Tohoku J. Exp. Med., 2022, **256**, 85-91

# Predictors of Treatment Response and Long-Term Outcomes in Young Children with Steroid-Dependent Nephrotic Syndrome Treated with High-Dose Mizoribine as First-Line Steroid-Sparing Agent

**Shuichiro Fujinaga,[1] Shota Endo,[1] Toshimasa Morishita,[1] Yoichi Takemasa,[1] Yuta Onuki,[1] Koji Sakuraya[1] and Daishi Hirano[2]**

[1]Division of Nephrology, Saitama Children's Medical Center, Saitama, Saitama, Japan
[2]Department of Pediatrics, The Jikei University School of Medicine, Tokyo, Japan

Mizoribine may be a safe and effective treatment for children with steroid-dependent nephrotic syndrome (SDNS). However, predictors of treatment response and long-term outcomes after mizoribine discontinuation remain unknown. We retrospectively reviewed the clinical course of 22 children aged ≤ 10 years (median age, 5.3 years) with SDNS who received high-dose mizoribine as the initial steroid-sparing agent (SSA). Mizoribine was administered at a single daily dose of 10 mg/kg (maximum, 300 mg/day) after breakfast. The dose was adjusted to maintain 2-h post-dose mizoribine levels of > 3 $\mu$g/mL and was tapered off after 12 months of steroid-free remission. Patients who regressed to SDNS were switched from mizoribine to other SSAs. The primary endpoint was probability of survival without regression to SDNS after mizoribine initiation. Ten patients were able to discontinue SDNS (response group), whereas twelve were switched from mizoribine to other SSAs (non-response group) during a median observation period of 6.0 years after mizoribine. The steroid-dependent dose prior to mizoribine was significantly lower in the response group than in the non-response group ($p < 0.05$). The Kaplan-Meier analysis revealed that the probability of regression-free survival was significant higher in patients with steroid-dependent dose of < 0.25 mg/kg/day than in those with steroid-dependent dose of ≥ 0.25 mg/kg/day ($p < 0.05$). During a median follow-up of 5.5 years after mizoribine discontinuation, all but one patient did not develop SDNS. High-dose mizoribine may be an attractive treatment option as initial SSA in young children with low steroid-dependent dose for improved long-term outcomes.

**Keywords:** children; high-dose mizoribine; long-term outcome; regression-free survival; steroid-dependent nephrotic syndrome
Tohoku J. Exp. Med., 2022 January, **256** (1), 85-91.

## Introduction

Although approximately 40% of pediatric patients with idiopathic nephrotic syndrome develop frequently relapsing (FR)/steroid-dependent nephrotic syndrome (SDNS), there is no consensus on effective first-line steroid-sparing agents (SSAs) for these patients (Fujinaga et al. 2013). The recently updated German Best Practice Guideline indicates that calcineurin inhibitors (CNIs), such as cyclosporine and tacrolimus, and mycophenolate mofetil (MMF) should be considered as SSAs in children with FR/SDNS, whereas the use of cyclophosphamide is no longer recommended due to side effects, including gonadal toxicity (Ehren et al. 2021). However, long-term CNI use is also associated with a significant risk of CNI-induced nephrotoxicity and patients may subsequently develop hypertension and chronic kidney disease during adulthood (Fujinaga et al. 2006; Takemasa and Fujinaga 2021). Although MMF is a valuable SSA without nephrotoxic effects, its use for children with FR/SDNS is off-label in many countries, including Japan (Fujinaga et al. 2007, 2009).

Mizoribine, which has been developed in Japan, is a

Received September 14, 2021; revised and accepted October 10, 2021. Published online January 28, 2022; doi: 10.1620/tjem.256.85.
Correspondence: Shuichiro Fujinaga, M.D., Ph.D., Division of Nephrology, Saitama Children's Medical Center, 1-2 Shintoshin, Chuo-ku, Saitama, Saitama 330-8777, Japan.
e-mail: f_shuich@d2.dion.ne.jp

selective inhibitor of inosine monophosphate dehydrogenase (IMPDH) in the *de novo* pathway of purine nucleotide synthesis; therefore, its immunosuppressive activity is very similar to that of MMF. We previously demonstrated that high-dose mizoribine therapy might be a safe and effective approach for pediatric patients with SDNS prior to cyclosporine treatment (Fujinaga et al. 2011). However, no study to date has reported predictive factors of treatment response and prognosis after discontinuation of mizoribine. In the present single-center study, we investigated long-term outcomes in young children with SDNS who were treated with mizoribine as the initial SSA.

