A Clinical Response–Adjusted Steroid Treatment Protocol for Children With Newly Diagnosed Idiopathic Nephrotic Syndrome

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Rationale & Objective: Prednisone protocols for children with idiopathic nephrotic syndrome (INS) are generally similar in dose and duration, despite wide variations in time to response. We assessed the feasibility of a novel clinical treatment protocol characterized by a shorter duration and lower cumulative dose for children with early clinical response.

Study Design: Nonrandomized pilot clinical trial.

Setting & Participants: The study population included 59 children with newly diagnosed INS treated between 2014 and 2019 who responded to treatment within 8 days.

Intervention: The intervention group (n = 27) was treated with a response-adjusted protocol during which responders received an 8-week course of tapering doses of prednisone. The usual care group (n =32) was treated with the standard protocol (prednisone, 60 mg/m^2/24 hours for 6 weeks, followed by 40 mg/m^2/48 hours for 4 weeks, followed by a slow taper for a total of 24 weeks).

Outcome: Consent rate, cumulative prednisone dose, the development of frequently relapsing or steroid-dependent nephrotic syndrome (FRNS or SDNS, respectively), relapses per year, treatment with steroid-sparing therapies, and adverse effects of steroid therapy over 3 years of follow-up observation.

Results: The consent rate was 88%. The mean cumulative steroid dose for the initial treatment was 70 mg/kg and 141 mg/kg ($P < 0.001$) in the intervention and usual care groups, respectively. None of the patients in the intervention group relapsed while on faster steroid taper down. The occurrence of FRNS and SDNS in the intervention group was not statistically different than in the usual care group, hazard ratios were 0.80 (95% CI, 0.37-1.73) and 0.61 (95% CI, 0.30-1.27), respectively. The proportions of relapse-free patients were similar ($P = 0.5$), and adverse steroid events did not differ between the groups.

Limitations: Lack of randomization and small sample size.

Conclusions: These findings demonstrate the feasibility of a shortened duration of steroid dosing for INS when patients demonstrate an initial clinical response to treatment. A larger study is needed to characterize the relative efficacy and toxicity of this novel treatment regimen.

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Trial Registration: Registered at ClinicalTrials.gov with study number NCTO2649413.

Visual Abstract online

Complete author and article information provided before references.

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Idiopathic nephrotic syndrome (INS) is the most common chronic glomerular disease in children; the incidence is 2-7 per 100,000 and the prevalence is 16 per 100,000. In almost 80% of affected children, minimal change disease is an underlying pathology.[1,2] Corticosteroids, used as first-line treatment for newly diagnosed nephrotic syndrome since the 1950s, induce remission in more than 90% of patients.[3-6]

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Several prednisone protocols are available for treatment of the first episode of INS in children, although all of them are based on similar dosing principles during the first 8 weeks. Accordingly, prednisone 60 mg/m^2 or 2 mg/kg per day is administered for 4-6 weeks, followed by 40 mg/m^2 every other day or 1.5 mg/kg every other day for 4 weeks. Extending the steroid regimen was initially assumed to improve clinical outcome[7]; however, randomized controlled trials conducted in the last 10 years reported similar clinical end points for 8- to 12-week and 24-week protocols, with no differences in the number of patients who relapsed or developed steroid-dependent nephrotic syndrome (SDNS) or frequently relapsing nephrotic syndrome (FRNS).[8-10] The lack of a clinical benefit in prolonging treatment was further supported by a large meta-analysis published in 2015,[11] and by the recent double-blind PREDNOS study.[12] In the previously mentioned prospective controlled studies, the total treatment length was 2-3 times shorter than in the conservative protocol arm; however, the cumulative dose of prednisone was reduced by only 25%, and the number of high-dose prednisone days was the same.[8-10,12]

The time to response to prednisone in patients with newly diagnosed nephrotic syndrome varies widely, from as early as 5-8 days to as late as 35-42 days.[2,13] In none of the protocols for a first episode of nephrotic syndrome is the dose or duration of therapy adjusted to the response day or to any other clinical or patient-specific factor.[1,2,5,6] This contrasts with most of the treatment protocols for

PLAIN-LANGUAGE SUMMARY

The first episode of idiopathic nephrotic syndrome in children is often effectively treated with steroids. However, this treatment is long, involves a high cumulative steroid dose, and may cause significant side effects and inconvenience to patients and their families. Several studies on lower steroid dose regimens for relapsing nephrotic syndrome in children showed promising results and inspired this pilot study of the feasibility of a novel protocol for response-adjusted initial treatment to achieve shorter duration therapy and a lower cumulative steroid dose. Although the size of this study was small, the findings suggest that substantial reduction in steroid dosage in the initial treatment phase is feasible and may potentially reduce steroid-related side effects. Further research is needed to understand the efficacy and safety of this novel treatment approach.

