Treatment with microemulsified cyclosporine in children with frequently relapsing nephrotic syndrome

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Abstract

Background. We previously established a treatment protocol for conventional cyclosporine (Sandimmune, Novartis, Basel, Switzerland) in children with frequently relapsing nephrotic syndrome; ~50% of patients remained relapse free for 2 years, without serious adverse events. Recently, microemulsified cyclosporine (Neoral, Novartis), which has a more stable absorption profile than conventional cyclosporine, has been developed. We tested the hypothesis that microemulsified cyclosporine is at least as effective as conventional cyclosporine.

Methods. To evaluate the safety and efficacy of microemulsified cyclosporine, a prospective, multicentre trial was conducted according to the previously established protocol, using microemulsified cyclosporine instead of conventional cyclosporine. The duration of treatment was 24 months. During the first 6 months, patients received microemulsified cyclosporine in a dose that maintained the trough level between 80 and 100 ng/mL of cyclosporine. For the next 18 months, the dose was adjusted to maintain a level between 60 and 80 ng/mL.

Results. A total of 62 patients (median age, 5.4 years; 48 males, 14 females) were studied. The frequency of relapse decreased from 4.6 ± 1.4 to 0.7 ± 1.5 times per year (P<0.0001). The probability of relapse-free survival at Month 24 was 58.1% (95% confidence interval, 45.8–70.3%). The probability of progression (to frequently relapsing nephrotic syndrome)-free survival at Month 24 was 88.5% (95% confidence interval, 80.4–96.5%). Cyclosporine nephrotoxicity was detected in only 8.6% of patients who underwent renal biopsy after 2 years of treatment. Antihypertensive agents were administered to 12.9% of the patients to control hypertension without severe sequelae.

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Conclusions. Microemulsified cyclosporine administered according to our treatment protocol is safe and effective in children with frequently relapsing nephrotic syndrome.

Keywords: clinical trial; microemulsified cyclosporine; nephrotic syndrome; paediatric nephrology

Introduction

Managing frequently relapsing nephrotic syndrome (FRNS) in children remains challenging despite progress in treatment. The development of immunosuppressive therapies other than corticosteroids has been enthusiastically attempted to date [1–4] because repeated treatment with corticosteroids can lead to serious adverse events.

Cyclosporine is one treatment of choice for children with FRNS or steroid-dependent nephrotic syndrome [5–10]. For such patients, we have already established a safe and effective protocol for treatment with conventional cyclosporine, Sandimmune (Novartis, Basel, Switzerland), in a prospective, randomized, multicentre trial [11]. With our protocol, the dose of cyclosporine is titrated on the basis of the whole-blood trough level. Approximately 50% of children with FRNS treated according to this protocol are expected to remain relapse free for 2 years, without serious adverse events.

Microemulsified cyclosporine, Neoral (Novartis, Basel, Switzerland) is a newer formulation of cyclosporine, designed to promote stable absorption and improved bioavailability [12–15]. Several small studies have compared safety and efficacy between conventional cyclosporine and microemulsified cyclosporine in children with nephrotic syndrome [16] and recipients of renal transplants [17,18]; microemulsified cyclosporine has consistently been suggested to be more effective, without compromising safety.

Because cyclosporine is stably absorbed after administration of microemulsified cyclosporine, the dose of microemulsified cyclosporine can be titrated on the basis of the area under the concentration-time curve during the first 4 h after treatment (AUC_{0–4h}) or the 2-h post-dose cyclosporine level (C2) in children who receive kidney transplants [19,20]. The clinical efficacy of microemulsified cyclosporine titrated by monitoring AUC_{0–4h} or C2 in patients with nephrotic syndrome is also expected but remains to be confirmed.

We performed a prospective, single-arm, multicentre trial according to our previously established protocol, using microemulsified cyclosporine instead of conventional cyclosporine. The principal aim of this trial was to evaluate the efficacy in terms of relapse-free survival probability and the safety of microemulsified cyclosporine in children with FRNS. The benefits of AUC_{0–4h} and C2 monitoring in this clinical setting were also assessed.