## Patients and Methods

*Patients*

We retrospectively reviewed the medical records of 22 consecutive children aged ≤ 10 years, including 16 boys and 6 girls, who were diagnosed with SDNS and received mizoribine as initial treatment between January 2006 and October 2018 at Saitama Children's Medical Center. Patients with steroid-resistant nephrotic syndrome, those with a follow-up period of < 2 years, those with high-dose steroid dependence, and those who received other SSAs before mizoribine therapy were excluded from the study. The clinical course of six patients during the treatment period has been previously published (Fujinaga et al. 2011).

The definitions and criteria for nephrotic syndrome, remission, relapse, frequent relapse, steroid dependency, and steroid resistance adopted in the present study have been described in the Clinical Practice Guideline for Pediatric Idiopathic Nephrotic Syndrome in Japan (Ishikura et al. 2015a). The present study was approved by the Ethics Committee of Saitama Children's Medical Center (approval no, 2019-06-010).

*Therapeutic protocol*

Treatment with mizoribine (Bredinin®; Asahi Kasei Pharma, Tokyo, Japan) was initiated at a single daily dose of 5 mg/kg (maximum dose, 150 mg/day), which was administered after breakfast in patients who achieved complete remission with prednisolone. White blood cell counts of patients were measured two weeks after therapy initiation, and mizoribine dose was increased by 10 mg/kg/day and adjusted to maintain a 2-h post-dose (C2) mizoribine level of > 3 $\mu$g/ml, for a maximum daily dose of 300 mg in patients with white blood cell count > 4,000 cells/$\mu$l, in accordance with previous study (Fujinaga et al. 2011). Mizoribine was tapered off within 6 months by reducing 25-100 mg every 4 weeks after 12 months of steroid-free remission. Mizoribine levels in plasma samples were evaluated using high-performance liquid chromatography by Asahi Kasei Pharma. During mizoribine therapy, patients with relapse were treated with 1-2 mg/kg/day prednisolone (maximum, 60 mg/kg) until no proteinuria was observed for three consecutive days. Thereafter, prednisolone was administered on alternate days and tapered off over six months by dose reduction of 2.5-5 mg every 2-4 weeks. Patients who regressed to SDNS despite mizoribine therapy were switched to other SSAs such as cyclophosphamide.

The primary endpoint was probability of survival without regression to SDNS, i.e., regression-free survival, defined as time between mizoribine initiation to switching to other SAAs. Treatment failure was defined as a condition requiring other SAAs during mizoribine therapy. Steroid-dependent dose was defined as the prednisolone dose (mg/kg/day) that maintained complete remission prior to the relapse of nephrotic syndrome.

To assess treatment outcomes and determine potential drug toxicity, clinical and laboratory assessments were performed two weeks after mizoribine therapy initiation, followed by assessments performed every 1-3 months. Laboratory assessments included C2 mizoribine level; complete blood count; and serum urea, creatinine, electrolyte, albumin, cholesterol, transaminase, bilirubin, amylase, and uric acid levels.

*Statistical analysis*

Categorical variables were presented as frequencies and percentages and compared using the chi-square or Fisher's exact test, as appropriate. Unless indicated otherwise, continuous variables were expressed as medians with interquartile range (IQR) and compared using the parametric two-sample Wilcoxon signed-rank test or the non-parametric Mann-Whitney *U* test, as appropriate. Receiver-operating characteristic (ROC) curve analysis was used to determine optimal cut-off point of steroid-dependent dose. The Kaplan-Meier method with the log-rank test was used to analyze relapse-free and regression-free survival probabilities. Cox proportional hazard model was used for multivariate analysis of predictive risk factors for treatment failure. All analyses were performed using R version 3.6.1 or EZR version 3.2.2 (Saitama Medical Center, Jichi Medical University). Statistical significance was set at a $p$ value of < 0.05.