relapses, in which steroid reduction is dependent on the response day.[6] The evidence that rapid responders are at lower risk of a complicated clinical course with many relapses prompts the need for a more individualized approach to patients with newly diagnosed disease.[13-17]

In our experience, about 85% of children with INS who respond to prednisone do so by the eighth day of therapy. We hypothesized that patients who respond early are at lower risk and can therefore be managed with fewer steroids.[5,13] We performed a pilot study in which patients who had a response to steroid therapy within 8 days of initiation subsequently received a rapid steroid reduction. Patients enrolled in the pilot study were compared with a previous cohort of patients who had received treatment according to KDIGO (Kidney Disease: Improving Global Outcomes) guidelines. The goals of this study were (1) to determine the feasibility of a subsequent full-scale trial based on the willingness of patients and caregivers to enroll in this study and continue participation over 3 years of follow-up observation, (2) to determine whether the protocol leads to a reduced cumulative steroid dose during the initial treatment phase and over the follow-up period, and (3) to provide point estimates and associated measures of precision for efficacy and safety outcomes that will allow estimation of the sample size needed for a future randomized clinical trial.

Methods

Study Overview

In January 2016, the response-adjusted prednisone protocol was first introduced at our hospital. We conducted a nonrandomized pilot clinical trial at a tertiary pediatric medical center from January 2016 to November 2019. The intervention group consisted of children aged 1-17 years treated for a first episode of INS. The diagnosis of INS was based on the presence of nephrotic-range proteinuria (spot urinary protein-creatinine ratio [UPCR] ≥2 mg/mg), hypoalbuminemia (serum albumin <2.5 g/dL), and edema, without signs of systemic or other primary kidney disease. A history of immunosuppressant administration, other underlying renal pathology, and the absence of parental informed consent were exclusion criteria. The patients were selected consecutively.

The usual care group included patients whose disease was diagnosed during 2014-2015 and were part of the prospective observational study conducted in our hospital before the introduction of the response-adjusted protocol. This group also included patients whose disease was diagnosed after the introduction of the response-adjusted protocol in January 2016 but whose parents did not give consent to receive that treatment. The eligibility criteria for the usual care group were the same as for the intervention group.

Patients who did not achieve remission after 4 weeks of therapy were considered high risk for steroid resistance. Accordingly, they were excluded from the study, continued the standard treatment protocol, and were switched to alternative therapies later.

Intervention

Patients who responded within 8 days received a response-adjusted protocol: prednisone 60 mg/m^2/24 hours (maximum 60 mg/d) for 2 weeks, including the days before the remission, followed by 45 mg/m^2/24 hours for 2 weeks, 30 mg/m^2/48 hours for 2 weeks, and 15 mg/m^2/48 hours for 2 weeks, for a total protocol duration of 8 weeks.

The usual care group received the standard initial KDIGO protocol of 60 mg/m^2/24 hours for 6 weeks, followed by 40 mg/m^2/48 hours for 4 weeks, and then a slow taper down of 5-10 mg every 2 weeks for 10-14 weeks, for a total protocol length of 20-24 weeks.

After treatment initiation, participants were requested to check urine protein at the following frequencies using home-use dipsticks: daily until remission, 2-3 times a week during the first month after remission, and weekly thereafter. In addition, urine protein was checked during each clinic visit using urinalysis and the spot UPCR. The response day was defined as the first of 3 consecutive days of trace or negative proteinuria on urine dipstick analysis.

Relapses

Relapse was defined as proteinuria of 2+ or more by dipstick, or a spot UPCR of 2 mg/mg or more, which was persistent for more than 3 days; or generalized edema associated with 3+ proteinuria after achieving remission. Relapse treatment was similar for all patients and included 30-60 mg/m^2/24 hours of initial prednisone, with a gradual taper down to alternate-day dosing after a response for a total duration of 8-10 weeks. When a relapse occurred during the initial treatment, patients were treated for relapse and discontinued the initial protocol.

FRNS and SDNS

FRNS was defined as 2 or more relapses within 6 months after completion of the initial treatment, or 4 relapses within any 12-month period including initial treatment. SDNS was defined as 2 consecutive relapses during prednisone treatment or up to 2 weeks after its cessation.[6]

Nonsteroid Immunosuppression

Mycophenolate mofetil or cyclophosphamide were used as first-line treatment and rituximab as second line. The switch to alternative treatment was usually made after determination of FRNS or SDNS. The use of nonsteroid immunosuppression in our institution has not changed since 2014.

Collected Data

The clinical and laboratory characteristics of all the patients were recorded at the time of diagnosis and included age, sex, anthropometric measurements, blood pressure, and blood and urine laboratory results. After treatment initiation and until remission, clinic visits were scheduled weekly. Visits were scheduled every 3-6 weeks once remission was achieved and subsequently every 3 months until completion of the treatment protocol. The clinical assessment, treatment side effects, anthropometric measurements, and urine tests (urinalysis and UPCR) were repeated at each follow-up visit. Data from the visits at 6, 12, 24, and 36 months after diagnosis and treatment initiation were collected for the purpose of this study. The cumulative steroid dose for the entire initial therapy was calculated for every patient. The cumulative steroid dose for each relapse treatment course was calculated as well.