Materials and methods

Patients
The study group comprised children (1–18 years of age) with FRNS who had idiopathic nephrotic syndrome. Patients were excluded if they had any of the following conditions: (i) other renal or systemic forms of nephrotic syndrome diagnosed on the basis of renal biopsy, clinical features or serology; (ii) poorly controlled hypertension; (iii) chronic renal dysfunction (creatinine clearance of ≤60 mL/min/1.73 m²); (iv) active infectious disease; (v) severe liver dysfunction; (vi) a history of treatment with cyclosporine; or (vii) pregnancy.

The criteria for and definitions of nephrotic syndrome, remission, and relapse were in accordance with the International Study of Kidney Disease in Children [21]. FRNS was defined as two or more relapses of nephrotic syndrome within 6 months after the initial episode, three or more relapses within any 6-month period, or four or more relapses within any 12-month period. Steroid dependence was defined as the occurrence of two consecutive relapses on tapering the steroid dosage or within 14 days after the termination of steroids.

‘Ethical Guidelines for Clinical Research’, requiring that all protocols for clinical studies are reviewed by an external ethics committee, were issued by the Japanese Ministry of Health, Labour and Welfare in 2003. At the start of our trial (January 2000), the study protocol was approved by the director or other responsible person at each participating centre and was not reviewed by an external review board. Therefore, at the time of the submission for publication, a retrospective approval by an ethical committee was performed. The ethical standards laid down in the Declaration of Helsinki were applied accordingly in the design and execution of this study. Informed consent was obtained from all patients or their parents.

Protocol
The total duration of treatment was 24 months. For the first 6 months, all patients received microemulsified cyclosporine in a dose that maintained a whole-blood trough level between 80 and 100 ng/mL of cyclosporine; for the next 18 months, the dose was adjusted to maintain a trough level between 60 and 80 ng/mL. Maintenance prednisolone was not prescribed. After 2 years of treatment, all patients were scheduled to undergo renal biopsy, and the dose of cyclosporine was tapered by 0.5–1.0 mg/kg per day every week. The concomitant use of drugs other than corticosteroids and immunosuppressants was not restricted. Antihypertensive agents, including angiotensin-converting enzyme inhibitors, and HMG-CoA reductase inhibitors (statins) were also permitted.

Blood analysis (complete blood cell count and blood chemistry) and urine tests (urinalysis and quantitative proteinuria) were performed monthly during follow-up. The trough level of cyclosporine was measured monthly by monoclonal radioimmunoassay. In addition to the trough level, other indices of cyclosporine absorption (i.e. AUC_{0–4h} and C2) were examined at Month 1. For cyclosporine AUC_{0–4h} and C2 sampling, time lags of ±5 mins were allowed. AUC_{0–4h} was calculated by the linear trapezoidal method.

Patients in whom FRNS or steroid-resistant nephrotic syndrome developed during treatment received off-protocol therapy, left to the discretion of the physician in charge.

Corticosteroid treatment
To treat relapses of nephrotic syndrome immediately before study entry, patients received 2 mg/kg/day of prednisolone in three divided doses (maximum dose, 80 mg/day) for 4 weeks, followed by a single dose of 2 mg/kg of prednisolone administered in the morning on alternate days for 2 weeks, 1 mg/kg on alternate days for 2 weeks and 0.5 mg/kg on alternate days for 2 weeks. Patients who had relapses of nephrosis during the study period received 2 mg/kg/day of prednisolone in three divided doses (maximum, 80 mg/day) until remission, followed by a single dose of 2 mg/kg of prednisolone administered in the morning on alternate days for 2 weeks, 1 mg/kg on alternate days for 2 weeks and 0.5 mg/kg on alternate days for 2 weeks.

