent relapsing nephrotic syndrome:** Less than 2 relapses per 6 months within 6 months of disease onset or less than 4 relapses per 12 months in any subsequent 12-month period.
- **Frequent relapsing nephrotic syndrome:** Two or more relapses per 6 months within 6 months of disease onset or four or more relapses per 12 months in any subsequent 12-month period.
- **Steroid-dependent nephrotic syndrome:** Two consecutive relapses during therapy with prednisone or prednisolone (either at full dose or during tapering) or within 15 days of prednisone or prednisolone discontinuation.

Estimated glomerular filteration (eGFR) was calculated by using Bedside Schwartz formula; eGFR = 0.413 mL/min/1.73 m^2.

Ethical considerations

Approval was obtained from Sohag Faculty of Medicine Research Ethics Committee before study onset. For the prospective part of the study, informed written consents were obtained from patients' legal guardians for participation in the research. For retrospectively reviewed participants, the requirement for informed consent was waived due to the retrospective nature. All patients' data were treated according to the ethical guidelines with complete respect of patient's privacy and anonymousness.

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 24.Qualitative data were expressed as frequency and percentage. Quantitative data were expressed as mean ± standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for abnormally distributed data. The following tests were used for numerical data: Paired t-test for comparing the distribution of differences between the paired measurements before and after cyclosporine therapy when they were normally distributed while Wilcoxon signed rank test was used to compare the distribution of differences between the paired measurements when they were abnormally distributed. Probability (*p*-value) was utilized as the following: $p < 0.05$ was considered significant, $p < 0.001$ was considered as highly significant and $p > 0.05$ was considered insignificant.

Results

This study included 50 nephrotic patients; their ages ranged from 4-15 years with mean ± SD was 11.4 ± 3.1 years. There were 37 (74%) males and 13 (26%) females with male: female ratio was 2.8:1. **Table (1)**

Table (1): Clinico-demographic data of studied patients.

Patients´ characteristics		Studied patients (N = 50)	
Sex	Male	37	74%
	Female	13	26%
Age (years)	Mean ±SD	11.4± 3.1	
	Range	4 – 15	
Weight percentile	Median	45.3	
	IQR	11-72.8	
Height	Median	25.45	

percentile	IQR	6.88 – 43.15

N: number, *IQR*: Interquartile range, *SD*: standard deviation.

The median with IQR values of age at disease onset, disease duration, age at introduction of cyclosporine, duration of cyclosporine treatment together with the mean ± SD with range values of initial cyclosporine dose and cyclosporine dose at relapse are illustrated in **Table (2).**

Table (2): Disease onset and duration and cyclosporine use.

		Studied patients (N = 50)
Age at disease onset (years)	Median	4
	IQR	2 – 6
Disease duration (years)	Median	7
	IQR	3.88 – 9.63
Age at cyclosporine introduction (years)	Median	7
	IQR	4.75– 10
Initial cyclosporine dose (mg/kg/day)	Mean ±SD	4.8 ± 0.3
	Range	3.5 – 5.5
Cyclosporine dose at relapse (mg/kg/day)	Mean ±SD	2.8 ± 0.9
	Range	1.2 – 4.5
Duration of cyclosporine treatment (years)	Median	4
	IQR	1.5 – 6

N: number, *IQR*: Interquartile range, *SD*: standard deviation

Our study revealed high statistical significance ($p < 0.001$) in reduction of dependent steroid dose after cyclosporine use [median (IQR) dose: 0.25 (0.5-0.33) mg/kg/ every other day] compared with dependent steroid dose before cyclosporine [median (IQR) dose: 1.5 (0.88-2) mg/kg/ every other day]. Highly statistically significant ($p < 0.001$) reduction in rate of relapses after cyclosporine use [median (IQR): 2(1-2.93) per year] compared with relapse rate before cyclosporine [median (IQR): 5(4.6-6) per year] was achieved also, in addition to this, there were no relapses after cyclosporine administration in 13 patients who represented 26% of total patients. **Table (3)**

Table (3): Comparisons of dependent steroid doses and number of relapses per year before and after cyclosporine use.

		Before drug use (N = 50)	After drug use (N = 37)	*p*-value
Dependent steroid dose (mg/kg/ every other day)	Median	1.5	0.25	< 0.001
	IQR	(0.88 - 2)	(0.15 - 0.33)	
Relapse (per year)	Median	5	2	< 0.001
	IQR	(4.6 - 6)	(1 - 2.93)	

N: number, *IQR:* interquartile range.

