RESEARCH PAPER

Levamisole in Frequently-relapsing and Steroid-dependent Nephrotic Syndrome

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Objectives: To evaluate the efficacy of levamisole in children with frequently relapsing nephrotic syndrome (FRNS) and steroid dependent nephrotic syndrome (SDNS) when administered on an alternate day ('initial therapy' in all cases) or daily basis ('rescue therapy' in whom alternate day therapy failed). **Methods:** The records of 95 children (age 1-18y) with FRNS (62) and SDNS (33), who were treated at the Pediatric nephrology clinic, and received levamisole therapy (maximum 2 y duration, between 2010-2013) with a follow-up period of minimum 1 y, were included. **Results:** Alternate day levamisole therapy was efficacious in 73.7% (*n*=70). The overall efficacy of levamisole therapy was 88.4% (*n*=84). Levamisole therapy decreased the mean (SD) number of relapses from 4.22 (0.46)/y to 1.35 (0.36)/y (*P*<0.01); and cumulative median (IQR) prednisolone dosage from 4200 (3200–4300) mg/m^2 to 1100 (IQR 500–2900) mg/m^2 (*P*<0.001). On a one-year follow up of the cases in whom levamisole therapy was efficacious during therapy (median 24 mo) (*n*=84), a frequently relapsing or steroid dependent course continued to persist in 48.8% (41), necessitating oral cyclophosphamide (*n*= 22) or mycophenolate mofetil (*n*=19). **Conclusions:** Daily levamisole therapy was useful in 56% of children who demonstrated failure while on alternate day levamisole therapy, and could be a useful therapeutic option in FRNS and SDNS.

Keywords: *Corticosteroids, Immunomodulators, Proteinuria, Outcome, Treatment.*

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Of all the children with nephrotic syndrome who experience relapses, approximately 50% will develop frequently-relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS), placing them at risk for steroid toxicity [1]. Levamisole is a common immunosuppressive drug used as a first line steroid sparing agent in the management of FRNS and SDNS [2-5]. There are only few published studies regarding usage of levamisole in FRNS and SDNS from India [2,5]. Most studies and guidelines refer to alternate day levamisole therapy [1,3,5,6]. There is limited information regarding the usage of daily levamisole [2,7]. We conducted this study with the primary objective of evaluating the efficacy of levamisole in SDNS and FRNS children. The secondary objectives were to compare the efficacy of levamisole between SDNS and FRNS children and evaluate its efficacy when administered on daily or alternate day schedules .

Methods

This retrospective record-based study was conducted in May and June 2016 after obtaining approval from the Institute Ethics Committee. We retrieved data from the case records of patients who were initiated on levamisole therapy between 2010-2013, with the last follow-up being completed in March 2016. The records of children aged 1-18 years with FRNS and SDNS who attended the Pediatric nephrology clinic and received levamisole therapy with a follow-up period of 1 year were included. Infantile nephrotic syndrome, congenital nephrotic syndrome and secondary nephrotic syndrome (such as lupus nephritis and IgA nephropathy) were excluded. Waiver of consent was obtained as anonymity of subjects was maintained.

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Definitions for FRNS, SDNS, remission and relapse were as per the Indian Pediatric Nephrology Group guidelines [1]. Other definitions used in the study were adapted from the same reference [1]: success of levamisole therapy: less than 2 relapses over a 6-month period while on alternate or daily levamisole; and failure of levamisole therapy: two or more relapses over a 6-month period while on alternate or daily levamisole.