Histopathological examination
A pathologist at each study centre examined each renal biopsy specimen. An independent investigator at the coordinating centre who was blinded to all patient data also reviewed the histologic sections. Arteriolar changes, tubular atrophy and interstitial fibrosis were graded semi-quantitatively on a scale of 0–3+ as follows: 0, none; 1+, mild; 2+, moderate; and 3+, intense.
Statistical analysis

The primary end point was the probability of relapse-free survival, based on the period until the first relapse. The secondary end point was the probability of progression-free survival, based on the period until the development of FRNS. Survival curves were estimated by the Kaplan–Meier method. Survival curves from our previous study of conventional cyclosporine are included in the figures of this study. Multivariate analyses using Poisson regression were performed to estimate the relations of AUC0–4h or C2 to the incidence of relapse, adjusting for sex, age and steroid dependence. Data were analysed according to the intention-to-treat. A two-sided P-value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of the software package SAS for Windows, release 9.13 (SAS Institute Inc., Cary, NC, USA).

Clinical trial registration

This study has been registered in a public trials registry, the University Hospital Medical Information Network (UMIN, ID C000000010, http://www.umin.ac.jp/ctr/index.htm).

Results

Data set

Between January 2000 and December 2005, a total of 66 children were enrolled at 21 institutions, and 4 patients were excluded from all analyses. Therefore, 62 children (59 with minimal change nephrotic syndrome and 3 with mesangial proliferative glomerulonephritis; 48 males and 14 females) received treatment and were included in analysis (Figure 1). Their median ages at diagnosis and at study entry were 3.0 years (range, 1.3–14.5) and 5.4 years (range, 1.7–15.3), respectively. The clinical characteristics of the patients at entry are shown in Table 1.

As for concomitant medications, antihypertensive agents were given to eight patients (angiotensin-converting enzyme inhibitors, 4 patients; calcium channel blockers, 3; and both drugs, 1). A HMG-CoA reductase inhibitor (statin) was given to one patient.

Table 1. Patient’s characteristics

| Age (years) | Sex (n) | Number of relapses before entry (n) | Steroid dependence (n) |
|-------------|---------|------------------------------------|------------------------|
|             | Male    | Female | NA | ≥2<–4/year | ≥4<–6/year | ≥6/year | NA | (−) | (+) |
| All ages    | 48      | 14     | NA | 17         | 32         | 12      | 1  | 29  | 32  |
| 0–<3        | 6       | 5      | 0  | 1          | 6          | 4       | 0  | 3   | 8   |
| 2–<6        | 18      | 8      | 0  | 7          | 15         | 4       | 0  | 13  | 13  |
| 2–6<10      | 12      | 0      | 1  | 5          | 5          | 1       | 1  | 4   | 7   |
| 210–<15     | 10      | 1      | 0  | 4          | 4          | 3       | 0  | 7   | 4   |
| ≥15         | 2       | 0      | 0  | 0          | 2          | 0       | 0  | 2   | 0   |

NA, not available.
Cyclosporine dosage and trough level

The mean dose of cyclosporine required to maintain the whole-blood trough level between 80 and 100 ng/mL during the first 6 months of treatment was 5.1 mg/kg/day. During the next 18 months, the mean dose of cyclosporine required to maintain a trough level between 60 and 80 ng/mL was 4.5 mg/kg/day. The distributions of the trough level are shown in Figure 2.

Decreased frequency of relapses after treatment with cyclosporine

Before treatment, the mean number of relapses was 4.6 ± 1.4 times per year. During the 2 years of treatment with cyclosporine, the mean number of relapses decreased significantly to 0.7 ± 1.5 times per year (paired t-test, P<0.0001).

Probability of relapse-free and progression-free survival

The estimated relapse rate, defined as the total number of patients who had relapse during the trial divided by the duration of observation for all patients, was 0.28 (95% confidence interval, 0.17–0.39) per year. Figure 3 shows the results of Kaplan–Meier analysis. At Month 24, the probability of relapse-free survival was 58.1% (95% confidence interval, 45.8–70.3%). In this figure, the probability of relapse-free survival in the present study was compared with that in our previous trial [11]. The probability of relapse-free survival in Group A [24 patients (18 males); median age, 7.3 years], which received conventional cyclosporine according to the same protocol, was 50.0%, while that in Group B [20 patients (17 males); median age, 6.9 years old], which received a fixed dose of conventional cyclosporine (2.5 mg/kg) from Month 7 onwards, was 15.0%.