## Results

The median age at the time of nephrotic syndrome diagnosis was 3.5 (IQR, 1.8-4.9) years. All patients developed SDNS and received high-dose mizoribine as first-line SSA at a median age of 5.3 (IQR, 3.7-7.8) years. During the first two years after mizoribine initiation, the relapse-free and regression-free survival rates were 14% (3/22) and 50% (11/22), respectively (Fig. 1A, B). During the observation period of 6.0 (IQR, 3.4-10.4) years after mizoribine initiation, 10 patients were able to discontinue SDNS (response group) whereas 12 patients were switched from mizoribine to other SSAs, including cyclophosphamide, mycophenolate mofetil, and cyclosporine in 10, 1, and 1 patient, respectively, because of regression to SDNS (non-response group). In the response group, treatment with mizoribine (median treatment period, 2.3 years; IQR, 1.9-2.9 years) resulted in a reduction in the median predniso-

Fig. 1A

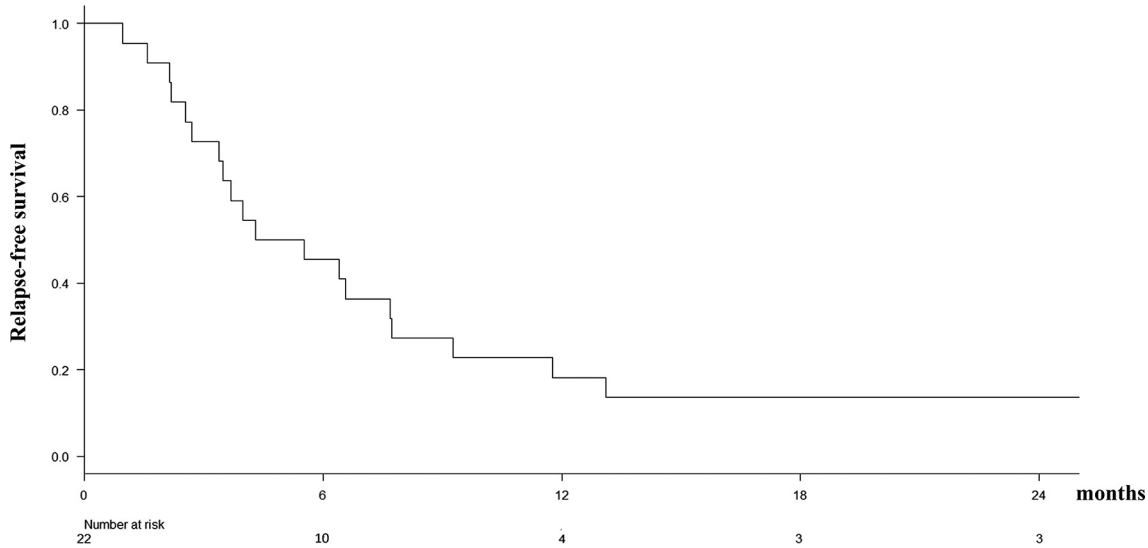


Fig. 1B

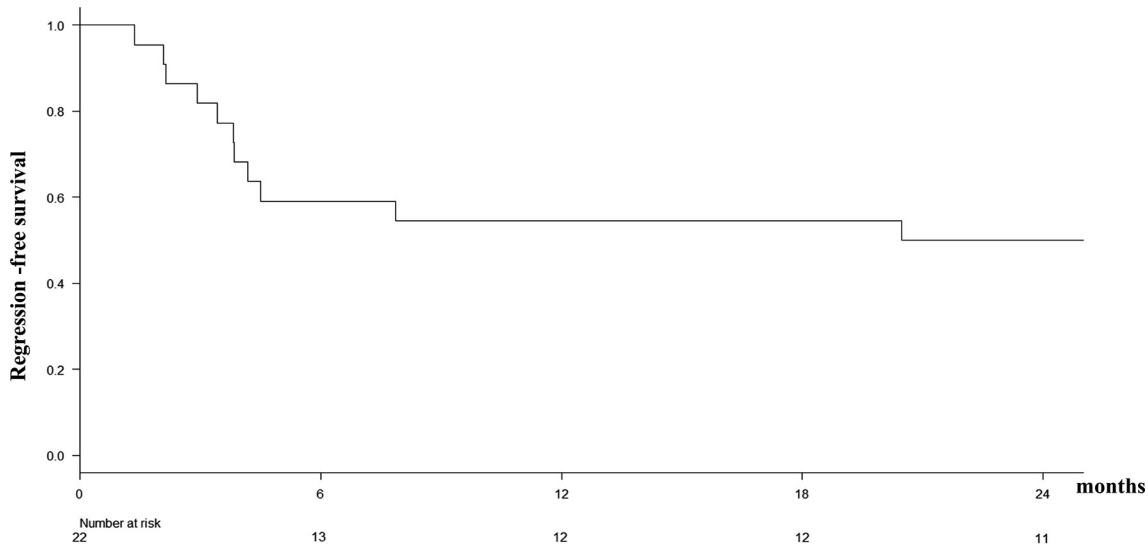


Fig. 1. Kaplan-Meier curve.
A. The probability of survival without relapse of nephrotic syndrome after mizoribine initiation in all patients. B. The probability of survival without regression to SDNS, i.e., regression-free survival, after mizoribine initiation in all patients.

