Levamisole treatment in steroid sensitive nephrotic syndrome

Hammad O. Alshaya, CABP, FRCPCH, *Jameela A. Kari,* MD, FRCP (UK).

ABSTRACT

Objective: To evaluate the effectiveness of levamisole in maintaining remission in children with steroid-sensitive nephrotic syndrome (SSNS) who had a frequent relapsing or steroid-dependant course.

Methods: All children with SSNS who had a frequent relapsing or steroid-dependent course and were treated with levamisole between 1997 and 2001 at King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia were reviewed. All patients were treated by the same steroid protocol used in our unit. Levamisole was considered effective if the patient successfully remained in remission on Prednisolone 0.5 mg/kg/48 hours or less.

Results: Nine children were treated with levamisole (3mg/kg/48 hours) with median (range) age of 6 (3.5-10) years. Seven received levamisole for more than 6 (6-24) months and 2 were excluded because they did not adhere to treatment. Levamisole was effective in 4 patients (57%) with remarkable reduction in the number of relapses and the steroid maintenance dose. Renal biopsy was performed in 4 patients: 2 responders with biopsy findings of minimal change disease (MCD) and mesangioproliferative glomerulonephritis and another 2 non responders with biopsy findings of MCD and focal segmental glomerulosclerosis. No significant side effect was observed.

Conclusion: Levamisole is effective in maintaining remission in steroid SSNS in Arab children and has few side effects.

Keywords: Steroid sensitive nephrotic syndrome, levamisole, remission.

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The most common form of childhood idiopathic nephrotic syndrome (INS) is characterized by minimal change histology (MCNS), which is usually steroid sensitive (SSNS). However subsequent relapses of NS is the usual course of this disease in most patients[1,2] and up to 43% will be frequent relapsers.[3] Treatment of recurrent relapses is often complicated by the toxicity of the therapeutic regimen with corticosteroids and therefore a substantial proportion of steroid sensitive nephrotics will require further immunosuppressive treatment. One or more courses of cytotoxic agent either cyclophosphamide[4] or chlorambucil[5] or prolonged course of cyclosprin[6] has been shown to be effective in reducing the number of relapses and therefore avoiding steroid side effect. However such treatment is hampered with considerable side effects. An alternative immune-modulating agent is levamisole, which was used sporadically with variable success and minimal side effects in the 80's.[7-9] This was followed by randomized studies, which showed the high response rate and significant steroid sparing effect of levamisole.[10-13] In view of the results of these studies, levamisole had been recommended as the treatment of frequent relapsing SSNS and this has led to successful reports from different parts of the world,[14-16] however, to date there is no report of its use in Arab children. We treated a group of children

From the Department of Pediatrics, King Abdul-Aziz University Hospital, Jeddah, *Kingdom of Saudi Arabia*.

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Address correspondence and reprint request to: Dr. Jameela Kari, Associate Professor, Pediatrics Department, King Abdul-Aziz University Hospital, PO Box 80215, Jeddah 21589, *Kingdom of Saudi Arabia*. Tel. +966 (2) 55677904. Fax. +966 (2) 6743781. E-mail: jkari@doctors.org.uk

(mainly Arab) with frequently relapsing SSNS, with levamisole and report the result of its use. We also discuss the difficulty of obtaining the medication by some parents, which resulted in non-adherence to treatment.

Methods. Nine children (6 males and 3 females), suffering from frequently relapsing or steroid dependent INS, aged 3.5-10 years (median 6.5) were treated with levamisole between 1997 and 2001 at King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia. Median (range) age at the onset of the disease was 2.5 (2-7.5) years and median duration of the disease 1.5 (0.5-8 years). All the patients had frequent relapses as defined by 2 or more episodes of nephrosis within 6 months of the initial response or 4 or more within any 12-month period. Some of the patients were steroid dependant with recurrence of nephrosis when the dose of corticosteroids is reduced or within 2 weeks after discontinuation of therapy. Levamisole, at a dose of 3 mg/kg body weight on alternate days, was instituted immediately after induction of remission by daily prednisolone (60mg/m^2/day). Prednisolone was then tapered to alternate days (40mg/m^2/48 hours), and by 2.5-5 mg every 4 weeks while levamisole was continued at the same dose. An attempt was made to stop prednisolone after 4-6 months. Base line blood leukocyte counts were performed at regular 2-month intervals. Neutropenia was defined as a neutrophil count of less than 1,500/mm^3. Relapses that occurred during administration of levamisole were treated with the prednisolone regimen mentioned above while levamisole was continued. Levamisole was considered effective when it was possible to reduce the maintenance dose of prednisolone to less than 0.5mg/kg on alternate days. Levamisole was given for at least 6 months before considering it ineffective, and defined as occurrence of relapse on prednisolone of more than 0.5mg/kg on alternate days.