In children with FRNS and SDNS, following treatment of a relapse, prednisolone was gradually

tapered to maintain the patient in remission on alternate day doses of 0.5-0.7 mg/kg, which was administered for 9-18 months. If the steroid threshold to maintain remission was more than 0.5-0.7 mg/kg prednisolone on alternate days, after induction of remission with prednisolone (2 mg/kg/day), levamisole was administered at a dose of 2-2.5 mg/kg on alternate days for 24 months [1,8]. Co-treatment with prednisolone at a dose of 1.5 mg/kg on alternate days was given for 4 weeks; its dose was gradually tapered at the rate of 0.25 mg/kg every 4 weeks. If there was failure of alternate day levamisole therapy, daily doses of levamisole 2-2.5 mg/kg were administered along with alternate day prednisolone [6]. Total leukocyte count was performed 6-monthly while on levamisole therapy. If there was failure of daily levamisole therapy, oral cyclophos-phamide or mycophenolate mofetil were used.

The cumulative doses of prednisolone and the number of relapses during therapy (and the year preceding the commencement of levamisole therapy) were recorded in a structured proforma. In children in whom levamisole therapy (alternate or daily) was a success, after completion of the 2-year course, the drug was discontinued. The number of relapses over the succeeding year was documented.

Statistical analysis: Data were compared using student t or Mann Whitney U test. Proportions were compared using Chi-square test or Fisher exact test. Data were analyzed using SPSS version 20.

RESULTS

A total of 95 children were included (***Table* I**). In both SDNS and FRNS children taken together, levamisole (alternate day or daily therapy) was effective in 84 (88.4%) children. Children with FRNS showed a better response to levamisole as compared to SDNS (82% *vs* 58%, $P=0.01$). Daily levamisole therapy was successful in 14/25 (56%) children who failed on alternate day levamisole. No adverse effects such as leukopenia, hepatotoxicity, rash or flu-like illnesses were recorded. The mean (SD) threshold of prednisolone for starting levamisole in FRNS was 0.92 (0.14) mg/kg while the corresponding threshold for SDNS was 0.88 (0.17) mg/kg ($P=0.22$).

The relapse rates as well as the cumulative dose of steroids decreased significantly during levamisole therapy ($P<0.01$) (***Table* II**). Overall, there was an increase in relapse rate to a mean of 2.57relapses/year after completion of therapy. In 41/84 (48.8%) of children in whom levamisole therapy was efficacious, the effect of levamisole was not sustained after stopping the drug, and a frequently-relapsing or steroid-dependent course continued to persist necessitating alternative immunosuppressants *viz*. oral cyclophosphamide ($n=22$), and mycophenolate mofetil ($n=19$).

DISCUSSION

Beneficial effects of levamisole in terms of reduction in relapse rates and significantly reduced cumulative dosage of steroids have been documented in published literature [6-14]. A meta-analysis has also documented the efficacy of levamisole [4]. We too found that alternate day levamisole along with initial low dose steroid therapy can be effective in children with FRNS/SDNS (with a better efficacy in FRNS). However, the observation that almost half of the children continue to have a frequently relapsing or steroid dependent course after discontinuation of the drug, implies lack of a

TABLE I CLINICAL CHARACTERISTICS OF CHILDREN WITH NEPHROTIC SYNDROME TREATED WITH LEVAMISOLE ($N=95$)

	FRNS, n=62	*SDNS, n=33*	*P value*
Age at enrolment	8 (61,2.5)	9.5 (5.5,14)	0.30
Age at onset	2.5 (1.9,4)	2 (1.8,4)	0.39
Age at initiation of levamisole	5 (3,8)	6 (3,8)	0.65
Males [*n* (%)]	37 (59.7)	18 (54.6)	<0.001
Duration of Levamisole therapy (mo)			
In children in whom it was efficacious (mo)	24 (12.5,24)	24 (7.8,24)	0.16
In children in whom it was not efficacious (mo)	7 (5.25,8)	6 (6,9)	0.01
Efficacy of alternate day levamisole therapy (%)	82	58	0.01
Overall efficacy of levamisole (daily and alternate therapy) (%)	93.5	79	0.03

Value in median (IQR) unless specified otherwise; FRNS: Frequently relapsing nephtotic syndrome; SDNS: Steroid dependent nephrotic syndrome.