Outcomes

The feasibility objectives included consent rate and retention, and the occurrence of relapse during the faster prednisone taper down of the initial treatment prompting discontinuation of the intervention protocol. The treatment efficacy outcomes were time to relapse, the occurrences of FRNS and SDNS, the number of relapses per year, and the need for steroid-sparing therapies. The safety outcomes were steroid-related adverse effects leading to its discontinuation or to switching to an alternative therapy. These included weight gain, growth failure/failure to gain height, hypertension (defined as systolic or diastolic blood pressure ≥95th percentile for sex, age, and height), cataract, glaucoma, severe infections (defined as non-self-limiting or invasive bacterial infections requiring hospitalization), and parent-reported behavioral changes. Occurrences of FRNS and SDNS were selected as primary outcomes; other outcomes, together with cumulative prednisone use (in mg/kg per year), were secondary. All the outcomes were assessed at 6, 12, 24, and 36 months after the diagnosis.

Statistical Analysis

Data are expressed as percentage, mean and standard deviation, and median and IQR for nonparametric variables. For baseline characteristics, we compared distributions of continuous variables between groups using the Welch t test or Wilcoxon rank test, depending on the shape of the distribution. We analyzed categorical variables using the χ^2 test or Fisher's exact test. P values were two-tailed and were considered statistically significant at the 0.05 alpha level.

To describe time periods to FRNS, SDNS, first relapse, and alternative treatment, the Kaplan-Meier method and log-rank test were used. For these outcomes, the Cox proportional hazard model was used to assess the influence of the novel protocol and to estimate hazard ratios (HR) and 95% CI. The model was adjusted for patient sex and diagnosis at under age 3 years, the known risk factors for more severe clinical course as reported in other studies.[7-9,18-20]

For the intervention and usual care groups, the number of relapses per person-year was calculated as the total number of relapses divided by the total observed person-years. A permutation test was used to compare the number of relapses per person-year between groups. All statistical analyses were performed using the R version 4.0.5 (R Foundation).

Ethical Approval and Informed Consent

The study was approved by the Helsinki committee of Rabin Medical Center (RMC-695-15 and RMC-216-14 for the observational part since 2014) and the Israel Ministry of Health (20151637). Written informed consent was obtained from the parents of all the participants.

Results

INS was diagnosed in 57 patients between January 2016 and November 2019. We excluded 11 patients from the analysis (Fig 1). Thirty-four patients were approached for consent to participate in the study and to be treated by the response-adjusted treatment protocol. Considering the 30 patients whose parents gave informed consent, the consent rate was 88% in the intervention group.

During 2014-2015, there were 26 patients diagnosed with nephrotic syndrome and treated with the standard KDIGO protocol; 5 were excluded from the analysis, and 21 were included in the usual care group (Fig 1). Also, INS was diagnosed in 16 patients during 2016-2019 who were considered members of the usual care group: 4 patients whose parents refused their receiving the study treatment protocol and 12 patients who transferred to our hospital after starting the standard KDIGO treatment protocol in other hospitals. Thus, the usual care group comprised 37 patients.

Thirty-two of 37 patients in the usual care group and 27 of 30 in the intervention group responded to treatment within 8 days after initiation of steroid therapy and were analyzed for the study outcomes. The groups did not differ in demographic, clinical, and laboratory characteristics at the time of diagnosis (Table 1).

All but 1 patient in the usual care group were evaluated for more than 2 years; 27 of 32 completed the entire

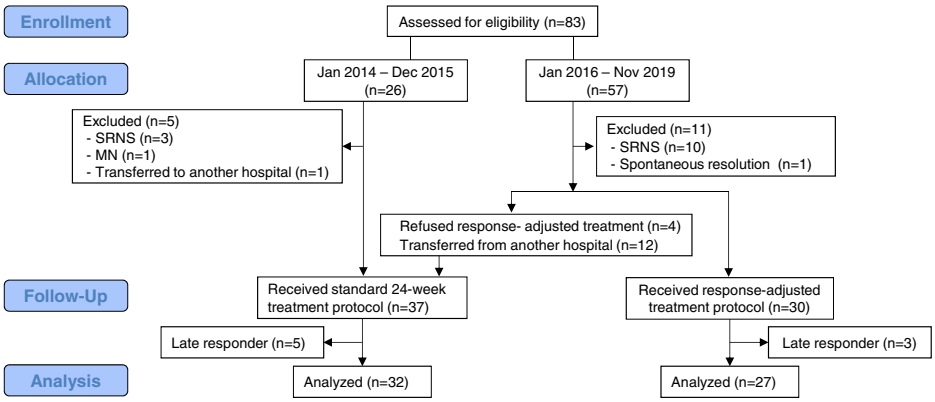

Figure 1. Flow chart of the patients included in the study. Abbreviations: MN, membranous nephropathy; SRNS, steroid-resistant nephrotic syndrome.

