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ORIGINAL ARTICLE

Viktória Sümegi · Ibolya Haszon · Béla Iványi · Csaba Bereczki · Ferenc Papp · Sándor Túri

Long-term effects of levamisole treatment in childhood nephrotic syndrome

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Abstract The effects of levamisole treatment on long-term outcome were evaluated in a retrospective study of frequently-relapsing (FRNS, *n*=15), steroid-dependent (SDNS, *n*=13), and steroid-resistant (SRNS, *n*=6) nephrotic syndrome in 34 children (21 boys, 13 girls, mean age 5.0±3.4 years) during a 60-month follow-up period. The definition of frequent relapses was ≥4 relapses per year. The current relapse was treated with prednisolone 60 mg/m^2 per day for 4 weeks, then with 40 mg/m^2 every other day for 4 weeks, after which the dose was tapered by 10 mg weekly. >From the beginning of the 5th week, levamisole was introduced at a dose of 2 mg/kg per day. The duration of levamisole treatment was 17±7 months. Before starting levamisole treatment the mean level of proteinuria was 2.17±1.34 g/day and the relapse rate was 4.41/year. By the end of levamisole therapy, proteinuria had fallen to 0.142±0.211 g/day and the relapse rate to 0.41/year. No relapse occurred in 23 of the 34 patients during levamisole treatment. In the 24-month follow-up period after the discontinuation of levamisole, 28 children remained in total remission, while 6 had relapses. The cumulative steroid dose before levamisole therapy was 7,564.4±3,497.1 mg/year and following the introduction of levamisole 1,472.9±1,729.9 mg/year (P<0.0001). We observed reversible neutropenia in 5 patients, but no other side effects were seen. Our findings suggest that in FRNS and SDNS levamisole significantly reduces both the relapse rate and the cumulative steroid dose; therefore, it could be recommended for these patients. In SRNS patients it has also some benefit because proteinuria and the cumulative steroid dose could be reduced significantly.

Keywords Nephrotic syndrome · Levamisole · Prednisolone · Relapse rate · Cumulative steroid dose

V. Sümegi (✉) · I. Haszon · C. Bereczki · F. Papp · S. Túri
Department of Pediatrics,
University of Szeged,
14 Korányi Street, 6721 Szeged, Hungary
e-mail: sumegi@pedia.szote.u-szeged.hu
Tel.: +36-62-545330
Fax: +36-62-545330

B. Iványi
Department of Pathology,
University of Szeged,
Hungary

Introduction

Primary nephrotic syndrome, the most common glomerular disease in children, generally has a favorable long-term prognosis. The goal of treatment is to induce complete remission and to minimize complications, mortality, and therapeutic side effects [1].

About 90% of affected children exhibit an excellent glucocorticoid responsiveness, but most suffer at least one relapse [2]. Histologically, the condition usually corresponds to minimal change nephrotic syndrome (MCNS) [3, 4, 5]. According to the literature, about 40% of the steroid-sensitive (SSNS) cases are frequently relapsing (FRNS) and they commonly become steroid dependent (SDNS) [6]. Steroid resistance (SRNS) develops in 10% of children and many of these exhibit focal segmental glomerulosclerosis (FSGS) [7].

Treatment of the FRNS patients remains a great challenge because they often require prolonged courses of steroids with potential for serious side effects and complications (growth failure, cushingoid obesity, hypertension, osteoporosis, cataracts, and psychological disturbances) [2, 8, 9]. The therapeutic aims are to reduce the rate of relapses, the cumulative dose of corticosteroids, and the incidence of serious complications [10]. Second-line drugs, including cyclophosphamide, chlorambucil, cyclosporin A (CsA), levamisole [11, 12], and recently mycophenolate mofetil, can be used in FRNS [13]. They vary in potency and side effects, and there has been no consensus as to which should be used as the first choice of second-line drug [14, 15, 16].

The effectiveness of cytotoxic therapy depends on the histology of the lesion. The toxicity of cyclophosphamide (2–3 mg/kg per day) [17, 18, 19] and chlorambucil

(0.2 mg/kg per day for 8–12 weeks) [20, 21] is generally mild and reversible, but it includes bone marrow depression, hemorrhagic cystitis, hair loss, infertility, seizures, and, rarely, oncogenesis [20, 21, 22].

