Artificial
Organs

Effect of Cyclosporine Therapy With Low Doses of Corticosteroids on Idiopathic Nephrotic Syndrome

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Abstract: Cyclosporine (CyA) has an immunosuppressive effect that might suggest a therapeutic role in idiopathic glomerular conditions. We focused on the optimization of CyA treatment control in patients with idiopathic nephrotic syndrome by using trough-level CyA measurements (C0) and the 2-h postdose levels (C2). Twenty-two patients (14 male, 8 female) with idiopathic nephrotic syndrome and the mean age of 51 ± 18 months (mean [M] ± standard deviation [SD]) were enrolled in our study during a period of 10 months (range: 3–18 months). All of the patients received CyA (2–3 mg/kg) in combination with methylprednisolone. In the present study protocol CyA concentrations (C0, C2), renal function, lipid profile, and degree of proteinuria were determined. The mean proteinuria of our patients before treatment was 11 972 ± 7953 mg/24 H (±SD) and the mean creatinine level (Cr) was 0.99 ± 0.37 mg/dL (±SD). Proteinuria decreased significantly already from the first month of therapy with CyA to 3578 ± 2470 mg/24 H (M± SD), and during the whole study period this reduction was significant (0.56 ± 0.37 gr/24 H (M ± SD), $P < 0.05$). At the same time renal function preserved, 1.09 ± 0.48 mg/dL (M ± SD). The blood levels of C0 were 135.10 ± 97.36 ng/mL (M ± SD) and the blood levels of C2 were 725 ± 256 ng/mL (M ± SD) at the first month of therapy. At the same time renal function preserved, 1.09 ± 0.48 mg/dL (M ± SD). Total cholesterol levels reduced significantly during study period (276.89 ± 45.57 to 200.67 ± 40.27 mg/dL [M ± SD]). The mean number of antihypertensive medication remained the same. The whole therapeutic protocol did not provoke any kind of side effects and CyA was quite tolerated by our patients. Treatment of idiopathic nephrotic syndrome with low doses of CyA with methylprednisolone leads to remission of proteinuria without deterioration of renal function. Blood levels of C0 for monitoring and treatment of nephrotic syndrome agrees with recent literature, while our study focus on establishing the proper levels of C2 for the treatment of nephrotic syndrome. The efficacy of CyA is combined with safety and tolerance. **Key Words:** Cyclosporine—Nephrotic syndrome—Corticosteroids—Renal function.

Cyclosporine (CyA) has been used in the treatment of idiopathic glomerular disease associated with the nephrotic syndrome (idiopathic nephrotic syndrome, or INS) in children and adults since 1985. Despite its proven efficacy, there remains a lack of coherent guidelines to aid clinicians to its use (1). For years, steroids were the major therapy for nephrotic syndrome, which garnered great results. Depending on primary causes of the nephrotic syndrome, steroids have been used alone or with other immunosuppressive agents. CyA was one of them.

One of the main safety concerns of cyclosporine therapy is its potential nephrotoxicity. Two methods of measurement are available: trough-blood levels (C0, predose concentration) or C2 levels (concentration at 2-h postdose). Trough-level monitoring is common, but it does not necessarily reflect CyA exposure as a function of drug intake. This may be better assessed by measuring the concentration of CyA 2 h after drug intake (C2) (2). The clinical benefits and target ranges for C2 monitoring in INS are currently being researched and only preliminary data are available.

CyA is a "critical dose drug": this means that a small change in dose or plasma concentration may result in a clinically significant change in efficacy and/or toxicity. Individual drug dosing during CyA

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therapy is necessary because CyA has a formulation-dependent bioavailability, and there is a wide inter-individual variation in CyA absorption. CyA can cause increased vascular resistance, resulting in reduced renal flow, decreased clearance of endogenous creatinine, and increased serum creatinine. Whether this is the mechanism that leads to the chronic tubular interstitial and vascular changes associated with chronic calcineurin toxicity is unclear at present.

In the present study we focused on optimization of CyA treatment control in patients with INS by using trough-level CyA measurements (C0) and the 2-h post-dose levels (C2). Specifically, we tried to determine efficacy of therapy, safety, and potential side effects, and to evaluate the better therapeutic and safe levels of CyA for patients with nephrotic syndrome. On the basis of the previously mentioned results, the aim of our study was to offer guidelines to aid clinicians on its use.