lone dose from 0.50 (IQR, 0.44-0.65) to 0.16 (IQR, 0.1-0.23) mg/kg/day ($p < 0.01$), and the median relapse rate from 2.7 (IQR, 2.0-2.9) to 0.4 (IQR, 0.07-0.57) episodes/12 months ($p < 0.01$). In the non-response group, 10 of the 12 patients received a 12-week cyclophosphamide regimen (cumulative dose, 200 mg/day) followed by retreatment with high-dose mizoribine. After switching from mizoribine to cyclophosphamide, 9 of the 10 patients (90%) were able to discontinue SDNS, whereas the use of cyclosporine was needed in the remaining one patient who continued to exhibit steroid dependency. We compared the baseline characteristics and clinical course between the patients in the response group and those in the non-response group (Table 1). The steroid-dependent dose prior to mizoribine was significantly lower in the response group than in the non-response group (0.22 vs. 0.27 mg/kg/day, $p < 0.05$). The ROC curve analysis revealed that steroid-dependent dose of 0.25 mg/kg/day before MZR was optimal in discriminating response group from non-response group, and the area under the ROC curve, sensitivity, and specificity were 0.792, 70.0%, and 83.3%, respectively (Fig. 2). The proportion of low-dose steroid-dependent patients (< 0.25 mg/kg/day) was significantly higher in the response group than in the non-response group (70% vs. 13%, $p < 0.05$). The Kaplan-Meier analysis also revealed that the probability of regression-free survival was significant higher in patients with steroid-dependent dose of < 0.25 mg/kg/day than in those with steroid-dependent dose of ≥ 0.25 mg/kg/

Table 1. Comparison of the baseline characteristics and clinical course between the response and non-response groups.

| | All (n = 22) | Response group (n = 10) | Non-response group (n = 12) | *p* value |
|---|---|---|---|---|
| Sex (male/female), n | 15/7 | 8/2 | 7/5 | 0.38 |
| Age at onset of nephrotic syndrome (years) | 3.4 (2.4-4.9) | 3.3 (1.8-4.2) | 3.5 (2.4-7.6) | 0.41 |
| Age at mizoribine initiation (years) | 5.3 (3.7-7.8) | 5.4 (3.8-6.6) | 5.0 (4.3-8.4) | 1 |
| Number of relapses before mizoribine (per year/patient) | 2.6 (1.9-3.9) | 2.7 (1.5-2.7) | 3.4 (1.8-4.0) | 0.28 |
| Steroid-dependent dose before mizoribine (mg/kg/day) | 0.27 (0.21-0.48) | 0.22 (0.10-0.31) | 0.27 (0.26-0.81) | 0.023 |
| Mizoribine dose (mg/kg/day) | 10.2 (8.9-11.8) | 9.8 (8.7-11.0) | 10.2 (9.8-13.4) | 0.38 |
| 2-h post-dose mizoribine level ($\mu$g/mL) | 3.9 (3.1-4.6) | 3.8 (2.7-4.4) | 4.0 (3.4-4.5) | 0.60 |

Median (IQR, interquartile range) is shown except for sex (male/female).
*p* value, the response group vs. non-response group.

