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Extended versus standard corticosteroid treatment in primary nephrotic syndrome onset

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ABSTRACT

Introduction. The standard treatment for the onset of primary nephrotic syndrome (PNS) consists of 8 weeks of prednisone. Alternatively, it was postulated that extending treatment to 12 weeks is associated with fewer relapses. We aimed to evaluate whether relapses' cumulative incidence (CI) at 2 years was lower with extended treatment.

Population and methods. This is a retrospective cohort study of patients with PNS who were followed for 2 years and grouped according to the initial treatment received.

Results. Thirty-seven patients were included per regimen. The time to first relapse was similar (p = 0.63), and the CI of relapses at 2 years was 75.6% with standard treatment and 72.9% (p = 0.79) with extended treatment; relative risk was 0.96 (95%CI 0.73-1.26). Relapse-free survival in the 2 years of follow-up was also similar (log-rank test = 0.51).

Conclusion. Relapse CI at 2 years was similar with both treatment regimens.

Keywords: *nephrotic syndrome; corticosteroids; duration of therapy; pediatrics.*

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INTRODUCTION

Primary nephrotic syndrome (PNS) is the most common glomerular pathology in pediatrics, with a worldwide incidence of 1.5-16.9 per 100,000 children per year.[1] In 1960, it was proposed an initial treatment with corticosteroids for 8 weeks (prednisone 2 mg/kg/day for 4 weeks and then 1.5 mg/kg on alternate days for 4 weeks), which has been universally accepted and continues to be used in many countries, including ours.[1,2] However, since 80% of patients responding to the initial regimen (steroid-sensitive) have relapses, some years later it was proposed to extend this regimen to 12 weeks (2 mg/kg/day 6 weeks + 1.5 mg/kg on alternated days for 6 weeks), to consolidate the remission.[3] Nevertheless, many studies comparing these schemes presented contradictory results and methodological deficiencies. On the other hand, the latest update of the *Kidney Disease: Improving Global Outcomes (KDIGO) 2024* guidelines states that there is not enough evidence to choose between 8 and 12 weeks of treatment and, in the same line, the consensus on the nephrotic syndrome of the Sociedad Argentina de Pediatría proposes the use of both schemes interchangeably.[2,4]

The primary objective of this study was to assess whether the cumulative incidence (CI) of relapses at 2-year follow-up in patients who were initially treated with the extended course (12 weeks) was lower than that of patients receiving the standard (8 weeks). Secondly, we analyzed whether the extended treatment decreased the time to the first relapse and its impact on the course of the disease.

POPULATION AND METHODS

Design and study population

Retrospective cohort study of patients with PNS. Given that since the start of extended treatment as a therapeutic option, both schemes have been used interchangeably in our service, we reviewed the medical records of patients with PNS who had completed 2 years of follow-up until January 2020. Patients were selected consecutively from this date backward until the sample size was collected, taking the day of the debut as the start date of admission to the cohort for each patient. Inclusion criteria: age 1 to 16 years at debut and a minimum follow-up of 2 years. Exclusion criteria: pre-onset treatment with corticosteroids or other immunosuppressants, secondary NS indicators, corticosteroid-resistant patients, and those biopsied with histology incompatible with PNS.

Variables of study

The exposure variable was the treatment received in the first episode: 1) standard regimen (prednisone 2 mg/kg/day 4 weeks + 4 weeks 1.5 mg/kg on alternate days), or 2) extended schedule (treated at similar doses for 6 weeks continuous and 6 on alternate days). The event of interest was the relapse and the end of follow-up was 2 years after the onset.

Data collection

Data was collected from medical records: age, sex, dose of prednisone (or its equivalent) received, treatment duration (days), time to first relapse (days), number of relapses, use of other immunosuppressive agents, side effects of corticosteroids and histological findings (if renal biopsy was performed).