The most prevalent cyclosporine side effect was hirsutism in 47 (94%) patients, followed by gum hyperplasia which was noticed in total 19 (38%) patients with13 (26%) patients had mild affection, 4 (8%) patients developed moderate gum hyperplasia, while severe affection developed only in 2 (4%) patients. The prevalence of all cyclosporine side effects recorded in our patients is shown in **Table (4).**

Table (4): Cyclosporine side effects in all studied patients.

Cyclosporine side effects	N= 50	%	Cyclosporine side effects	N= 50	%
Hirsutism	47	94%	Hyperlipidemia	8	16%
Gum hypertrophy	19	38%	Elevated liver enzymes	7	14%
GIT disturbances	16	32%	Depression	7	14%
Nephrotoxicity	14	28%	Hyper-urecimia	6	12%
Anorexia	14	28%	Conjunctivitis	6	12%
Myalgia	14	28%	Thrombocytopenia	6	12%
Hypertension	13	26%	Insomnia	6	12%
Anemia	10	20%	Tremors	6	12%
Hypomagnesemia	9	18%	Leukopenia	3	6%
Urinary tract infections	9	18%	Burning sensation in hands and feet	2	4%
Hyperbilirubinemia	9	18%			

N: number.

The two patients who developed severe gum hyperplasia interfering with food intake were shifted from cyclosporine to tacrolimus.

As regard to blood pressure control; there was statistically significant (p = 0.009) increased percentage of captopril use as an antihypertensive medication to reach 35 (70%) patients after cyclosporine treatment, versus 22 (44%) patients before cyclosporine use but there was no statistically significant difference (p = 0.123) in captopril dose before and after cyclosporine use, as the median (IQR) captopril dose was 1.1 (0.73 – 2) mg/kg/day before cyclosporine use and 1.5 (1.2 – 2) mg/kg/day after its use. No statistically significant difference (p = 0.063) in blood pressure control before and after cyclosporine. Before cyclosporine use, the 22 hypertensive patients were all controlled by captopril only, while after cyclosporine use, there were 30 hypertensive patients controlled by captopril alone while the remaining 5 hypertensive patients required additional therapy to obtain blood pressure control (amlodipine in a dose of 5-10 mg/day and carvedilol in a dose of 0.1-0.5 mg/kg/day)**.**

Pre-cyclosporine biopsies of our 50 patients showed "No change under light microscopy = minimal change disease". Renal biopsies were performed after cyclosporine in 39 patients (78% of total studied patients). Biopsy samples of 14 (35.9%) biopsied patients showed signs of histological nephrotoxicity in the form of stripped interstitial fibrosis with patchy lymphocytic infiltration, marked hydropic degeneration of tubules with patchy injury and hyaline casts, arteriolar myocyte vacuolization. Early focal segmental glomerulosclerosis was noticed in one biopsy. Biopsy samples of 25 (64.1%) biopsied patients revealed no changes under light microscopy. Renal biopsies were not performed in 11 patients; 9 of them were on cyclosporine for duration less than 2 years without deterioration of renal function and 3 patients refused the procedure. Patients who had signs of cyclosporine nephrotoxicity in their renal biopsy developed a degree of drop in the eGFR during their treatment course, but some improvement was achieved with reduction of cyclosporine dose.

Our study showed a high statistically significant variation in serum creatinine level and eGFR during cyclosporine treatment (p < 0.001). Before cyclosporine use; the median serum creatinine level was 0.45

(IQR: 0.3 - 0.51) mg/dl and at 24 months after cyclosporine treatment, median serum creatinine level was 0.63 (IQR: 0.54 - 0.8) mg/dl**. Table (5, 6)**

Table (5): Serum creatinine levels throughout 24 months of cyclosporine use.

Time of measurement	Creatinine level Median	(IQR)	*p*-value
Before drug use	0.45	(0.3 - 0.51)	< 0.001
3 months	0.53	(0.42 - 0.63)	
6 months	0.605	(0.54 - 0.7)	
12 months	0.65	(0.56 - 0.7)	
18 months	0.65	(0.52 - 0.71)	
24 months	0.63	(0.54 - 0.8)	

IQR: Interquartile range

Table (6): Estimated glomerular filtration rate throughout 24 months of cyclosporine use.