PATIENTS AND METHODS

Twenty-two patients (14 male, 8 female), with INS and age of 51 ± 18 months (mean [M] ± standard deviation [SD]), were enrolled in our study during a period of 10 months (range: 3–18 months). Primary causes of nephrotic syndrome are shown in Table 1. All of our patients had biopsy-proven glomerulonephritis. The definitions of terms used in INS are shown in Table 2. All of the patients received CyA (2–3 mg/kg) in combination with methylprednisolone (0.4 mg/kg body weight). Nineteen patients were on antihypertensive drugs. In the present study protocol CyA concentrations (C0, C2), renal function, lipid profile, liver enzymes, bilirubin, and degree of proteinuria were determined every month during the therapy.

TABLE 1. *Primary causes of nephrotic syndrome*

Membranous nephropathy	15
Minimal change disease	4
IgM nephropathy	1
IgA nephropathy	1
Mesangiocapillary glomerulonephritis	1

Data were expressed as the mean ± SD. Student's *t*-test was used to compare the data. The values were considered significant when $P < 0.05$.

RESULTS

The mean proteinuria of our patients before treatment was 11 972 ± 7953 mg/24 H (M ± SD) and the mean creatinine level (Cr) was 0.99 ± 0.37 mg/dL (M ± SD). The majority of our study population was presented with nephrotic syndrome, edema, hypoalbuminenia, and proteinuria. Proteinuria was already decreased significantly during the first month of therapy, with CyA at 3578 ± 2470 mg/24 H (M ± SD), and during the whole study period this reduction was significant (0.56 ± 0.37 gr/24 H [M ± SD], $P < 0.05$) (Table 3).

At the same time renal function was preserved, 1.09 ± 0.48 mg/dL (M ± SD). The blood levels of C0 were 135.10 ± 97.36 ng/mL (M ± SD) and the blood levels of C2 were 725 ± 256 ng/mL (M ± SD) at the first month of therapy (Table 3).

Total cholesterol levels reduced significantly during study period (276.89 ± 45.57 to 200.67 ± 40.27 mg/dL [M ± SD]). The mean number of antihypertensive medication remained the same. Our policy was to stop diuretic therapy within 1–2 months after the beginning of CyA, and we did it.

The entire therapeutic protocol did not provoke any kind of side effect, and CyA was quite tolerable for our patients. No significant adverse effects of

TABLE 2. *Definitions of terms used in idiopathic nephrotic syndrome*

Term	Idiopathic nephrotic syndrome definitions	
	Adult	Pediatric
Relapse	Proteinuria ≥3.5 g day^{-1} occurring after complete remission has been obtained for >1 month	Albu-stix 3+ or proteinuria >40 mg m^{-2} h^{-1} occurring on 3 days within 1 week
Frequently relapsing	2+ relapses within 6 months	2+ relapses within 6 months
Complete remission	Reduction of proteinuria to ≤0.20 g day^{-1} and serum albumin >35 g L^{-1}	<4 mg m^{-2} h^{-1} on at least 3 occasions within 7 days serum albumin >35 g L^{-1}
Partial remission	Reduction of proteinuria to between 0.21 g day^{-1} and 3.4 g day^{-1} ± decrease in proteinuria of ≥50% from baseline	Disappearance of edema. Increase in serum albumin >35 g L^{-1} and persisting proteinuria >4 mg m^{-2} h^{-1} or >100 mg m^{-2} day^{-1}
Steroid-resistant	Persistence of proteinuria despite prednisone therapy 1 mg kg^{-1} day^{-1} × 4 months	Persistence of proteinuria despite prednisone therapy 60 mg m^{-2} × 4 weeks
Steroid-dependent—INS recurs when treatment stops or decreases	Two consecutive relapses occurring during therapy or within 14 days of completing steroid therapy	Two relapses of proteinuria within 14 days after stopping or during alternate-day steroid therapy

TABLE 3. *Proteinuria and cyclosporine levels during treatment*

	Proteinuria (mg/24 H)	C0 (ng/mL)	C2 (ng/mL)
1 month	3578 ± 2470	135 ± 107	725 ± 256
2 months	2653 ± 1431	167 ± 97	793 ± 218
3 months	1491 ± 1073	148 ± 65	669 ± 47
4 months	832 ± 1273	104 ± 61	448 ± 144
5 months	668 ± 76	74 ± 36	237 ± 14

CyA, such as hypertension, liver dysfunction, or leukoencephalopathy were observed in any of the study participants. None of our patients appeared to have relapsed into the primary disease up to now (some of our patients are 2 years under therapy).