The estimated rate of progression to FRNS was 0.06 (0.02–0.11) per year. The probability of progression (to FRNS)-free survival at Month 24 was 88.5% (95% confidence interval, 80.4–96.5%). Steroid-resistant nephrotic syndrome did not develop in any patient during the trial.

AUC\(_0\)–\(_4\)h, C2 and relapse

The mean AUC\(_0\)–\(_4\)h at 1 month was 1493.4 ± 681.2 ng × h/mL, and that of C2 was 486.0 ± 203.9 ng/mL. Table 2 shows the results of Poisson regression analysis for

| Age/sex | Relapse during treatment | Progression to FRNS during treatment | AUC\(_0\)–\(_4\)h at 1 month (ng × h/mL) | C2 at 1 month (ng/mL) | Mean trough level (ng/mL) | Hypertension | Renal histology |
|---------|--------------------------|--------------------------------------|----------------------------------------|------------------------|--------------------------|-------------|----------------|
| 2.9 male| Yes                      | No                                   | 1063                                   | 290                    | 91.1                     | (+)         | Mild arteriolar hyalinosis |
| 3.9 male| No                       | No                                   | 2160                                   | 690                    | 92.4                     | (−)         | Mild tubular atrophy |
| 5.4 male| No                       | No                                   | 2251                                   | 720                    | 72.2                     | (−)         | Mild interstitial fibrosis |
| 6.2 male| No                       | No                                   | 975                                    | 380                    | 60.0                     | (−)         | Mild arteriolar hyalinosis and vacuolation |
| 10.8 male| Yes                    | No                                   | 619                                    | 160                    | 72.0                     | (+)         | Mild tubular atrophy |

FRNS, frequently relapsing nephrotic syndrome, AUC\(_0\)–\(_4\)h, the area under the concentration-time curve during the first 4 h after treatment; C2, the 2-h post-dose cyclosporine level.
AUC\textsubscript{0–4h}, adjusted for important prognostic factors. None of the four risk factors analysed [AUC\textsubscript{0–4h} (continuous), sex (male or female), age (≥6 years or <6 years), steroid dependence (yes or no)] were significantly related to relapse. The hazard ratio for AUC\textsubscript{0–4h} was 0.95 (95% confidence interval, 0.87–1.04; P=0.23) for each 100-ng × h/mL increment.

The results of Poisson regression analysis using C2 in place of AUC\textsubscript{0–4h} were similar, and the hazard ratio for C2 was 0.86 (95% confidence interval, 0.64–1.15; P=0.30) for each 100-ng/mL increment.

**Growth**

Before cyclosporine treatment (at study entry), the mean standard deviation (s.d.) score for body height was −0.27 ± 1.01 (n=62); at the end of the trial, the mean s.d. score for body height was 0.33±0.97 (n=58). The s.d. score for height increased significantly from the start to the end of 2-year treatment (paired t-test, P<0.001).

**Adverse events**

Renal biopsies were performed in 58 patients at the end of 2 years of treatment. The results are shown in Table 3. Mild nephrotoxicity attributed to cyclosporine occurred in 5 (8.6%) of the 58 patients. Other adverse events are shown in Table 4. Hypertension, defined as a requirement for antihypertensive agents during the trial, was detected in 12.9% of the patients. Severe sequelae of hypertension, such as encephalopathy, seizures and cardiac dysfunction, were not detected. One patient had a mild elevation of the serum creatinine concentration, which was transient and resolved. No patient had serious adverse events that required discontinuation of the trial.

**Discussion**

This prospective, open-label, multicentre trial evaluated the safety and efficacy of 2 years of treatment with microemulsified cyclosporine (Neoral) in children with FRNS. Our results showed that microemulsified cyclosporine significantly decreased the frequency of relapse and increased the probability of relapse-free survival, suggesting that treatment with microemulsified cyclosporine is effective for children with FRNS. Renal biopsy was performed after 2 years of treatment and showed that the treatment protocol was safe in terms of nephrotoxicity.