CsA (5 mg/kg per day) acts by diminishing the expression of the interleukin-2 receptor at the transcriptional level. The efficacy and toxicity of CsA correlate with its serum concentration. The most common side effects are nephrotoxicity, a transient increase in serum creatinine concentration, a decreased glomerular filtration rate, gingival hyperplasia, hypertrichosis, and gastric discomfort [8, 10, 15]. Therefore it is important to have a safe medication, at least for the relapses of childhood nephrotic syndrome, without the toxicity of steroids and alkylating agents.

Levamisole was originally developed as an antihelminthic drug with a non-specific immunomodulatory effect. It has been hypothesized to normalize deficient cell-mediated immunity [9]. It enhances T-cell responses by stimulating T-cell activation and proliferation, it potentiates monocyte and macrophage functions, including phagocytosis and chemotaxis, and increases neutrophil mobility, adherence, and chemotaxis [23]. In this study we evaluated the effects of levamisole on the number of relapses and the cumulative dose of steroid treatment in FRNS, SDNS, and SRNS patients.

Patients and methods

A retrospective study was made of the medical records of 34 children (21 boys, 13 girls) with FRNS (15/34), SDNS (13/34), or SRNS (6/34) who were admitted to our Department of Pediatrics between January 1998 and January 2003. Their ages at the time of diagnosis ranged between 1.5 and 15 years (median 4.5 years).

Inclusion criteria were age at onset >1 year and <16 years, initial steroid sensitivity, FRNS or SDNS. Exclusion criteria were nephrotic syndrome secondary to other systemic diseases or syndromes and renal histology at onset or subsequently consistent with membranoproliferative or membranous nephropathy.

FRNS was defined as two or more relapses within the first 6 months of the initial episode or four or more relapses during any 12-month period. Steroid dependence was defined as two consecutive relapses occurring during corticosteroid therapy or within 14 days of its cessation. Relapse was defined as proteinuria $\geq$1.0 g/day (40 mg/m^2) for 3 consecutive days. Complete remission was defined as a reduction in urinary protein excretion to 0.1 g/day ($\leq$4 mg/m^2) for 3 consecutive days.

The first 34 patients who were admitted to our department for FRNS, SDNS, or SRNS and were treated with levamisole were included in the study. Renal biopsy was performed in 23 children and showed MCNS in 13, IgM nephropathy in 7, and FSGS in 3. Renal biopsy was not undertaken at the initial presentation in 11 steroid-sensitive children in the absence of risk factors indicative of histology other than minimal change disease. However, renal biopsy was performed prior to the introduction of cytotoxic therapy in children with FRNS or SDNS, or in those who developed steroid resistance. In the SRNS patients, levamisole was introduced following cytotoxic therapy when a new relapse developed and prednisolone was restarted. In the SRNS patients, levamisole was introduced following cytotoxic therapy, when a new relapse developed. Prednisolone was restarted because we wanted to investigate whether these patients would become steroid sensitive with a combined administration with levamisole.

The initial corticosteroid protocol at the start of the disease was prednisolone 60 mg/m^2 daily in two divided doses for 4 weeks, followed by 40 mg/m^2 in a single dose every other day for 4 weeks, the dose then being tapered by 10 mg/week. Relapses were treated with the same protocol. All patients received more than one steroid course; the median was four.

There were 19 patients that received other immunosuppressive therapy before levamisole [9 received cyclophosphamide (2–2.5 mg/kg per day for 8–12 weeks), 10 received chlorambucil (0.2 mg/kg per day for 8 weeks)].

Levamisole was introduced (2 mg/kg per day) after 4 weeks of daily corticosteroid treatment. Following another 4 weeks of alternate-day prednisolone, the dose of steroid was gradually tapered by 10 mg/week. The duration of levamisole treatment was 17±7 months (5–36 months). Levamisole was discontinued for 6 months when leukopenia (white blood cell count $\leq 3\times10^9$/l) occurred and was then restarted.

The level of proteinuria at the time of diagnosis was 4.13±2.51 g/day. Before the start of levamisole treatment, the proteinuria level was 2.17±1.34 g/day, the endogenous creatinine clearance was 108.0±47.7 ml per 1.73 m^2, and the relapse rate was 4.41/year. The cumulative steroid dose before the introduction of levamisole was 7,564.4±3,497.1 mg/year.

The patients were followed monthly. At each visit, besides the clinical assessment, urinalysis, 24-h urinary protein, complete blood count, serum creatinine, and liver function tests were performed. At the start of the study, all patients had a normal creatinine clearance corrected to body surface area, normal liver function tests, and a normal blood count.