TABLE II RELAPSE RATES AND CUMULATIVE DOSAGE OF PREDNISOLONE BEFORE, DURING AND AFTER LEVAMISOLE THERAPY

	1 year before therapy	*During therapy*	*1 year after discontinuation*
FRNS (n=62)			
No. of relapses per year, mean (SD)	4.21 (0.45)	1.11 (1.18)	2.55 (1.1)*
Cumulative dose of prednisolone, median (IQR) (mg/m^2)	4200 (3125, 5200)	1000 (400, 1400)	2500 (1250, 3900)*
SDNS (n=33)			
No. of relapses per year, mean (SD)	4.24 (0.56)	1.79 (1.58)	4.22 (0.46)#
Cumulative dose of prednisolone, median (IQR) (mg/m^2)	4200 (3500, 5600)	1300 (600, 4250)	3200 (2350, 4500)#
Overall (n=95)			
No. of relapses per year, mean (SD)	4.22 (0.46)	1.35 (0.36)	2.57 (1.06)$
Cumulative dose of prednisolone, median (IQR) (mg/m^2)	4200 (3200, 4300)	1100 (500, 2900)	2800 (1375, 4200)$

*P value <0.01 between the groups (within FRNS, SDNS and the overall subjects); FRNS- Frequently relapsing Nephrotic Syndrome; SDNS-Steroid Dependent Nephrotic Syndrome; *n=51 children (in whom the drug was efficacious); #n=19 children (in whom the drug was efficacious); $n=70 children (in whom the drug was efficacious).*

remnant effect of the drug. Our study also demonstrated that daily levamisole is a feasible and efficacious option in 56% of children who failed alternate day therapy. This is an important observation because current guidelines [1] recommend only alternate day levamisole and advise usage of other alternate immunosuppressants such as oral cyclophosphamide or mycophenolate mofetil in case of alternate-day levamisole failure.

The rationale for usage of daily levamisole is based on the fact that the half-life of levamisole is 5.2 hours [7,11]. Ekambaram, *et al*. [2] reported that daily levamisole was effective in 77.3% of 95 children. Fu, *et al*. [7] in a comparative study between daily and alternate day levamisole usage in children with FRNS and SDNS, reported that daily levamisole usage can be considered when response to alternate day usage is unsatisfactory. La Manna, *et al*. [11] studied the effect of levamisole on 13 FRNS and/or SDNS children. These children were treated with 2.5 mg/kg levamisole twice a week (Cycle A) for 2-16 months (mean 5.8 months). Following failure of the regime, 8 children were given the same dose of levamisole on a daily basis. A clinical improvement was observed in 6 children; 4 with cycle A and 2 with cycle B. The authors noted minimal side effects (*e.g.*, transient neutropenia) in both drug regimes. We did not observe any side-effects attributable to levamisole, similar to the observations of Ekambaram, *et al*. [2]

The study adds valuable information regarding the efficacy of alternate day or daily levamisole therapy. The retrospective nature of the study, however, makes it more susceptible to 'selection bias'. Randomized controlled trials evaluating daily levamisole in comparison to other therapeutic options in children who fail alternate day therapy with levamisole are needed to further validate these results. Nevertheless, based on the observations of our study, it may be prudent to recommend a trial of daily levamisole in children who demonstrate alternate day levamisole therapy failure before switching over to more potentially toxic therapeutic options.

Contributors: EMKS collected the data, was involved in protocol preparations and drafted the manuscript. SK managed the patients, conceptualized the study, reviewed the literature and critically reviewed the manuscript. SB and SM were involved in the management of the patients, performed the statistical analysis, and assisted in drafting the manuscript. All authors contributed to writing the paper and approved the final version of the manuscript.
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WHAT THIS STUDY ADDS?

- Daily levamisole therapy is a useful therapeutic option in nephrotic syndrome with failure of alternate day levamisole therapy.
- About half of children who complete levamisole therapy continue to have a frequently-relapsing or steroid-dependent course after discontinuation of the drug.

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