3-year follow-up period. Twenty-six of 27 patients in the intervention group were evaluated for more than 2 years, and 17 completed the 3-year follow-up period.

No occurrences of relapse were observed in the intervention group during the 8-week treatment protocol. Ten patients in the usual care group relapsed during the initial treatment protocol. Three of them relapsed 6 weeks after initiation of the treatment protocol and the rest, at 8 weeks or later, while on a low-dose of prednisone.

For the intervention and usual care groups, the starting prednisone dosages for body weight and surface area were similar (Table 2). The cumulative prednisone dose received was significantly lower in the intervention than the usual care group both during the initial course (mean of 70 vs 141 mg/kg; $P < 0.001$; Table 2) and during the first year (median of 105 [95% CI, 73-203] vs 198 [95% CI, 147-291]) mg/kg total; $P < 0.001$; Table 3), respectively. The median cumulative doses of steroids received in the first year, as relapse treatment after the initial treatment protocol, were 36 (95% CI, 0-140) and 85 (95% CI, 0-151) mg/kg for the intervention and usual care groups, respectively ($P = 0.4$). The steroid dose ratio (based on steroids per kilogram per person-year) was 0.78 (95% CI, 0.29-1.27) for the intervention group relative to the usual care group (Table 4).

The proportions of relapse-free patients over 36 months of follow-up evaluation were similar in the 2 groups ($P = 0.5$; Fig 2). There were no events competing with the first relapse or other clinical outcomes. The proportions of patients who relapsed in the intervention group compared with the usual care group were 72% versus 67% ($P = 0.7$), 77% versus 77% ($P = 0.9$), and 81% versus 71% ($P = 0.5$) at 12, 24, and 36 months' follow-up, respectively (Table 3).

Table 1. Baseline Characteristics

Characteristic	Intervention Group (n = 27)	Usual Care Group (n = 32)	*P*
Male sex	20 (74%)	21 (66%)	0.5
Age at onset, y			0.1[a]
Median	6.06 [3.61-6.91]	3.83 [2.41-5.17]	
Mean	5.61 ± 2.21	4.52 ± 3.12	
Febrile at onset	7 (26%)	10 (31%)	0.7
Acute kidney injury	2 (7%)	1 (3%)	0.6
Hypertension	1 (4%)	2 (6%)	0.3
Weight percentile	50 [21-88]	60 [30-76]	0.9
Height percentile	20 [10-78]	30 [18-60]	0.9
BMI, kg/m^2	15.91 [15.37-17.57]	16.31 [15.45-18.27]	0.7
BMI percentile	63 [38-90]	60 [44-82]	0.7
UPCR, mg/mg	7 [5.1-10.6]	10.0 [6.4-14.2]	0.1
eGFR, mL/min/1.73 m^2	160 [136-202]	150 [132-188]	0.6
Serum albumin, g/dL	1.7 [1.6-1.80]	1.6 [1.4-1.8]	0.4
Serum cholesterol, mg/dL	391 ± 114	367 ± 99	0.4
Hemoglobin, g/dL	13.26 ± 0.95	12.96 ± 1.4	0.3

Values for continuous variables given as mean ± SD or median [IQR]. Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; UPCR, urinary protein-creatinine ratio.
[a]Welch *t* test.

Table 2. Details of Therapeutic Intervention

	Intervention Group (n = 27)	Usual Care Group (n = 32)	P[a]
Initial steroid dose, mg/kg			0.9
Mean	2.35 ± 0.29	2.31 ± 0.41	
Median	2.35 [2.15-2.57]	2.42 [2.18-2.62]	
Initial steroid dose, mg/m^2			0.08
Mean	60 ± 5	57 ± 7	
Median	60 [56-62]	59 [53-62]	
Induction treatment duration, wk			<0.001
Mean	8.4 ± 1.1	19.0 ± 5	
Median	8.00 [8-8]	20.0 [15.8-23.2]	
Days to response			0.9
Mean	6.67 ± 1.0	6.47 ± 1.50	
Median	7 [6-7]	7 [6-7]	
Induction therapy cumulative dose, mg/kg			<0.001
Mean	70 ± 10	141 ± 38	
Median	69 [62-75]	138 [122-161]	
Induction therapy cumulative dose, mg/m^2			<0.001
Mean	1,771 ± 223	3,479 ± 830	
Median	1,745 [1,625-1,864]	3,402 [3,037-3,836]	

Values given as mean ± SD or median [IQR].
[a]Wilcoxon rank test.