DEFINITIONS

PNS: Hypoalbuminemia and massive proteinuria in the absence of secondary NS indicators.[2]

Relapse: Proteinuria ≥++ on urine dipstick or urinary protein creatinine ratio ≥2, without infección.[2]

Corticosteroid sensitivity: Remission of proteinuria for 3 consecutive days.[2]

Frequent relapse: >2 relapses in 6 months or >3 in 1 year.[2]

Corticosteroid dependence: 2 consecutive relapses when corticosteroids are lowered or within the 2 weeks after suspension.[2]

Statistical considerations

Since a 30% lower relapse CI was reported with the extended scheme,[3,5] 37 patients per group (80% power, confidence 95%) were necessary to show this difference. This group size was also sufficient for the secondary objective, as the average time to first relapse was 134 days with standard treatment and 222 with extended,[5] 19 patients per group (80% power, 95% confidence) were needed to detect this difference. Continuous variables had no normal distribution (Shapiro-Wilk) and were expressed as median (interquartile range). Categorical variables were given as frequency of presentation and percentage. The comparison between groups was performed with the Wilcoxon, chi^2, or Fisher's exact test, as appropriate. Relapse CI was estimated at 2 years for both groups with its relative risk. Survival (relapse-free survival)

was analyzed using the Kaplan-Meier method and compared with the log-rank test. Significance level p <0.05. It was analyzed with Statistix 7®. The Ethics Committee approved the study.

RESULTS

Ninety-five patient records were revised for nephrotic syndrome; of them, 74 were eligible and included in the study (37 for standard treatment and 37 for extended treatment). Both cohorts were comparable in age and sex. The time to remission and the first relapse were similar, as was the number of relapses per patient between treatments in the 2-year follow-up (*Table 1*). Relapse CI at 2 years was 75.6% for the standard treatment group and 72.9% for the extended (p = 0.79); relative risk 0.96 (95%CI 0.73-1.26) (*Table 2*). Relapse-free survival at 2-year follow-up was also comparable (*Figure 1*). The cumulative dose of corticosteroid, course of disease, and requirement for other immunosuppressants were also similar (*Table 1*). Biopsies were performed on two patients in the standard group (both with minimal change disease) and four in the long-term group (two were mesangial proliferative glomerulopathies and two were focal and segmental sclerosis). The presence of adverse events could not be analyzed because of inconsistent data input in medical records.

DISCUSSION

The main finding of this study was that relapse CI at 2-year follow-up was similar in both cohorts. Ehrich and colleagues observed, for the first time in 1993, that the extended scheme significantly decreased the relapse rate, achieving a sustained remission of 49% at 2-year follow-up.[3] These results encouraged using the extended scheme

Table 1. Characteristics of patients at the onset of primary nephrotic syndrome and effects of standard versus extended corticosteroid treatment in the course of the disease

Variable	Standard treatment (n = 37)	Extended treatment (n = 37)	*p*-value
Age. years	4 (2.83-6.12)	3.83 (2.58-5.7)	0.57
Male sex, n (%)	22 (59.5)	20 (54.1)	0.63
Time to remission, days	13.5 (8-18)	12 (9.5-18.5)	0.98
Time to first relapse, days	80 (49-171.5)	102.5 (57.2-172)	0.63
Prednisone dose	4040 mg/m² (2951-8483)	5151.5 mg/m² (4033.75-8143.75)	0.36
Number of relapses	3 (1-5)	3 (0-4.5)	0.28
Clinical course at 2 years, n (%)			
Single episode	8 (21.7)	12 (32.5)	0.29
Infrequent relapses	13 (35.1)	10 (27)	0.45
Frequent relapses/corticosteroid dependency	16 (43.2)	15 (40.5)	0.28
Patients treated with other immunosuppressors, n (%)			
Cyclophosphamide	13 (35.1)	11 (29.7)	0.8
> 1 drug	-	3 (8.1)	

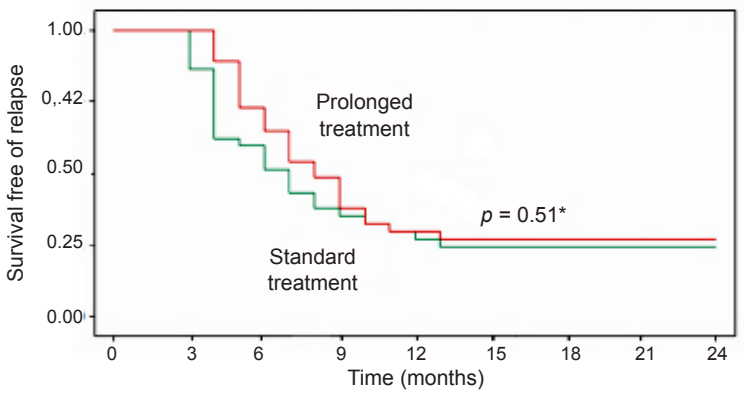
Continuous variables are expressed as median and interquartile intervals, and categorical variables as frequency of presentation (n) and percentage (%).
n: number.