Results. Of the 9 patients with SSNS, 2 patients had levamisole treatment for less than 6 months because of parental discontinuation as a result of difficulties in obtaining the medicine. A10th patient had levamisole prescribed but he did not receive it as the pharmacist told the parents that it was antihelmintic, another pediatrician who prescribed cyclophosphamide saw the patient. The other 7 patients received levamisole for a median of (range) 12 (6-24) months. Six patients were Arabs and one was Indian. Four of them had a renal biopsy; 2 had minimal change disease (MCD), one mesangioproliferative glomerulonephritis (MePGN) and one focal and segmental glomerulosclerosis (FSGS). Four patients (57%) responded to levamisole therapy: 2 with good response and 2 with partial response (**Table 1**). The first patient had no further relapses while on levamisole, he did not require any maintenance prednisolone for 12 months and he did not have further relapses after stopping the levamisole. The 2nd patient required low dose maintenance prednisolone (0.5mg/kg/48 hours) to keep him off relapses while the 3rd and 4th patients had infrequent relapses despite levamisole and low dose maintenance prednisolone. The remaining 3

Table 1 - Patients' details and response to levamisole.

Race	Age at levamisole treatment (years)	Duration of levamisole (months)	Response	Renal biopsy	Category of response
Arab	8	12	No relapses on no prednisolone	Not done	Good
Arab	4	16	No relapses on prednisolone <0.5mg/kg/48 hours	Not done	Good
Arab	6	15	In-frequent relapses on prednisolone <0.5 mg/kg/48 hours	MePGN	Partial
Indian	10	24	In-frequent relapses on prednisolone <0.5 mg/kg/48 hours	MCD	Partial
Arab	9	6	Frequent relapses on prednisolone <0.5 mg/kg/48 hours	Not done	Failed
Arab	4	7	Frequent relapses on prednisolone <0.5 mg/kg/48 hours	MCD	Failed
Arab	10	7	Frequent relapses on prednisolone <0.5 mg/kg/48 hours	FSGS	Failed

MePGN - mesangioproliferative glomerulonephritis, MCD - minimal change disease, FSGS - focal and segmental glomerulosclerosis

patients did not respond well and continued to relapse frequently despite levamisole and low dose maintenance prednisolone. Renal biopsy was performed on 2 of the non-responders; one had MCD and one had FSGS. All non-responders had a course of cyclophosphamide; the patient with FSGS did not respond and required cyclosporin A to control his recurrent relapses. The patient with MCD had no relapses for 8 months followed by frequent relapses. The option of cyclosporin A therapy was discussed with the parents but they could not afford it and therefore he was maintained on the lowest possible alternate dose of prednisolone with the plan to give him a 2nd dose of cyclophosphamide or chlorambucil if he showed any signs of steroid toxicity particularly growth impairment or sublenticular cataract. The 3rd patient who did not respond to levamisole was assumed to have MCD, was treated with a course of cyclophosphamide and has responded with no further relapses for the last 3.5 years. We did not observe any side effects in any of our patients who received levamisole.

Discussion. We found like others[7-16] that levamisole was effective in maintaining remission and reducing the number of relapses in children with SSNS. It was effective in 57% of all cases and in 50% of Arab children. This is similar to a report from England,[17] while others reported a higher response rate.[14] The response to levamisole was not sustained in most of our patients which is in agreement with previous studies. One patient had sustained remission, which could be explained by levamisole therapy or by the natural spontaneous remission of the disease. Levamisole is a potent antihelmintic with immunomodulatory properties.[18] It has a T cell and macrophage activating effect in vitro without any influence on antibody production.[18-19] It has been used in patients with frequently relapsing or steroid dependent SSNS to achieve sustained remission. Previous studies showed that levamisole administration on alternate days or twice weekly caused a decrease in the number of relapses and the amount of prednisolone required.[7-17] However, it's effect was not sustained as relapses occurred in the majority of cases after the treatment was stopped.[12,17]

Our case series indicates that levamisole alone or in combination with alternate days low dose prednisolone could reduce relapses and maintain remission in children with SSNS. We did not observe in any of our patients any side effect such as neutropenia,[9] rash[20] gastrointestinal upset or convulsions.[21] This is similar to observations from previous studies where minimal side effects were recorded.[10,15] Some of our patients experienced difficulty in obtaining levamisole for long course administration, which reflects the rarity of it's prolonged use by pediatricians and highlights the need to insure the availability of the medicine when it is prescribed to avoid incomplete course as occurred in 2 of our patients. Inadequate explanation regarding the history of the medicine and that it was originally used as an antihelmintic but found to be useful in cases of SSNS resulted in non-adherence to treatment in one patient.

In conclusion, the present case series demonstrates that levamisole therapy reduces the overall relapse rate in Arab children with SSNS and minimizes their dependency to steroids to keep them in remission. However double blind randomized studies are needed to confirm this conclusion.

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