The proportion of patients with FRNS at 12 months' follow-up was 22% in the intervention group versus 44% in the usual care group (P = 0.08; Table 3). At 24 months and 36 months' follow-up, the proportions of patients with FRNS were comparable in the intervention and usual care groups: 42% versus 48% (P = 0.7) and 47% versus 48% (P = 0.9), respectively. The rates of SDNS at 12 months' follow-up were 26% and 53% in the intervention and usual care groups, respectively (P = 0.03). At 24 months' and 36 months' follow-up, the proportions of

Table 3. Outcomes at 12-, 24-, and 36-Months of Follow-up

	Intervention Group	Usual Care Group	P[a]
12 months of follow-up			
No. of patients	27	32	
Relapsed	18 (67%)	23 (72%)	0.7
FRNS	6 (22%)	14 (44%)	0.08
SDNS	7 (26%)	17 (53%)	0.03
Cumulative steroids per year, mg/kg	105 [73-203]	198 [147-291]	<0.001
Cumulative steroids in the first year excluding the initial therapy, mg/kg	36 [0-140]	85 [0-151]	0.4
Alternative treatment	4 (15%)	13 (41%)	0.03
24 months of follow-up			
No. of patients	26	31	
Relapsed	20 (77%)	24 (77%)	0.9
FRNS	11 (42%)	15 (48%)	0.7
SDNS	11 (42%)	18 (58%)	0.2
Cumulative steroids per year, mg/kg	28 [0-92]	20 [0-112]	0.7
Alternative treatment	10 (38%)	14 (45%)	0.6
36 months of follow-up			
No. of patients	17	27	
Relapsed	12 (71%)	22 (81%)	0.5
FRNS	8 (47%)	13 (48%)	0.9
SDNS	7 (41%)	16 (59%)	0.2
Cumulative steroids per year, mg/kg	0 [0-0]	12 [0-38]	0.008
Alternative treatment	8 (47%)	13 (48%)	0.9

Values for steroid dose given as median [IQR]. Abbreviations: FRNS, frequently relapsing nephrotic syndrome; SDNS, steroid-dependent nephrotic syndrome.
[a]Wilcoxon rank sum test; Pearson χ^2 test; Fisher exact test.

Table 4. Number of Relapses and Total Steroid Dose

	Intervention Group	Usual Care Group
Duration of observation, person-years	74.25	91.83
Total no. of relapses	77	120
No. of relapses per person-year	1.04	1.31
Ratio of the no. of relapses (95% CI)	0.79 (0.38-1.20); *P* = 0.3	—
Total steroid dose, mg/kg (initial treatment excluded)	3,292	5,214
Steroid dose, mg/kg per person-year	44.3	56.7
Steroid dose ratio (95% CI)	0.78 (0.29-1.27); *P* = 0.3	—

patients with SDNS were 42% versus 58% (P = 0.2) and 41% versus 59% (P = 0.2) in the respective groups. Figure 3 presents Kaplan-Meier estimates of times to FRNS, SDNS, and alternative treatment. Table 5 presents the univariate HR for each outcome as well as multivariable Cox regression analysis adjusted for sex and age, which showed HRs of 0.89 (95% CI, 0.49-1.63) for the first relapse, 0.80 (95% CI, 0.37-1.73) for FRNS, and 0.61 (95% CI, 0.30-1.27) for SDNS in the intervention relative to the usual care group. Among male compared with female patients, the risks were nominally higher for first relapse, FRNS, and SDNS (HRs of 1.05 [95% CI, 0.56-1.99], 1.96 [95% CI, 0.78-4.9], and 1.46 [95% CI, 0.67-3.18], respectively), but these were not statistically significant. Compared with older patients, for patients younger than 3 years the risks for first relapse and SDNS were significantly higher (HRs of 2.68 [95% CI, 1.41-5.08] and 2.84 [95% CI, 1.37-5.88], respectively); the risk for FRNS was nominally higher though this result was not statistically significant (HR, 1.91 [95% CI, 0.86-4.25]). The number of relapses per person-year during the trial intervention period was 1.04 in the intervention group and 1.31 in the usual care group (ratio, 0.79 [95% CI, 0.38-1.20]; P = 0.3; Table 4).

With the exception of the first year of follow-up, the proportions of patients who received alternative treatment did not differ between the intervention and usual care groups at 24- and 36-months' follow-up: 38% versus 45% (P = 0.6) and 47% versus 48% (P = 0.9) (Table 3). There were no notable adverse effects of prednisone therapy in either group (Table 6), and no significant between-group differences at 12, 24, and 36 months in body mass index (BMI) percentile (P = 0.5, P = 0.5, and P = 0.6, respectively) or height percentile (P = 0.9, P = 0.3, and P = 0.9, respectively). At 12 months' follow-up, 6% of the parents of children in the usual care group and 4% of parents of children in the intervention group (P = 0.9) reported significant behavioral changes. No serious infections requiring hospitalization occurred in either group. In the usual care group, 1 patient had hypertension at 12-months' follow-up, which later resolved.