Table 2. Number of relapses in patients with primary nephrotic syndrome at 6, 12 and 24 months according to the duration of initial corticosteroid treatment

Time	Standard treatment (n = 37)		Extended treatment (n = 37)		*p*-value	Relative risk (95% CI)
	Relapse	No relapse	Relapse	No relapse		
0-6 months	18 (48.6%)	19 (51.4%)	13 (35.1%)	24 (64.9%)	0.23	0.72 (0.41-1.25)
>6-12 months	27 (72.9%)	10 (27.1%)	26 (70.2%)	11 (29.8%)	0.79	0.96 (0.72-1.28)
>12-24 months	28 (75.6%)	9 (24.4%)	27 (72.9%)	10 (27.1%)	0.79	0.96 (0.73-1.26)

95% CI: 95% confidence interval, n: number.

Figure 1. Relapse-free survival at 2-year follow-up in patients with primary nephrotic syndrome according to the duration of initial corticosteroid treatment



**Log-rank test.*

in many centers; however, subsequent studies showed mixed results. As seen in *Table 3*, which shows the published studies, those who did not find differences between the two treatments predominate.[3,6-11] In addition, a recent meta-analysis found a higher relapse rate with the standard scheme during the first year of follow-up, at 2 years was similar.[12] Notably, this meta-analysis also revealed that the remission rate with extended treatment was markedly lower (23%) than that reported in the pivotal Ehrich study (49%).[3,12]

Our results support the observations that indicate no benefit with the long-term treatment.[6-8,10-12] Remission CI was similar both at 1-year and at 2-years of follow up. Latency until the first relapse was also similar with both treatments, according to the findings of other authors.[3,10] Therefore, this study reinforces that the extended schedule at the beginning does not modify the evolution of PNS. In addition, since different studies that evaluated even longer treatments (> 12 weeks) did not demonstrate benefit,[1,5,13] the initial 8-week scheme seems to be sufficient.

This study provides information on the subject

Table 3. Studies that evaluated the effect of standard and early extended corticosteroid treatment in patients with primary nephrotic syndrome

Authors	Year	Number of patients (standard vs. extended)	Design	Follow-up	Primary result	Therapeutic benefit with the extended scheme
Ehrich et al.[3]	1993	37 / 34	Clinical trial	2 years	Relapsed after 2 years 81% (standard) vs. 51% (extended); p <0.05	Yes
Ksiazek et al.[6]	1995	44 / 68	Clinical trial	2 years	Relapsed after 2 years 27.3% (standard) vs. 20.6% (extended); p >0.05	No
Norero et al.[7]	1996	27 / 29	Clinical trial	18 months	Relapsed after 18 months 78% (standard) vs. 69% (extended); p = 0.77	No
Lande et al.[8]	2001	82 / 69	Retrospective cohort	1 year	Relapsed one year after 84.1% (standard) vs. 72% (extended); p = 0.08	No
Moundekhel et al.[9]	2012	46 / 46	Clinical trial	1 year	Relapsed after one year 72% (standard) vs. 30% (extended); p = 0.026	Yes
Paul et al.[10]	2014	31 / 41	Clinical trial	1 year	Relapsed after one year 64.5% (standard) vs. 73.2% (extended); p = 0.696	No
Lucchetti et al.[11]	2023	61 / 66	Retrospective cohort	2 years	Relapsed after 2 years 90.1% (standard) vs. 83.9% (extended); p = 0.079	No
This study	2024	37 / 37	Retrospective cohort	2 years	Relapsed after 2 years 75.6% (standard) vs. 72.9% (extended); p = 0.79	No

from our country. This is relevant because genetic implications in PNS due to minimal change disease have recently been recognized, which may limit the extrapolation of results from populations with different genetic background.[14] Additionally, histology was compatible with PNS in the few biopsied patients, confirming an adequate classification of the patients included. Among its limitations, given the retrospective nature, the selection of the scheme used was based on the treating physician's criterion; to minimize possible selection bias, we include all patients consecutively instead of considering the treating professional. Although the cumulative dose of corticosteroids was similar at 2 years between both groups, consistent with what other authors observed,[11] we could not evaluate the presence of adverse effects due to lack of adequate records in clinical histories. Despite this, we emphasize the importance of systematic evaluation of steroid toxicity in these patients.