Statistical analysis

The clinical data are reported as mean±standard deviation. Statistical analyses included the *t* -test for the comparison of parametric data. The level of statistical significance was taken as $P<0.05$.

Results

Of the 34 patients, 28 had SSNS and 13 of these became steroid dependent. Of the 34, 6 developed SRNS before starting levamisole treatment. The patients showed signs of steroid toxicity, including growth retardation, obesity, hypertension, or osteoporosis. Data on patients in the FRNS, SDNS, and SRNS groups are shown in Tables 1, 2, and 3, respectively.

The duration of levamisole treatment was 5–36 (median 17) months. There were 29 patients that received levamisole for at least 18 months, 5 received levamisole for a shorter period because of leukopenia. Of the 29 children, 23 received levamisole for 18 months; 6 had longer therapy because of relapses. The level of proteinuria was 4.13±2.51 g/day at the time of diagnosis and 2.17±1.34 g/day before the start of levamisole treatment.

During therapy the level of proteinuria fell significantly to 0.128±0.213 g/day ($P<0.0001$) and remained low after the cessation of the levamisole adjuvant therapy (0.134±0.301 g/day).

The relapse rate was 4.41/year before levamisole treatment and 0.41/year during levamisole therapy ($P<0.0001$). No relapse occurred in 23 of the 34 patients during this therapy, while 10 children had one, and only 1 child had two relapses per year. Following the levamisole treatment the relapse rate during the 24-month follow-up

Table 1 Patients with frequently relapsing nephrotic syndrome (FRNS) (*MCNS* minimal change nephrotic syndrome, *IgM NP* IgM nephropathy; *CP* cyclophosphamide)

Patient no.	Sex	Age (years)	Biopsy	Immunosuppression other than prednisolone before levamisole treatment	Proteinuria (g/day)			Cumulative steroid dose (mg)	
					At diagnosis	At start of l evamisole therapy	After levamisole therapy	Before start of levamisole therapy	During levamisole therapy
1	M	5	MCNS	CP	2.3	0.98	0	9,240	0
2	M	3	-	-	2.3	1.8	0.54	4,930	0
3	M	2	-	Chlorambucil	4.1	2.7	0	1,850	0
4	F	4.5	MCNS	-	3.2	2.7	0.01	7,390	3,080
5	F	3.5	MCNS	-	2.1	1.1	0	11,080	0
6	M	3	-	CP	4.8	2.4	0.612	7,390	0
7	F	6	IgM NP	CP	1.5	1.8	0.1	11,090	0
8	F	4	-	-	2.1	0.98	0	8,320	3,080
9	F	5	-	CP	5.0	1.5	0.17	3,080	0
10	M	1.8	-	-	1.5	0.9	0	3,400	1,680
11	F	2.5	-	-	2.1	0.7	0	15,400	0
12	F	5	MCNS	Chlorambucil	8.7	3.5	0	12,320	0
13	M	4.5	MCNS	Chlorambucil	3.7	2.3	0	7,530	4,920
14	M	4.5	-	-	1.7	0.98	0.05	6,460	2,060
15	F	5	-	-	1.4	1.1	0.016	6,080	4,920

Table 2 Patients with steroid-dependent nephrotic syndrome (SDNS) (*MP* methylprednisolone)

Patient no.	Sex	Age (years)	Biopsy	Immunosuppression other than prednisolone before levamisole treatment	Proteinuria (g/day)			Cumulative steroid dose (mg)	
					At diagnosis	At start of levamisole therapy	After levamisole therapy	Before start of levamisole therapy	During levamisole therapy
1	M	6	MCNS	MP, CP	6.0	2.5	0.54	12,320	0
2	M	5	-	-	2.9	1.2	0.1	9,240	3,080
3	M	15	FSGS	-	5.2	2.4	0.36	13,860	5,470
4	F	7	MCNS	Chlorambucil	6.0	2.6	0.01	6,160	0
5	M	1.5	-	-	5.4	3.2	0	3,330	1,100
6	M	14	MCNS	CP	11.16	2.6	0	6,160	1,680
7	M	4	MCNS	Chlorambucil	5.1	2.4	0.1	3,080	0
8	F	6	MCNS	Cholambucil	8.8	6.1	0.02	6,160	0
9	M	4	IgM NP	MP	2.5	2.5	0.4	6,160	3,080
10	M	4.5	IgM NP	CP	4.0	1.15	0.8	6,160	2,800
11	M	5	FSGS	-	10.3	5.8	0.08	6,510	2,050
12	M	5	IgM NP	MP	3.7	4.4	0.2	8,360	2,050
13	M	5	MCNS	-	4.93	2.4	0	5,600	0