The significant decrease in the frequency of relapse during 2 years of treatment suggested that microemulsified cyclosporine is effective in children with FRNS. The probability of relapse-free survival in the present trial was compared with that in our previous trial, in which conventional cyclosporine was given to children with FRNS [11]. The probability of relapse-free survival in the present trial (58.1% in 2 years) was higher than the lowest target level, which was the upper limit of the 95% confidence interval for the probability of relapse-free survival in Group B [given a fixed dose of 2.5 mg/kg conventional cyclosporine from Month 7 onwards in the previous trial (37.9%), i.e. standard treatment]. On the other hand, better outcomes in terms of probability of relapse-free survival with microemulsified cyclosporine as compared with conventional cyclosporine were not obtained. The dose of cyclosporine did not differ significantly (data not shown). In this regard, microemulsified cyclosporine was not superior to conventional cyclosporine. Further clinical studies are thus needed to confirm the efficacy of microemulsified cyclosporine in children with FRNS.

The results of our study do not allow us to make firm conclusions about whether AUC\textsubscript{0–4h} and C2 monitoring are clinically useful for titrating the dose of cyclosporine in children with FRNS. AUC\textsubscript{0–4h} and C2 monitoring have been shown to be a useful method for titrating the dose of cyclosporine, particularly the microemulsified formulation, in adults [22,23] and in children who receive renal transplants [19,20,24]. C2 is the best single time point predictor of AUC\textsubscript{0–4h}, but the trough level closely correlates with acute rejection [25]. On the other hand, limitations of C2 monitoring in renal transplant recipients have been demonstrated: C2 levels did not predict rejection or toxicity; poor and/or slow absorption were observed in a substantial number of patients; and C2 levels were not dose-proportional [26]. Moreover, in a randomized setting, C2 monitoring was not superior to trough monitoring in terms of graft survival in renal transplant recipients [27]. In the present trial, Poisson regression analysis was used to assess the relations of AUC\textsubscript{0–4h} and C2 to relapse. The risk of relapse was not dependent on AUC\textsubscript{0–4h} or C2, probably because the dose of cyclosporine was adjusted on the basis of trough levels, and neither AUC\textsubscript{0–4h} nor C2 had sufficient variability (or power) to test the relation to relapse. To settle these issues, further studies are required; another new multicentre randomized controlled trial supported by the Ministry of Health, Labour and Welfare, entitled ‘Cyclosporine C2 monitoring for frequently relapsing nephrotic syndrome in children: a randomized controlled trial’, is now being conducted in Japan to evaluate the safety and efficacy of C2 monitoring for cyclosporine (Neoral).

Improvement in the mean height s.d. score is another encouraging result of our trial. Growth failure is a serious adverse effect of steroids in children. Improvement in the mean height s.d. score is attributed to the steroid-sparing effect of cyclosporine. This effect is an important reason for using immunosuppressants such as cyclosporine in children with FRNS. At the same time, our protocol for the use of prednisolone in this trial appears to be appropriate.
Treatment with microemulsified cyclosporine in nephrotic children

Adverse events associated with cyclosporine were acceptable in our trial. The main adverse events of cyclosporine are nephrotoxicity, neurotoxicity including encephalopathy and seizures, hypertension, gingival hyperplasia, hirsutism, and hypomagnesaemia [10,28–30]. In our trial, five patients (8.6%) had nephrotoxicity, and four (6.9%) had interstitial fibrosis. Fibrosis was mild in all of our patients. However, since irreversibility of interstitial fibrosis has been reported [31] and paediatric patients have a long life expectancy, nephrotoxicity due to cyclosporine should be closely monitored, and renal biopsy should be performed to confirm safety in patients who receive repeated or prolonged treatment with cyclosporine. Hypertension, defined as a requirement for antihypertensive agents, was detected in 12.9% of our patients. Although severe sequelae of hypertension such as seizures did not occur in this study, management of blood pressure is an important concern whenever cyclosporine is administered. No patient had serious adverse events that required the discontinuation of treatment during the trial.