Time of measurement	eGFR		*p*-value
	Median	(IQR)	
Before drug use	136.9	(104.5 - 177.5)	< 0.001
3 months	103. 6	(91.5 - 132.07)	
6 months	91.1	(78.3 - 106.5)	
12 months	87.05	(72.4 - 102.1)	
18 months	90.8	(78.02 - 106.6)	
24 months	91.5	(81 - 106.9)	

eGFR: estimated glomerular filtration rate
IQR: Interquartile range

Discussion

This is a single-center study that investigated the effectiveness and adverse outcomes of cyclosporine in children with SDNS and FRNS. This represents one of the few studies in Upper Egypt that discussed the use and side effects of cyclosporine in childhood NS.

The total number of studied patients was 50 children and adolescents who received cyclosporine for SDNS and FRNS in our pediatric nephrology clinic in Sohag university hospital. The median (IQR) age at disease onset was 4(2-6) years while that at the initiation of cyclosporine therapy was 7 (4.75-10) years. There were 37 males (74%)

and 13 females (26%) with median (IQR) disease duration of 7 (3.88-9.63) years.

As regard to the effectiveness of cyclosporine therapy in those patients; we found that the median (IQR) number of relapses before starting cyclosporine was 5 (4.6-6) relapses/patient/year which decreased to 2 (1-2.93) relapses/patient/year after starting cyclosporine treatment by a reduction percentage of 64.4%. The median (IQR) least effective steroid dose (dependent dose) was 1.5(0.88-2) mg /kg /day before starting cyclosporine therapy and decreased to 0.25 (0.15-0.33) mg /kg /day by a reduction percentage of 79.3% after starting cyclosporine. The mean cyclosporine dose at relapse was 2.8 ± 0.9 (1.2-4.5)mg/kg/day.

These findings can be compared with a study in 2017 conducted by Kuroyanagi et al. where they observed a notable reduction in the average number of relapses. Prior to the initiation of cyclosporine treatment, the mean number of relapses/patient/year was 3.0. After the administration of cyclosporine, this figure decreased significantly to 0.47relapses/patient/year, reflecting 84.3% reduction percentage. Additionally, there was a substantial decrease in the total steroid dose. Before the commencement of cyclosporine treatment, the median value was 354.4 mg/kg/year (0.97 mg/kg/day), and after cyclosporine administration, it decreased to a median value of 48.9 mg/kg/year (0.14 mg/kg/day), indicating 85.5% reduction.[7]

After conducting a meta-analysis of 22 randomized controlled trials in children with NS, Filler G et al. came to the conclusion that cyclosporine should be used as a treatment for SDNS.[8] A large-scale, multi-center, placebo-controlled study conducted in Japan unequivocally demonstrated that administering cyclosporine for six months lowered the relapse rate and the total amount of corticosteroids required for patients with SDNS.[9] Additionally, it was noted that the majority of SDNS patients relapsed after stopping cyclosporine.[10]

Additionally, in a 2012 study by Jayaweera A. & Abeyagunawardena A., 83% of patients had their steroid dose tapered by at least 50% after beginning cyclosporine therapy after completing at least 6 months of starting cyclosporine therapy.[11] Another study conducted in 2017 by Alsaran et al, revealed that the cumulative steroid dose was reduced by more than 60% after 12 months of using the cyclosporine drug, indicating that cyclosporine is a good steroid sparing agent in SDNS. The relapse rate per patient per year decreased from 4.1 prior to the introduction of cyclosporine to 1.5 relapse/patient/year, one year after starting cyclosporine.[12]Nonetheless, a number of studies suggest that MMF therapy may be a less harmful substitute for cyclosporine or, in certain situations, a helpful supplemental drug that enables a decrease in the dosage of cyclosporine.[13] To balance efficacy against side effects, more research comparing the effectiveness of cyclosporine versus MMF is required.

In the final assessment of our patients, the most important observed side effects of cyclosporine were as follows: hirsutism emerged as the most prevalent side effect, affecting 47(94%) patients. The second most prevalent side effect was gum hyperplasia manifested in 19 (38%) patients, which was severe in 2 (4%) patients and necessitated shifting to tacrolimus. Pathological nephrotoxicity was observed in 14 (28%) patients, and new onset hypertension in 13 (26%) patients.