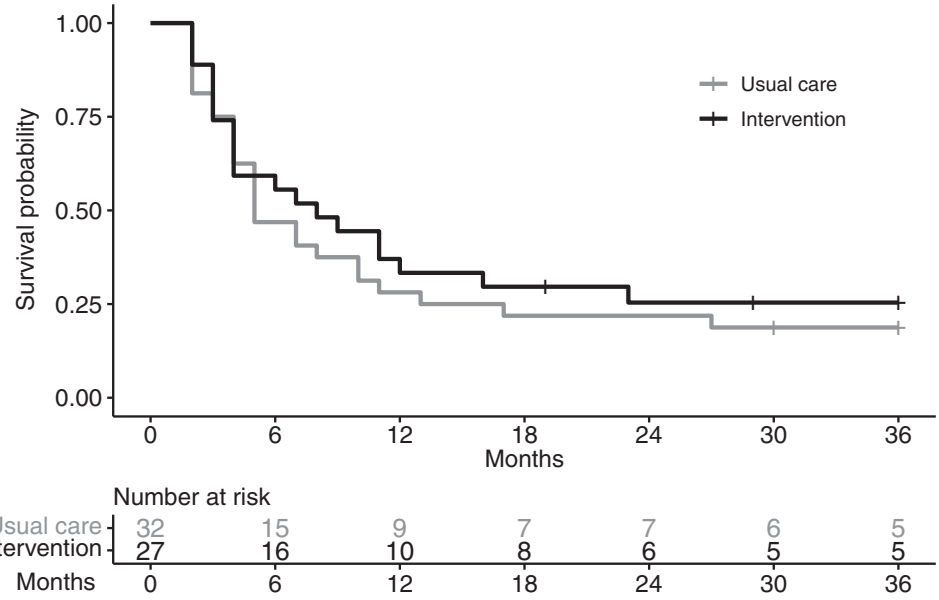

Figure 2. Relapse-free survival. The proportions of patients with sustained remission in the intervention group (treated with a response-adjusted study protocol) and the usual care group (treated with the standard protocol).