Table 3 Patients with steroid-resistant nephrotic syndrome (SRNS)

Patient no.	Sex	Age (years)	Biopsy[a]	Immunosuppression other than prednisolone before levamisole treatment	Proteinuria (g/day)			Cumulative steroid dose (mg)
During levamisole therapy					At diagnosis	At start of levamisole therapy	After levamisole therapy	Before start of levamisole therapy
1	F	1.5	MCNS	Chorambucil	5	3.3	0.02	2,870	0
2	F	1.5	IgM NP	CP	2.5	0.4	0.01	6,660	0
3	M	2	IgM NP	MP, CP	2	0.5	0.024	5,540	3,900
4	M	15	FSGS	Chlorambucil	2.5	1.5	0.15	11,370	2,050
5	M	3	MCNS	Chlorambucil	2.4	1.8	0.32	14,689	3,080
6	M	5.5	IgM NP	Chlorambucil	3.4	1.7	0.18	7,390	0

[a] Patients had a history of MCNS (in patient 4 FSGS). MCNS was combined with IgM NP in patients 2, 3, and 6

was 0.22/year; 28 of the 34 children remained in complete remission and only 6 of them relapsed. The changes in the level of proteinuria and the cumulative steroid dose are shown in Table 4.

In 23 of the 34 children, steroid administration could be stopped and they were in remission on levamisole alone [10]. Of the 34, 11 still needed prednisolone treatment because of relapses and in 1 the treatment was supplemented with CsA.

There were 2 of 15 of the FRNS patients, 6 of 13 of the SDNS patients, and 3 of 6 of the SRNS patients that suffered a relapse during the levamisole therapy. The corresponding rates were 3 of 15 in the FRNS group, 2 of 13 in the SDNS group, and 1 of 6 in the SRNS group 2 years after cessation of levamisole therapy (Table 5).

The endogenous creatinine clearance did not change significantly during the follow-up period, being 108.2±45 before the start of levamisole therapy and 108.0±47.7 ml/min per 1.73 m^2 after its completion. Significant changes were not observed in the electrolyte and liver functions.

During the follow-up period, 5 of our patients developed reversible neutropenia (white blood cell count $\leq 3\times10^9$/l). After normalization of the white blood cell count, the levamisole treatment was restarted. None of our patients developed gastrointestinal, cutaneous, or other side effects [23, 24, 25, 26, 27, 28]. Side effects of glucocorticoid therapy disappeared during the observation period in all patients.

Discussion

One of the most difficult tasks in pediatric nephrology is the care of idiopathic nephrotic syndrome patients with multiple relapses, and the situation is even more difficult in SDNS and SRNS patients. These patients are candidates for treatment with steroid-sparing agents [13, 19, 29, 30].

Attempts to maintain remission and to prevent relapses are associated with certain risks. The immunomodulatory agent levamisole has been used as an adjunctive therapy in such patients [31, 32, 33, 34, 35, 36, 37, 38] as a good alternative to major immunosuppressives [39]. This treatment leads to decreases in the number of relapses and the amount of prednisolone required. Niaudet et al. [32] treated 30 SDNS patients with levamisole for a mean duration of 9.9 months. Almost half of the patients had no relapses, despite the achievement of a significant reduction in the dose of prednisolone.

The British Association for Paediatric Nephrology (BAPN) reported prolonged remission in patients with SDNS given alternate-day levamisole for 16 weeks [36]. However, relapses occurred in the majority of patients after the treatment was stopped. Neuhaus et al. [13] likewise observed that levamisole at a dose of 2.5 mg/kg on alternate days for 6–18 months was effective in inducing remission in more than half of the patients. Bagga et al. [11] suggested that long-term levamisole therapy with low-dose prednisolone can lead to a significant re-