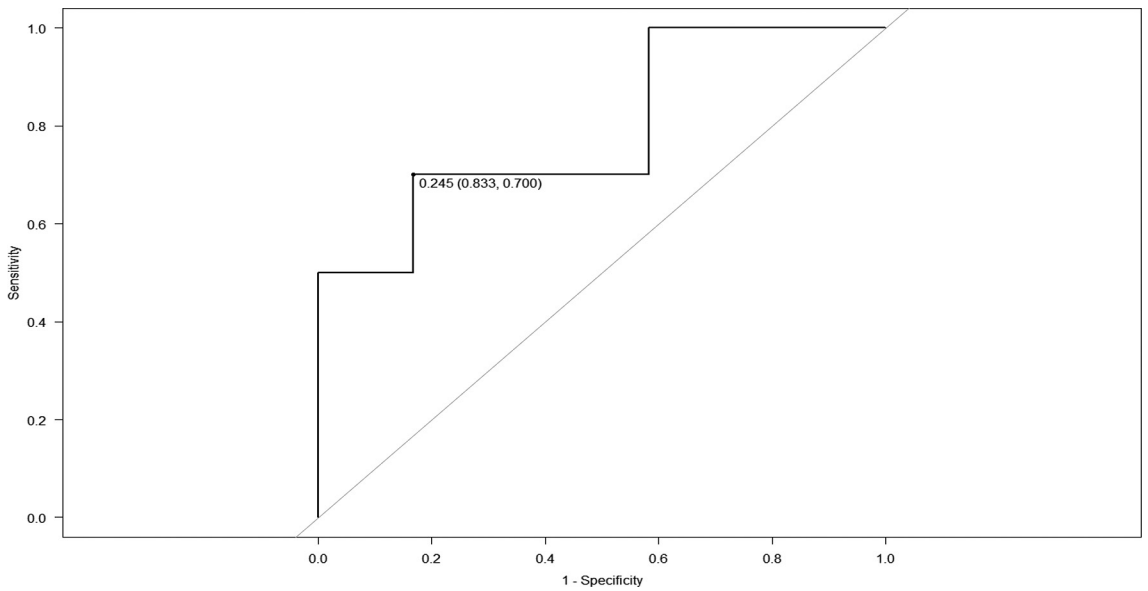


Fig. 2. Receiver-operating characteristic curve for discriminating responder group from non-responder group by steroid-dependent dose before mizoribine.

day ($p < 0.05$, log-rank test) (Fig. 3). In addition, the predictive factors for treatment failure by multivariate analysis using the Cox proportional hazard model are shown in Table 2. Steroid-dependent dose of ≥ 0.25 mg/kg/day prior to mizoribine was the only significant independent risk factor for treatment failure during mizoribine therapy.

No severe adverse events requiring discontinuation of the drug were observed in any of the patients in the response group during a median of 2.26 (IQR, 1.9-2.9) years of treatment with mizoribine. During a median follow-up period of 5.5 (IQR, 2.7-9.0) years after mizoribine discontinuation, only one patient received MMF because of regression to SDNS; however, all patients achieved treatment-free remission at the last visit (median age, 13.8 years; IQR, 12.3-18.8 years).

## Discussion

In the present study of young children with SDNS treated with mizoribine as first-line SSA, we found that the first two-year relapse-free rate after the therapy was relatively low. However, our analyses suggest that mizoribine might be safe and effective for low-dose steroid-dependent patients (response rate, 78%). Most of the patients in the response group did not regress to SDNS after the discontinuation of mizoribine. To the best of our knowledge, this is the first study to identify predictive factors of response to mizoribine and to demonstrate the long-term favorable prognosis after mizoribine discontinuation in children with SDNS.

Despite significant variability in the selection of first-line SSAs across the globe, most pediatric nephrologists indicate that MMF is the preferred choice for patients with FR/SDNS (Schijvens et al. 2021). However, in our institution we prefer to administer mizoribine prior to MMF because the use of MMF for FR/SDNS is off-label in Japan. MMF is a noncompetitive inhibitor of IMPDH, whereas