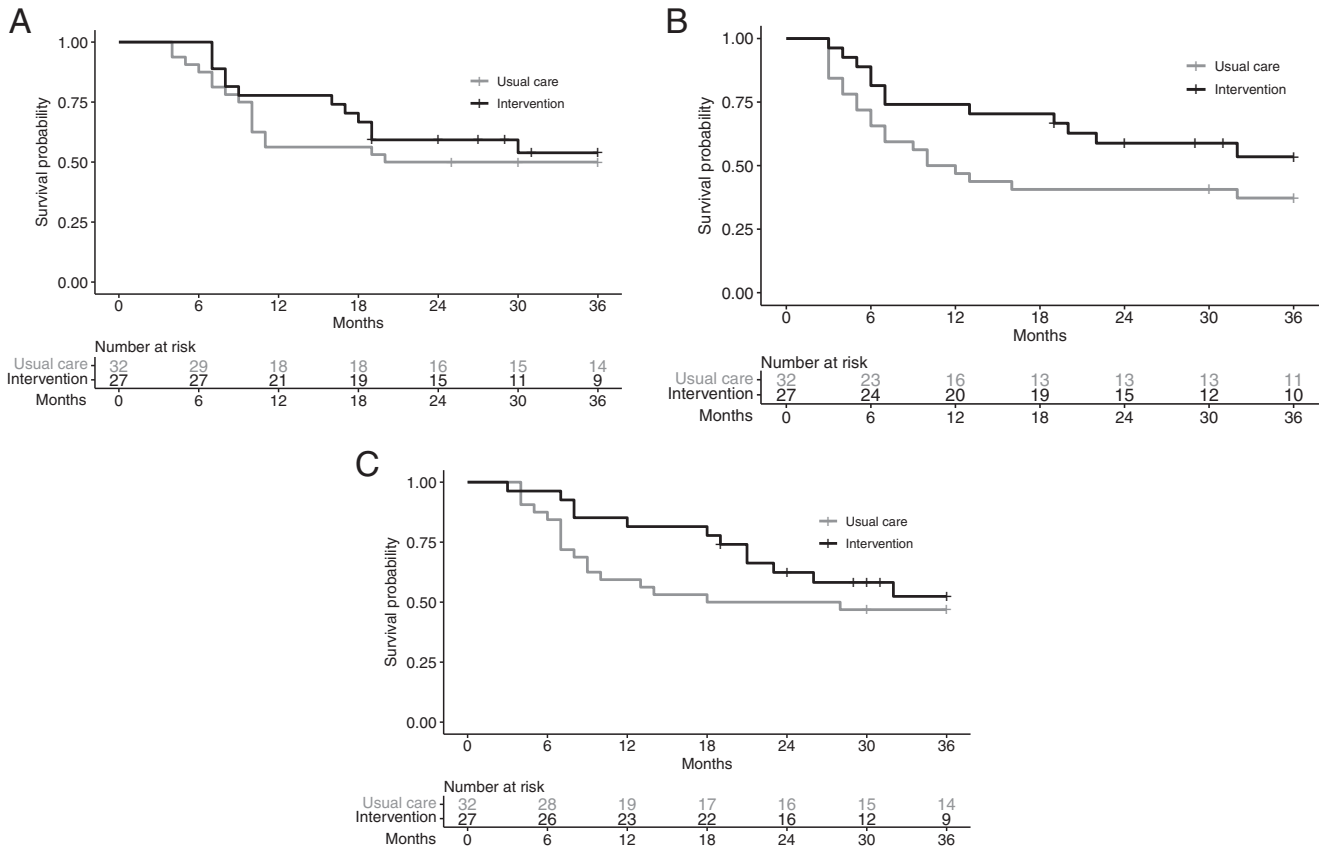

Figure 3. Kaplan-Meier curves for survival probability without (A) frequently relapsing nephrotic syndrome (FRNS), (B) steroid-dependent nephrotic syndrome (SDNS), and (C) the need for alternative treatment.

Based on the results of this study, we calculated the required sample size for the noninferiority test, for assessing HRs for FRNS and SDNS using Bonferroni correction for multiple testing, with a 1.25 margin based on expert opinion. For a one-sided 5% significance level and 70% power, 250 patients are needed in each group.

Discussion

This pilot study addressed the feasibility of a protocol that individualizes treatment of the first episode of INS based on the timing of patient response. The high consent rate for participation was expected because parents are cautious about steroid treatments. This, together with the lack of dropout, may promote the feasibility of larger studies.

None of the patients in the usual care group relapsed during the first 6 weeks of treatment. This corroborates reports of rare relapse events during the first 8 weeks of the fixed high-steroid standard protocol. Importantly, no relapses were observed in the intervention group during the faster taper down of the 8 weeks of the treatment protocol.

The mean cumulative steroid doses during the initial treatment and the first year were significantly lower in the intervention than the usual care group. Sibley et al[21] proposed 2,000-2,500 mg/m^2 as a safe minimal steroid dose for treating a first episode of INS in children. In

Table 5. Effects of Treatment Group, Sex, and Age on Outcomes

	First Relapse	FRNS	SDNS
Univariate analysis			
Intervention vs usual care	0.82 (0.45-1.47)	0.79 (0.38-1.68)	0.57 (0.28-1.16)
Sex: male vs female	0.94 (0.51-1.74)	1.75 (0.71-4.32)	1.18 (0.55-2.55)
Age: ≤3 y vs 3 y	2.70 (1.43-5.10)	1.86 (0.86-4.03)	2.89 (1.42-5.88)
Multivariable analysis[a]			
Intervention vs usual care	0.89 (0.49-1.63)	0.80 (0.37-1.73)	0.61 (0.30-1.27)
Sex: male vs female	1.05 (0.56-1.99)	1.96 (0.78-4.90)	1.46 (0.67-3.18)
Age: ≤3 y vs 3 y	2.68 (1.41-5.08)	1.91 (0.86-4.25)	2.84 (1.37-5.88)

Values given as HR (95% CI). Abbreviations: FRNS, frequently relapsing nephrotic syndrome; HR, hazard ratio; SDNS, steroid-dependent nephrotic syndrome.
[a]Cox analysis adjusted for the treatment group, age, and sex.

Table 6. Corticosteroid-Associated Adverse Effects

	Intervention Group	Usual Care Group	*P*
6 months of follow-up			
No. of patients	27	32	
Height percentile	22 [10-84]	30 [12-56]	0.8
BMI, kg/m^2	16.58 [15.32-18.92]	16.85 [15.74-18.87]	0.5
BMI percentile	70 [32-96]	80 [60-95]	0.5
Serious infection	0	0	
Behavioral changes			0.9
No	21 (78%)	23 (77%)	
Insignificant	6 (22%)	6 (20%)	
Significant	0	1 (3%)	
Hypertension	0	1	0.9
12 months of follow-up			
No. of patients	27	32	
Height percentile	25 [10-75]	40 [18-65]	0.9
BMI, kg/m^2	16.42 [15.20-18.66]	16.50 [15.73-19.10]	0.6
BMI percentile	60 [25-96]	70 [57-95]	0.5
Serious infection	0	0	
Behavioral changes			0.9
No	21 (78%)	26 (81%)	
Insignificant	5 (19%)	4 (12%)	
Significant	1 (4%)	2 (6%)	
Hypertension	0	1	0.9
24 months of follow-up			
No. of patients	26	31	
Height percentile	54 [26-76]	48 [14-64]	0.3
BMI, kg/m^2	16.51 [15.46-17.63]	16.72 [15.46-19.05]	0.4
BMI percentile	62 [29-83]	76 [50-90]	0.5
Serious infection	0	0	
Behavioral changes			0.7
No	19 (83%)	26 (84%)	
Insignificant	3 (13%)	5 (16%)	
Significant	1 (4%)	0	
Hypertension	0	0	
36 months of follow-up			
No. of patients	17	27	
Height percentile	46 [27-65]	45 [15-70]	0.9
BMI, kg/m^2	15.98 [15.11-18.94]	16.20 [15.62-18.46]	0.9
BMI percentile	56 [20-97]	67 [46-90]	0.6
Serious infection	0	0	
Behavioral changes			0.9
No	12 (92%)	25 (93%)	
Insignificant	1 (8%)	2 (7%)	
Significant	0	0	
Hypertension	0	0	

