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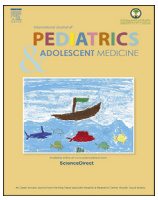

Full length article

Experience with second line drugs in frequently relapsing and steroid dependent childhood nephrotic syndrome in a large Saudi center

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ABSTRACT

Aim and objective: To assess the efficacy and safety of second line drugs used at our center in frequently relapsing and steroid dependant (FR/SD) childhood nephrotic syndrome.
Methods: This was a retrospective study over a period of 3 years (July 2012 to July 2015) on the use of 4 s line drugs in FR/SD nephrotic syndrome in children treated at our center. These drugs were Levamisole, Mycophenolate Mofetil (MMF), Cyclophosphamide and Cyclosporine. We studied the relapse rate per year, cumulative dose of steroids, success and failure and side effects of these drugs. Statistical analyses were done with the help of a statistician using the T-test and the "N-1"Chi–Square test.
Results: We reviewed the charts of 60 children. All had FR/SD nephrotic syndrome. All received a 3 month protocol of prednisolone. 20 received Levamisole (33%), 12 received Cyclophosphamide (20%), 20 received MMF (25%) and 13 received Cyclosporine (22%).
All the four drugs significantly reduced the relapse rate and the cumulative dose of steroids ($P < 0.0001$). Treatment success was best with Cyclosporine (69.2%) and treatment failure was the least with Cyclosporine (7.6%). However treatment success and failure with Cyclosporine when compared to other three drugs, was not statistically significant. No dangerous side effects were seen with any of the 4 drugs in the observation period.
Conclusion: All the second line drugs in our study were equally effective. However, we recommend that the initial treatment of FR/SD nephrotic syndrome should be chosen with the least toxic yet equally efficacious drug Levamisole.

1. Introduction

Idiopathic nephrotic syndrome (INS) occurs commonly between the ages of 1–6 years. The sex ratio is usually 2:1. The annual incidence of INS in children in USA and Europe has been estimated to 1–3 per 100,000 children below the age of 16 with a cumulative prevalence of 16 per 100,000 children [1]. Histopathologically it could be minimal change, diffuse mesangial proliferation or focal and segmental glomerulosclerosis. The International Study of Kidney Disease in Children (ISKDC) found minimal change in 76.6% of children with primary nephrotic syndrome [1].

90% of INS are steroid responsive and 10% are steroid resistant. Among the steroid responsive cases, 30% are cured after the initial episode, 10% are infrequent relapsers and 60% are either frequent relapsers or steroid dependant or both [2]. This group of frequent relapsers and steroid dependant idiopathic nephrotic syndrome required repeated courses of corticosteroids which predisposes them to side effects of steroids such as stunted growth, hypertension, hyperglycemia, gastric hyperacidity and ulceration, osteoporosis and metabolic bone disease.

In order to avoid steroid toxicity certain second line drugs have been used. These are Levamisole, Cyclophosphamide, Mycophenolate mofetil, Cyclosporine, Tacrolimus and Rituximab.

Levamisole is an immunostimulant and immunomodulator. It is

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quite effective in reducing the relapse rate but after stopping it the relapses start occurring again. The most common side effect is reversible neutropenia. But, its long-term safety is not well established. Oral cyclophosphamide is an alkylating agent which effectively suppresses the T-cells. But because of its serious side effects like bone marrow suppression, gonadal toxicity and cancer it is used with caution (not exceeding the cumulative dose). Mycophenolate mofetil is a T-cell immunosuppressant. Its efficacy is dose dependant. A higher than the recommended dose is more effective in reducing the relapse rate. But, its main drawback is that the relapses start occurring again as soon as it is stopped. Its main side effect is diarrhea.

Calcineurin inhibitors (cyclosporine and tacrolimus) are effective T-cell immunosuppressants. They have a higher efficacy than the other previously mentioned drugs but they carry serious side effects like nephrotoxicity, neurotoxicity, hypertension, hyperglycemia and diabetes mellitus. Also, the patient relapses as soon as these drugs are stopped.

Recently several reports described the efficacy and safety of rituximab in FR/SD INS. Rituximab is an anti-CD20 chimeric monoclonal antibody which effectively suppresses the B-cells leading ultimately to the suppression of T-cells.

Since it carries the risk of serious infection, it is currently reserved for difficult cases of FR/SD nephrotic syndrome.