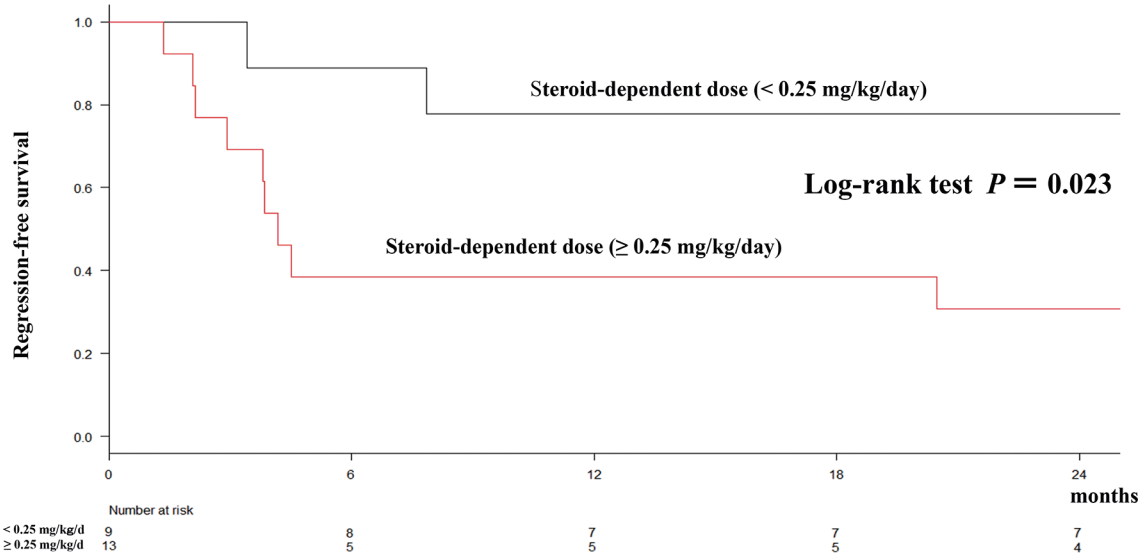


Fig. 3. Kaplan-Meier curves showing the probability of survival without regression to SDNS, i.e., regression-free survival, after mizoribine initiation in patients with steroid-dependent dose of < 0.25 mg/kg/day and in those with steroid-dependent dose of ≥ 0.25 mg/kg/day.
p = 0.023, log-rank test.

Table 2. Predicted risk factors for treatment failure using multivariate Cox proportional hazard model.

| | Hazard ratio | 95% confidence interval | *p* value |
|---|---|---|---|
| Sex (male) | 1.02 | 0.31-3.37 | 0.97 |
| Age at mizoribine initiation (≥ 6 years) | 3.87 | 0.91-16.4 | 0.066 |
| Steroid-dependent dose before mizoribine (≥ 0.25 mg/kg/day) | 9.14 | 1.62-51.47 | 0.012 |

mizoribine is a competitive inhibitor of the same enzyme. Therefore, therapeutic drug monitoring of mizoribine may be more critical for its immunosuppressive effects compared to MMF. In a randomized controlled trial of Japanese pediatric patients with FRNS who received standard-dose mizoribine (4 mg/kg/day) without therapeutic drug monitoring, the relapse rate did not differ significantly between the treatment and placebo groups (Yoshioka et al. 2000). Furthermore, in a retrospective study of Japanese pediatric patients with SDNS who received standard-dose mizoribine with lower therapeutic drug levels (4 mg/kg/day; maximum, 150 mg/day; C2 <2.0 $\mu$g/mL), Kondoh et al. (2019) reported that the mizoribine responders, defined as those who did not need other SSAs after mizoribine, comprised only one-third of the entire cohort. Based on these unfavorable outcomes of patients treated with standard-dose mizoribine, the Clinical Practice Guideline for Pediatric Idiopathic Nephrotic Syndrome in Japan has indicated that mizoribine should be administered at higher dose of 7-10 mg/kg/day, once daily, to achieve higher C2 or C3 mizoribine levels of > 3.0 $\mu$g/mL, in patients with FR/SDNS (Ishikura et al. 2015a). In the present study, we found that half of the patients were able to discontinue SDNS during the two-year period after mizoribine initiation. The relatively high response rate in the present study might be due to the high mizoribine dose (10 mg/kg/day; maximum, 300 mg/day) administered to maintain high C2 mizoribine levels of > 3.0 $\mu$g/mL. Furthermore, in a recent prospective study of Chinese pediatric patients with FRNS, Xia et al. (2019) used the sigmoidal $E_{max}$ model to estimate that the therapeutically effective C2 mizoribine levels were > 2.0 $\mu$g/mL. Therefore, we suggest that therapeutic drug monitoring of mizoribine to maintain high C2 levels might be crucial for favorable outcomes in pediatric patients with FR/SDNS.

In general, the selection of first-line SSAs for SDNS is based on the degree of steroid-dependent dose before SSA initiation. However, whether low-dose prednisolone should be continued for a long duration or replaced by SSAs in low-dose steroid-dependent patients remains under debate. The Indian Pediatric Nephrology Group recommends long-term administration of low-dose prednisolone to prevent relapse in patients with SDNS (Sinha et al. 2021), whereas the German Society for Pediatric Nephrology indicates that this approach should only be considered in individual cases (Ehren et al. 2021). In the present study, steroid toxicity such as growth retardation, obesity, and ocular hypertension developed even in low-dose steroid-dependent patients before mizoribine initiation. During mizoribine therapy, seven of the nine patients (78%) with low-dose steroid

dependence were able to discontinue SDNS without any adverse events. Therefore, high-dose mizoribine may be a useful treatment approach in patients with low-dose steroid dependence, especially in those experiencing steroid toxicity.