Values for continuous variables given as median [IQR]. Abbreviation: BMI, body mass index.

randomized controlled studies that compared treatment duration protocols, even higher doses of 2,700-3,500 mg/m^2 were used.[8,9] Nevertheless, the mean cumulative induction dose using our protocol was considerably lower (1,771 mg/m^2).

The probability for relapse over 36 months of follow-up as estimated by the complementary probability of Kaplan-Maier estimator was 81% for patients treated with a shorter response-adjusted protocol and 75% for those treated with the standard protocol. within the range of 60%-80% reported in other studies.[1,2,6,8,9,12,22]

The proportions of relapsed patients at each follow-up timing were similar in the 2 groups. The lower proportions of FRNS and SDNS in the intervention compared with the usual care group, albeit not statistically significant and with wide confidence intervals, may be due to the small sample size and younger age at diagnosis in the usual care group. Younger age has been shown to constitute a

risk factor for FRNS and SDNS.[7,18-20] The longer duration of steroid treatment among the patients in the usual care group, who relapsed while on low doses of steroids, could also have contributed to the larger proportion of patients defined as SDNS in the first year. This difference, as expected, was less prominent in the following years. At the end of the follow-up period, the SDNS and FRNS proportions in both study groups were similar to the previously reported data of 40%-50%.[2,5,6,8-10,12,23,24] Male sex and age 3 years and younger were risk factors for worse clinical outcome, corroborating other studies.[7,18-20] A higher proportion of patients in the usual care group received alternative treatment during the first follow-up year due to increased incidences of FRNS and SDNS during this period. No such difference was demonstrated in the subsequent years. The lack of an increased steroid or alternative treatment requirement during the follow-up years is evidence of a lack of difference in the severity of clinical course between the 2 groups.

Our study demonstrated no relapses occurring during the faster taper down and no increased or even similar risks for FRNS and SDNS after implementation of the response-adjusted protocol. These findings support the feasibility of conducting further studies to investigate the efficacy of the protocol.

The lack of difference in adverse effects between the intervention group and the usual care group, which received more than twice the cumulative dose, may be due to the relative rarity of some adverse effects, even with longer corticosteroid treatment protocols, and the small sample size. Though some reports have described steroid-related adverse effects,[25-28] there are a number of studies comparing longer versus shorter steroid protocols that could not demonstrate a difference.[8-10,12,29] We also did not find a decrease in growth velocity or a significant increase in BMI during the follow-up period. At 6 months of follow-up evaluation, however, the median BMI percentile in the usual care group was 20 percentile points higher than at baseline when the 2 groups were similar. No such change was observed for the intervention group. This trend suggests that the lower steroid dose dictated by the response-adjusted protocol may reduce risks of transient corticosteroid-related adverse effects on body mass.

Our study has several limitations. First, although performed prospectively, the study was not randomized or controlled. Second, the small sample size makes valid comparisons between the groups challenging. Nevertheless, the patients of the 2 groups had similar baseline clinical characteristics. The high consent and the lack of dropout are notable and mitigate the possibility of selection bias. A third limitation is the lack of accurate data regarding behavioral changes, which is one of the main concerns of high-dose steroid treatment. A more standardized behavior assessment tool (eg, questionnaire) could be useful in future studies. Fourth, the study was performed in a single center. However, our hospital is a major university-affiliated medical center with about 15 new diagnoses of nephrotic syndrome each year. Finally, given the low rates of steroid-related adverse effects, demonstrating the superiority of the response-adjusted protocol in terms of safety is unlikely even in a larger study.

In conclusion, this pilot study examined a feasibility response-adjusted protocol that dictated a significantly lower cumulative prednisone dose as a possible treatment for children with a first episode of INS who respond early to the initial treatment. The feasibility demonstrated of recruiting participants and performing a trial, and the encouraging descriptive statistics will promote the planning of a larger-scale multicenter study, focusing on efficacy and safety noninferiority of the investigated regimen.

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