Our study was an observational retrospective study on 4 commonly used second line drugs in FR/SD INS in children. The main aim was to compare the efficacy and safety of these 4 s line drugs so as to plan future prospective studies on second line drugs in FR/SD INS. The second aim was to develop a systematic approach and protocol of the use of these second line drugs in FR/SD INS.

2. Methods

We reviewed the charts of children with FR/SD idiopathic nephrotic syndrome presenting to our center over a period of 3 years (July 2012 to July 2015).

2.1. Definitions

The definitions of nephrotic syndrome, remission, relapse, frequent relapse and steroid dependant were as per the International Study of Kidney Disease in Children (ISKDC) (Table 1).

2.2. Treatment of first episode of nephrotic syndrome

All the patients received a 3-month protocol of corticosteroids [3], as follows:

2.3. Month protocol

Prednisolone 60 mg/m [2] once daily (OD) x 6 weeks, then 40 mg/m [2] every other day (EOD) x 4 weeks, then 20 mg/m [2] EOD x 1 week, then 10 mg/m [2] EOD x 1 week and then stop.

2.4. The treatment of relapses was as follows [3].

Prednisolone 60mg/m [2] OD till urine protein was negative for 5 days, thereafter 40 mg/m [2] EOD x 4weeks, then 30mg/m [2] EOD x 4 weeks, then 20mg/m [2] EOD x 4 weeks and then stop.

2.5. Measurements

We recorded the following parameters weight, mean age at first episode, mean age at entry into study, serum creatinine, serum albumin, lipid profile, urine protein/creatinine ratio, at the first episode, at entry into the study and at the end of the study. We also recorded the serum drug levels (Cyclosporine), number of relapses per year and the cumulative dose of steroids before and after second line therapy. Calculation of cumulative dose of prednisolone was as follows: it was the total steroid dose over 1 year (in mg) adjusted to a surface area of 1 m^2.

2.6. The patients received the following second line drugs in the following doses

Levamisole 2.5 mg/kg EOD for 1 year, oral Cyclophosphamide 2 mg/kg x 12 weeks, Mycophenolate Mofetil (MMF) 1200 mg/m^2/day in 2 divided doses for one year and Cyclosporine 5 mg/kg/day in 2 divided doses for one year (Serum drug level 80–100 mg/ml). All these second line drugs were accompanied by low dose alternate day prednisolone.

2.7. Inclusion and exclusion criteria

2.7.1. Inclusion criteria

- All patients who had FR/SD idiopathic nephrotic syndrome.
- All patients who had received low dose prednisolone less than 0.75 mg/kg EOD initially for at least 1 year.

2.7.2. Exclusion criteria

- All patients of FR/SD who had received previous immunosuppressive drugs.
- All patients of steroid resistant syndrome.
- All patients of genetic nephrotic syndrome (e.g $NPSH_2$, $NPSH_1$).
- All patients of congenital or infantile nephrotic syndrome.

The following parameters were recorded and analyzed:

1. Mean relapse rate per year.
2. Mean cumulative dose of corticosteroids before, during and after stopping second line drugs per year.
3. Treatment success was number and percentage of patients with complete absence of proteinuria with only low dose prednisolone but without second line drugs in the third year.

Table 1
Definitions.

Nephrotic syndrome: proteinuria >40 mg/h/m^2 or >50 mg/kg/day or protein/creatinine ratio >0.2 g/mmol (>2 g/g) and hypoalbuminemia <25 g/L with or without edema
Remission: proteinuria < 4 mg/h/m^2 or 0-trace on Albustix for 3 consecutive days
Steroid responsive: complete remission achieved with steroid therapy
Steroid resistant: failure to achieve remission following 4 week prednisolone 60 mg/m^2 followed by 3 methylprednisolone pulses
Relapse: proteinuria ≫ 40 mg/h/m^2 or > 50 mg/kg/day or Albustix+++ for 3 consecutive days after having been in remission
Frequent relapser: 2 or more relapses within 6 months of initial response for 4 or more relapses within a period of 1 year
Steroid dependence: 2 consecutive relapses during corticosteroid therapy or within 14 days after cessation of therapy
Early nonresponder: steroid resistance during the first episode
Late nonresponder: steroid resistance in a patient who had previously responded to-corticosteroids therapy

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