We previously demonstrated that high-dose mizoribine after cyclophosphamide therapy might be associated with favorable outcomes in pediatric patients with moderate-dose (< 0.6 mg/kg/day) steroid dependence (Mizutani et al. 2019). In the present study, most patients in the non-response group were able to discontinue SDNS after switching from mizoribine to cyclophosphamide. In our opinion, therefore, CNIs such as cyclosporine and tacrolimus should be indicated only in pediatric patients with high-dose steroid dependence because early initiation of cyclosporine is not associated with improved long-term outcomes of SDNS, based on studies reporting worsening relapsing disease course and the development of hypertension and chronic kidney disease during adulthood after the use of cyclosporine (Ishikura et al. 2015b; Aydin et al. 2019). Similar to our strategy, a recent review has also indicated that CNIs are recommended in pediatric patients with SDNS with a prednisolone dependence dose of > 0.7 mg/kg and that antiproliferative agents such as MMF and cyclophosphamide should be used in those with a prednisolone dependence dose of 0.3-0.7 mg/kg/day (Ravani et al. 2017).

In conclusion, in the present study we found that high-dose mizoribine as initial SSA therapy might be associated with favorable outcomes in young pediatric patients with low-dose (< 0.25 mg/kg/day) steroid dependence. We recommend that cyclophosphamide should be considered in patients who fail mizoribine therapy or in those with moderate-dose (0.25-0.6 mg/kg/day) steroid dependence. We also propose that cyclosporine should be used only in patients who fail cyclophosphamide therapy or in those with high-dose (> 0.6 mg/kg/day) steroid dependence. We believe that this strategy might reduce the rate of chronic kidney disease and hypertension later in life for young pediatric patients with SDNS. However, although the same therapeutic protocol for SDNS was used, the present single-center study is limited by the retrospective design and the absence of a placebo control group. Furthermore, the number of patients in the present study was insufficient to draw robust conclusions. Therefore, future prospective studies are warranted to determine the proper choice of first-line SSAs in pediatric patients with FR/SDNS.

## Acknowledgments

SF has received Grants-in-Aid for research of Saitama Children's Medical Center (2021-B-3).

## Conflict of Interest

The authors declare no conflict of interest.

## References

Aydin, M., Franke, I., Kurylowicz, L., Ganschow, R., Lentze, M., Born, M. & Hagemann, R. (2019) The long-term outcome of childhood nephrotic syndrome in Germany: a cross-sectional study. *Clin. Exp. Nephrol.*, **23**, 676-688.

Ehren, R., Benz, M.R., Brinkkotter, P.T., Dotsch, J., Eberl, W.R., Gellermann, J., Hoyer, P.F., Jordans, I., Kamrath, C., Kemper, M.J., Latta, K., Muller, D., Oh, J., Tonshoff, B., Weber, S., et al. (2021) Pediatric idiopathic steroid-sensitive nephrotic syndrome: diagnosis and therapy -short version of the updated German best practice guideline (S2e) - AWMF register no. 166-001, 6/2020. *Pediatr. Nephrol.*, **36**, 2971-2985.

Fujinaga, S., Endo, A., Ohtomo, Y., Ohtsuka, Y. & Shimizu, T. (2013) Uncertainty in management of childhood-onset idiopathic nephrotic syndrome: is the long-term prognosis really favorable? *Pediatr. Nephrol.*, **28**, 2235-2238.

Fujinaga, S., Hirano, D., Nishizaki, N., Someya, T., Ohtomo, Y., Ohtsuka, Y., Shimizu, T. & Kaneko, K. (2011) Single daily high-dose mizoribine therapy for children with steroid-dependent nephrotic syndrome prior to cyclosporine administration. *Pediatr. Nephrol.*, **26**, 479-483.

Fujinaga, S., Kaneko, K., Muto, T., Ohtomo, Y., Murakami, H. & Yamashiro, Y. (2006) Independent risk factors for chronic cyclosporine induced nephropathy in children with nephrotic syndrome. *Arch. Dis. Child.*, **91**, 666-670.