These results coincided with a 2016 study by Khemani et al. that found the following side effects of cyclosporine at the end of the third month: nephrotoxicity in 2.5%, hypertension in 3.7%, gum hyperplasia in 3.7%, and hirsutism in 5% of participants. No other side effects were noted in this study.[14] In a different study conducted in 2016, Shah & Hafeez found that 16.66% of their patients had hypertension, 4.7% had mild abnormalities in their renal function tests, 80.95% had hypertrichosis, and 26.19% had gum hypertrophy.[15] Adverse reactions to cyclosporine in a 2017 study were observed after one year of induction of cyclosporine. It was found that all cases (13 cases) had mild hirsutism and gum hyperplasia, 4 cases had mild hypertension and no cases had impaired renal function. [12]

The long-term use of cyclosporine appears to ameliorate steroid-dependency in SDNS.[16] This is consistent with our findings, which show that long-term cyclosporine use improves steroid dependency and lowers the relapse rate in our SDNS patients. In the current study, we used cyclosporine to treat SDNS patients, keeping the trough level as low as feasible as long as the patients remained in remission. On the other hand, prolonged use of cyclosporine may cause chronic kidney damage.[17] Because of this, we performed

renal biopsies for patients included in our study who were on cyclosporine for more than two to three years.

Cyclosporine nephrotoxicity in NS patients has been documented in patients with SDNS, which is frequently identifiable through serum creatinine level monitoring (our data indicate a high statistically significant variation in serum creatinine level over the course of the study). Before cyclosporine, median serum creatinine level was 0.45 (IQR: 0.3 - 0.51) and at 24 months after cyclosporine treatment, median serum creatinine level was 0.63 (IQR: 0.54 - 0.8) that comes in agree with El-Husseini et al. who studied the long-term effects of cyclosporine in children with idiopathic NS and showed that the mean serum creatinine level was 0.56 ± 0.17 before starting cyclosporine therapy and raised to 0.68 ± 0.43 after treatment.[18]

In our study, 39 patients (78% of total patients) had post-treatment biopsy specimens compared to pretreatment biopsy specimens in order to histologically evaluate cyclosporine nephrotoxicity. Of the 11 patients who had no renal biopsies, 9 were on cyclosporine treatment for less than two years without experiencing a decline in their renal function, and 3 patients had refused the procedure. Under light microscopy, biopsy samples from 25 (64.1%) biopsied patients showed no changes under light microscopy, whereas biopsy samples from 14 (35.9%) biopsied patients showed signs of histological nephrotoxicity. Even though nephrotoxicity was found in those 14 patients, their median cyclosporine trough level measured regularly at 3, 6, 12, 18, and 24 months after starting cyclosporine therapy was nearly within the target 12-hr level (57.9 - 90.5 ng/dl) throughout the study.

In 42 NS children who received cyclosporine with trough blood levels maintained at 100–200 ng/ml for 4–63 months, Habib & Niaudet compared post-treatment renal biopsy specimens with pre-treatment biopsy specimens; different grades of cyclosporine nephrotoxicity were observed: mild in 18 patients, moderate in 15, and severe in 9 patients.[19] Fifteen percent of patients with minimal change SDNS showed signs of mild cyclosporine nephrotoxicity, according to Hino et al.[16]

Regarding comparison between blood pressure levels prior to and following cyclosporine treatment, our findings indicate the following: Before cyclosporine use, there were 22 (44%) patients were hypertensive and controlled by captopril on a median dose of 1.1 mg/kg/day (IQR: 0.73 – 2 mg/kg/day). Following cyclosporine introduction, new onset hypertension developed in 13 (26%) patients. Hypertension control after cyclosporine use required an increase in median captopril dosage to 1.5 mg/kg/d (IQR: 1.2–2 mg/kg/d) and five patients required additional antihypertensive medications (amlodipine, carvedilol or both). El-Husseini et al. demonstrated that hypertension was detected one to eight weeks after the start of cyclosporine treatment and that it was much more common in children with SRNS (eight, 18.6%) than in those with SDNS (four, 5.4%). In ten patients, the hypertension was mild to moderate and easily controlled; in the other two patients, it was severe and difficult to control. Eleven patients received angiotensin-converting enzyme inhibitors, seven received beta blockers, and two received calcium channel blockers. [18]

Our study is not without limitations. It is a single center study with a small sample size which may underestimate our results. Moreover, it was only descriptive on a single group as there was no control group. Additionally, we did not compare cyclosporine with other immunosuppressive drugs used in treatment of FRNS and SDNS. Therefore, multicenter studies comparing different immune-suppressive medications of NS are recommended as future researches.

Conclusion

Cyclosporine appears to be a relatively safe and effective drug to be used as a steroid-sparing agent in steroid dependent and frequently relapsing nephrotic syndrome. However, safety of cyclosporine is not absolute, variable degrees of side effects were reported but these effects are still below the limit preventing the use of this drug and some of them are reversible after decreasing the dose or discontinuation of cyclosporine. Therefore, close observation and follow up of the side effects of cyclosporine is very important.

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