DISCUSSION

Fifteen years ago, a new oral microemulsion formation of CyA, named Neoral, which has been shown to have a more predictable pattern of absorption than Sandimmun, became available (3). Following its widespread clinical use, potentially more precise methods of CyA blood-level monitoring than the measuring of C0 have been investigated, mainly in renal transplant patients, because of the absence of a reliable correlation between the C0 and clinical events (4,5). It has been proposed that measurement of the blood concentration of CyA 2 h after a dose of Neoral (C2) might be a simple and useful method for the pharmacokinetic monitoring of CyA, based on the observation of a good correlation between the C2 and the 12-h area under the concentration ($AUC^{0–12h}$) time curve (4,5).

Because of the unpredictable pattern of absorption of CyA, our patients have been treated with low to moderate doses of the drug, administered orally twice daily, with C0 and C2 monitoring. While this treatment protocol was shown to have an effective steroid-sparing effect, CyA nephrotoxicity remained a major problem (6,7). It has been reported in children that young age at the start of CyA treatment and a higher frequency of relapses during CyA treatment may be risk factors for the development of chronic CyA nephrotoxicity (8). Thus, the development of an optimal CyA treatment strategy for INS, with administration of as low a dose of CyA as possible was sought in order to minimize the treatment toxicity, while maintaining the treatment's efficacy. In this context, we previously reported the efficacy of low-dose CyA given as a single dose with peak blood level (C0–C2).

Taking into consideration the results of our study, we noticed that administration of CyA yields sufficient C2 point blood levels without associated elevation of the C0 and, therefore, a satisfactory steroid-sparing effect without serious adverse effects in a proportion of INS patients. Although there are several retrospective studies, to our knowledge there are not many prospective trials to assess the safety and effectiveness of long-term treatment with CyA in INS patients. Our results suggest that treatment with CyA for 6 months in a dosage that maintains the trough level between 74 and 135 ng/mL is an effective and relatively safe treatment for INS patients. This level is similar also in children with nephrotic syndrome, according to a recent study (9).

A study by Alexopoulos et al. (10) has shown that prolonged treatment of patients with membranous nephropathy (12 months) with low-dose cyclosporine increased remission rates and that prolonged treatment with low-dose cyclosporine (1.4–1.5 mg/kg) is useful in maintaining remission. Relapse occurred more frequently when C0 CyA levels decreased below 100 ng/mL. Patients who relapsed had a mean C0 CyA level of 72 ± 48 ng/mL, compared to the mean level of nonrelapsers of 194 ± 80 ng/mL ($P < 0.03$). According to recent workshop recommendations on membranous nephropathy, treatment targets include complete or partial remission of proteinuria, maintenance of stable glomerular filtration rate (GFR) (±20% of pretreatment level), avoiding hypertension, and a cyclosporine level regarded as nontoxic (C0 = 125–175 ng/mL and C2 = 400–600 ng/mL) (1,11). In the case of minimal-change disease, recommendations of the same workshop include complete or partial remission of proteinuria, maintenance of stable GFR (±20% of pretreatment level), avoiding hypertension, and a C0 cyclosporine level of 80–120 ng/mL (1).

In the present study, we adjusted the drug dose to maintain the C2 point blood level, at least at the first 2–3 months of the study, in the range of 600–800 ng/mL, considering the results of the stable renal transplant patients receiving CyA treatment, even though the precise peak blood level of the drug for the treatment of INS remains to be elucidated. We did not notice a significant relapse rate in our study population, while renal function remained unchanged in all of our study participants.

Because of the relatively small number of patients and the short observation period, it is difficult to arrive at a definitive conclusion based on the results of our study as to which C0 and C2 levels are optimal to obtain the maximum efficacy, and as to the minimum toxicity of CyA therapy in INS patients.

CONCLUSION

It seems that C2 levels, approximately between 650–750 ng/mL, are effective enough at the beginning of the therapy (2–3 months) and at lower levels (250–450 ng/mL) are tolerated and have potential in stable patients after 3 months of therapy. CyA therapy provides sustained remission of proteinuria and is also effective in the long-term preservation of renal function in INS. Adherence to dosing guidelines plus regular patient monitoring will minimize the risk of nephrotoxicity, the major concern of nephrologists caring for these patients.

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