Fujinaga, S., Ohtomo, Y., Hirano, D., Nishizaki, N., Someya, T., Ohtsuka, Y., Kaneko, K. & Shimizu, T. (2009) Mycophenolate mofetil therapy for childhood-onset steroid dependent nephrotic syndrome after long-term cyclosporine: extended experience in a single center. *Clin. Nephrol*., **72**, 268-273.

Fujinaga, S., Ohtomo, Y., Umino, D., Takemoto, M., Shimizu, T., Yamashiro, Y. & Kaneko, K. (2007) A prospective study on the use of mycophenolate mofetil in children with cyclosporine-dependent nephrotic syndrome. *Pediatr. Nephrol.*, **22**, 71-76.

Ishikura, K., Matsumoto, S., Sako, M., Tsuruga, K., Nakanishi, K., Kamei, K., Saito, H., Fujinaga, S., Hamasaki, Y., Chikamoto, H., Ohtsuka, Y., Komatsu, Y., Ohta, T., Nagai, T., Kaito, H., et al. (2015a) Clinical practice guideline for pediatric idiopathic nephrotic syndrome 2013: medical therapy. *Clin. Exp. Nephrol.*, **19**, 6-33.

Ishikura, K., Yoshikawa, N., Nakazato, H., Sasaki, S., Nakanishi, K., Matsuyama, T., Ito, S., Hamasaki, Y., Yata, N., Ando, T., Iijima, K. & Honda, M.; Japanese Study Group of Renal Disease in Children (2015b) Morbidity in children with frequently relapsing nephrosis: 10-year follow-up of a randomized controlled trial. *Pediatr. Nephrol.*, **30**, 459-468.

Kondoh, T., Ikezumi, Y., Yokoi, K., Nakajima, Y., Matsumoto, Y., Kaneko, M., Hasegawa, H., Yamada, T., Kumagai, N., Ito, T. & Yoshikawa, T. (2019) Assessment of factors associated with mizoribine responsiveness in children with steroid-dependent nephrotic syndrome. *Clin. Exp. Nephrol.*, **23**, 1154-1160.

Mizutani, A., Fujinaga, S., Sakuraya, K., Hirano, D. & Shimizu, T. (2019) Positive effects of single-daily high-dose mizoribine therapy after cyclophosphamide in young children with steroid-dependent nephrotic syndrome. *Clin. Exp. Nephrol.*, **23**, 244-250.

Ravani, P., Bertelli, E., Gill, S. & Ghiggeri, G.M. (2017) Clinical trials in minimal change disease. *Nephrol. Dial. Transplant.*, **32**, i7-i13.

Schijvens, A.M., van der Weerd, L., van Wijk, J.A.E., Bouts, A. H.M., Keijzer-Veen, M.G., Dorresteijn, E.M. & Schreuder, M.F. (2021) Practice variations in the management of childhood nephrotic syndrome in the Netherlands. *Eur. J. Pediatr.*, **180**, 1885-1894.

Sinha, A., Bagga, A., Banerjee, S., Mishra, K., Mehta, A., Agarwal,

I., Uthup, S., Saha, A. & Mishra, O.P.; Expert Group of Indian Society of Pediatric Nephrology (2021) Steroid sensitive nephrotic syndrome: revised guidelines. *Indian Pediatr.*, **58**, 461-481.

Takemasa, Y. & Fujinaga, S. (2021) Adult chronic kidney disease in childhood-onset nephrotic syndrome. *Pediatr. Int.*, doi:org/10.111/ped.14846. [Epub ahead of print].

Xia, Z.K., Gao, Y.F., Rong, L.P., Dang, X.Q., Shen, Q., Jiang, X.Y., Yi, Z.W. & Xu, H. (2019) Usefulness of mizoribine administration in children with frequently relapsing nephrotic syndrome, and the relationship between pharmacokinetic parameters and efficacy: a multicenter prospective cohort study in China. *World J. Pediatr.*, **15**, 262-269.

Yoshioka, K., Ohashi, Y., Sakai, T., Ito, H., Yoshikawa, N., Nakamura, H., Tanizawa, T., Wada, H. & Maki, S. (2000) A multicenter trial of mizoribine compared with placebo in children with frequently relapsing nephrotic syndrome. *Kidney Int.*, **58**, 317-324.