Table 4 The distribution and data of patients with nephrotic syndrome

	FRNS (*n*=15)	SDNS (*n*=13)	SRNS (*n*=6)
Sex (male/female)	9/6	10/3	6/0
Age at diagnosis (years)	3.95±1.25	6.3±3.86	4.75±5.24
Age at start of levamisole therapy (years)	6.67±3.18	9.37±4.1	6.2±5.6
Proteinuria (g/day)			
at diagnosis	3.10±1.95	5.84±2.68	2.96±1.09
at start of levamisole therapy	1.69±0.84	3.02±1.53	1.53±1.05
after levamisole therapy	0.09±0.2**	0.2±0.25**	0.11±0.12*
Cumulative steroid dose			
at start of levamisole therapy	7,704.7±3,707.9	7,165.5±3,115.2	8,086.5±4,256.5
after levamisole therapy	1,316.0±1,860.7**	1,639.2±1,689.1**	1,505.0±1,749.7*

* $P<0.01$, ** $P<0.0001$ vs. start of levamisole therapy

Table 5 Relapses during levamisole therapy and during the follow-up period

	Number of relapsed patients during levamisole therapy	Number of relapsed patients 24 months after levamisole therapy
FRNS (*n*=15)	2	3
SDNS (*n*=13)	6	2
SRNS (*n*=6)	3	1

Table 6 Histopathology and therapeutic response

Histology	During levamisole therapy			24 months after levamisole therapy
	No relapse	1 relapse in 12 months	2 relapses in 12 months	Number of relapses
MCNS (*n*=13)	8	4	1	1
IgM NP (*n*=7)	3	4	-	1
FSGS (*n*=3)	2	1	-	1
Unknown histology (*n*=11)	10	1	-	3

duction in the relapse rate in SDNS patients. In a prospective trial, Donia et al. [38] treated 20 SDNS patients with levamisole for 6 months and followed them for a further 6 months. At the end of the 6-month treatment period, 10 patients were maintaining remission on levamisole alone. At the end of the 12-month study period, 5 patients (25%) were still in remission. Ksiazek and Krynski [40] reported a higher proportion (45.5%) of patients who were able to withdraw from steroids and maintain remission for more than 6 months after levamisole therapy, perhaps because they did not stop levamisole throughout the study. Tenbrock et al. [41] similarly reported a 10-month duration of remission; they may have studied FRNS patients.

Alsaran et al. [17] concluded that levamisole is a good alternative to cyclophosphamide as a second-line agent for FRNS patients. Asiri et al. [16] reported a retrospective comparative study in which levamisole was prescribed as a first steroid-sparing agent for 65 children; disease control was achieved in 30%. They concluded that levamisole is an attractive steroid-sparing agent.

We used approximately double the dose that used in the BAPN study, because they reported a number of relapses after the treatment was stopped. Therefore we decided to use a higher dose. In our study, no relapse occurred in 23 of the 34 patients (FRNS, SDNS, or SRNS) during levamisole treatment, i.e., 67.6% remained in remission, while 10 patients had one and 1 had two relapses in 12 months. In the 24-month follow-up period after discontinuation of levamisole, 28 children remained in total remission and only 6 had relapses, i.e., a remission rate of 82.3%. There were two relapses among the 15 FRNS patients, 6 among the 13 SDNS children, and 3 among the 6 SRNS patients. Although the number of our patients is small, the proportion of relapse-free patients during levamisole treatment is 50% or higher in all three groups. These results are better than previously reported studies. At the same time we recognize that this is a retrospective, non-randomized study and there was no control group.

The small number of patients involved in the study does not allow a reliable statistical analysis of the histological findings and the therapeutic effects during levamisole therapy. Renal biopsy was performed in only 23 of 34 patients. It is therefore difficult to draw any conclusion based on the total population when the histopathology was known in only about 75%. Nevertheless, our MCNS patients and those children with an unknown histology (indicating a clinical presentation that corresponds to MCNS) exhibited a better response to levamisole than those with IgM nephropathy and FSGS (Table 6).

The cumulative steroid dose was significantly lower following the introduction of levamisole treatment. The

positive effect of reducing the steroid dosage may be secondary to the previously given alkylating agents. To investigate this, a prospective study is needed with either the elimination of alkylating agents or with a separate group of patients treated with alkylating agents only versus alkylating agents followed by levamisole. The occurrence of side effects during levamisole treatment was rare. We found reversible neutropenia in 5 patients, but no other side effects.

Overall, therefore, our findings suggest that levamisole significantly reduces the relapse rate and the cumulative steroid dose in children with FRNS and SDNS and is also a beneficial and safe therapy for SRNS patients. Levamisole may have a place in preventing relapse even after courses of alkylating agents, and it may also have some benefit for the treatment of SRNS patients.

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