CONCLUSION

Both treatment regimens had similar relapse CI at 2 years. However, no benefit was observed regarding relapse-free survival, disease course, or cumulative corticosteroid dose. Prospective studies with more patients and more extensive follow-up will allow definitive conclusions to be drawn. ■

REFERENCES

1. Webb NJA, Woolley RL, Lambe T, Frew E, Brettell EA, Barsoum EN, et al. Long-term tapering versus standard prednisolone treatment for the first episode of childhood nephrotic syndrome: phase III randomized controlled trial and economic evaluation. *BMJ*. 2019;365:l1800.
2. Comité de Nefrología, Sociedad Argentina de Pediatría. Consenso de tratamiento del síndrome nefrótico en la infancia. *Arch Argent Pediatr*. 2014;112(3):277-84.
3. Ehrich JH, Brodehl J. Long versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Arbeitsgemeinschaft für Pädiatrische Nephrologie. *Europ J Pediatr*. 1993;152(4):357-61.
4. Kidney Disease Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2024 Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children. Public Preview Draft. [Accessed on: May 5, 2024]. Available at: https://kdigo.org/wp-content/uploads/2024/04/KDIGO-2024-Nephrotic-Syndrome-in-Children-Guideline-Public-Review-Draft.pdf
5. Bagga A, Hari P, Srivastava RN. Prolonged versus standard prednisolone therapy for initial episode of nephrotic syndrome. *Pediatr Nephrol*. 1999;13(9):824-7.
6. Ksiazek J, Wyszyńska T. Short versus long initial prednisone treatment in steroid-sensitive nephrotic syndrome in children. *Acta Paediatr*. 1995;84(8):889-93.
7. Norero Vodnizza C, Delucchi BMA, Lagos Rodríguez E, Rosati MP. Cuadro inicial del síndrome nefrósico primario del niño: evaluación a 18 meses de dos esquemas de tratamiento con prednisona. *Rev Med Chil*. 1996;124(5):567-72.
8. Lande MB, Gullion C, Hogg RJ, Gauthier B, Shah B, Leonard MB, et al. Long versus standard initial steroid therapy for children with nephrotic syndrome. A report from the Southwest Pediatric Nephrology Study Group. *Pediatr Nephrol*. 2003;18(4):342-6.
9. Moundekhel S, Khan GS, Afridi U. Management of Nephrotic Syndrome: ISKDC versus APN. *PJMHS*. 2012; 6(1):212-5.
10. Paul SK, Muinuddin G, Jahan S, Begum A, Rahman MH, Hossain MM. Long versus standard initial prednisolone therapy in children with idiopathic nephrotic syndrome. *Mymensingh Med J*. 2014;23(2):261-7.
11. Lucchetti L, Gatto A, Gianviti A, Vivarelli M, Emma F, Massella L. Treatment of idiopathic nephrotic syndrome at onset: a comparison between 8- and 12-week regimens in everyday clinical practice. *Pediatr Nephrol*. 2023;38(7):2101-6.
12. Schijvens AM, Teeninga N, Dorresteijn EM, Teerenstra S, Webb NJ, Schreuder MF. Steroid treatment for the first episode of childhood nephrotic syndrome: comparison of the 8 and 12 weeks regimen using an individual patient data meta-analysis. *Eur J Pediatr*. 2021;180(9):2849-59.
13. Yoshikawa N, Nakanishi K, Sako M, Oba MS, Mori R, Ota E, et al. A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment. *Kidney Int*. 2015;87(1):225-32.
14. Dufek-Kamperis S, Kleta R, Bockenhauer D, Gale D, Downie ML. Novel insights in the genetics of steroid-sensitive nephrotic syndrome in childhood. *Pediatr Nephrol*. 2021;36(8):2165-75.