An important limitation of the present trial is the study design: no control group was established. Because of several differences between the present trial and our previous trial, caution should be exercised when comparing the results. The results of the aforementioned randomized controlled trial are awaited to confirm our findings. Our study group was characterized by a significant male preponderance (48 boys and 14 girls), which has also been reported in children with nephrotic syndrome, including frequently relapsing nephrotic syndrome [7,9]. In our previous study, the male:female ratio was also as high as 35:9. Another concern is missing data, such as the results of renal biopsy after treatment and measurement of AUC₀₋₄h and C2. Some patients refused repeated renal biopsy because of associated risks. AUC₀₋₄h measurement, which requires multiple blood samples, was inconvenient and was occasionally not performed by the physicians in charge; a single C2 measurement might be more practical. Finally, lack of adequate statistical power, particularly on Poisson regression analysis, was also a weakness of the present study.

A major limitation of cyclosporine treatment for children with FRNS is relapse after drug withdrawal. Several studies have evaluated relapse after cyclosporine treatment, albeit the treatment protocols differed from ours [8,32,33]. Most patients had relapse of FRNS after the discontinuation of cyclosporine. Such patients require further treatment with cyclosporine or other immunosuppressants. We are continuing to follow up our patients to better define this critical issue.

In conclusion, treatment with microemulsified cyclosporine (Neoral) for 2 years in a dosage that maintains the trough level between 80 and 100 ng/mL for the first 6 months and 60–80 ng/mL for the next 18 months appears to be safe and effective in children with FRNS. Among several immunosuppressants recommended for children with FRNS, e.g. cyclophosphamide, levamisole, chlorambucil and mycophenolate mofetil, microemulsified cyclosporine is considered an important treatment option. Follow-up studies are being conducted to evaluate the risk of relapse after the withdrawal of cyclosporine.

Acknowledgements. The authors would like to thank the patients and physicians who participated in this trial: Akioka Y (Tokyo), Awazu M (Tokyo), Furuse A (Kumamoto), Fujinaga S (Saitama), Goto M (Tokyo), Hamada R (Tokyo), Hamahira K (Hyogo), Hamasaki Y (Tokyo), Harada T (Kanagawa), Hatae K (Fukuoka), Hataya H (Tokyo), Hattori M (Tokyo), Hiramatsu M (Oita), Igarashi T (Tokyo), Ikeda M (Tokyo), Kagami S (Tokushima), Kaku Y (Fukuoka), Kamei K (Tokyo), Kodama S (Kagoshima), Konimoto T (Miyazaki), Mishuku Y (Kanagawa), Nakamichi N (Osaka), Niimura F (Kanagawa), Nozu K (Hyogo), Ochiai R (Tokyo), Otsuka Y (Saga), Owada Y (Tochigi), Sako M (Tokyo), Sato T (Sagamihara), So H (Kagoshima), Tanaka Y (Saitama), Wakaki H (Kanagawa), Yoshidome K (Kagoshima). This study was supported in part by the Kidney Foundation, Japan.

Conflict of interest statement. N.Y. has received a grant from Novartis, Japan.

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A 5-year survey of biopsy-proven kidney diseases in Lebanon: significant variation in prevalence of primary glomerular diseases by age, population structure and consanguinity

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Abstract

Background. Differences in epidemiology of kidney disease across the Middle East may arise from variations in indication for biopsy, environmental exposure and socio-economic status. The Lebanese population is composed of different ethnicities, with distinct ancestry and religion, enabling comparison of their effect on the prevalence of kidney disease within a confined geographic setting and uniform practices. Here we report 5 years’ detailed epidemiology of renal diseases, based on histological diagnosis, in a sample from three large pathology centres in Lebanon.

Methods. Records of renal biopsies analysed at the American University of Beirut Medical Center, Hotel Dieu de France Hospital and the Institut National de Pathologie from January 2003 till December 2007 were retrospective-