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Review Article

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THE TREATMENT OF REFRACTORY NEPHROTIC SYNDROME IN CHILDREN

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ABSTRACT
Idiopathic nephrotic syndrome is the commonest chronic kidney disease in children. Most of them are response to steroid treatment. However, about 20% patients are frequently relapse, steroid-dependent, or steroid-resistant nephrotic syndrome. These patients need immune-superresion agents, such as cyclophosphamide, calcineurin inhibitors, or mycophenolate motifol to maintain completely remission. Recently, rituximab used to treat refractory nephrotic syndrome as well. The selection of the drug should be carefully consider according to the disease condition and patients family.

KEYWORDS: nephrotic syndrome; cyclophosphamide; calcineurin inhibitor; mycophenolate motifol; rituximab.

1. INTRODUCTION

Idiopathic nephrotic syndrome (INS) is the most common chronic glomerular disease in children, occurring in 2 of 100,000 children per year in western countries.[1] The peak age at initial presentation of childhood nephrotic syndrome is 2 years with 60-70% presenting prior to age 6 years.[2] Approximately 80% of these children have minimal change nephrotic syndrome, most of whom respond well to steroid therapy, steroid sensitive nephrotic syndrome (SSNS).[3] However, up to 50% of these SSNS children develop frequently relapsing nephrotic syndrome (FRNS), which is defined as at least 4 relapses per year or at least 2 in 6 months of the initial presentation. Some of them may be steroid dependent nephrotic syndrome (SDNS) defined relapsing during or within 2 weeks of cessation of steroid therapy according to the International Study of Kidney Disease in Children (ISKDC) criteria.[4] Also, 10-20% INS children have steroid resistant nephrotic (SRNS), defined as persistent proteinuria after 4 to 8 weeks course of oral predisonole.[4] For those children with SRNS, FRNS/SDNS, alternate agents, such as cyclophosphamide, calcineurin inhibitors, mycophenolate mofetil or rituximab could be considered after careful review of the pros and cons of each medication with the children's family. This review will discuss the treatment for SRNS, FRNS/SDNS.

2. Cyclophosphamide

Cyclophosphamide, a non-steroid immunosuppressive agent, has been used in the treatment of INS children for more than 4 decades.[5,6] It can reduce the relapse frequently and maintain the duration of remission of INS.

Cyclophosphamide for SRNS

Immunosuppressant agents should be used in all SRNS children. Bhimma et al.[7] reported a retrospective study. Two hundred and twenty-three children, 73(62.9%) had a course of predisone and oral cyclophosphamide therapy, 32(43.8%) achieved complete remission. In total, 61(52.6%) Indian children responded to a course of predisone and oral cyclophosphamide treatment. Of the 23 black children who received predisone and oral cyclophosphamid, 2(8.7%) initially responded but subsequently relapsed. Patients with minimal change nephrotic syndrome were more likely to go into complete remission using predisone and oral cyclophosphamide (66.6%), compared to those with FSGS(40.9%), proliferative disease(13.3%), or those with indeterminate histology(25.0%). Fifty (27.3%) patients received oral steroid and cyclophosphamide, 117 (63.9%) others who failed this treatment received pulse doses of intravenous methypredisolone and cyclophosphamide in combination with oral steroid, 4 of these patients had failed pulse doses of methypredisolone and oral cyclophosphamide and 6 (3.3%) received oral cyclosporine. Initially all patients were given oral predisone(2mg/kg, maximum 60mg) for 6 weeks followed by the same dose on alternate day for another 6 weeks and reduced to none over 2.5 months. Failure to respond was taken as steroid resistant. Second line treatment included low dose oral predisone (0.1-0.3mg/kg) given on alternate day with a daily dose of oral cyclophosphamide (2-3mg/kg) for 8-12 weeks. Black children were more likely to be treated with intensive therapy because of failure to respond to oral steroid and cyclophosphamide compared to Indian children 84(84.8%) vs 49(58.3%). Another retrospective study30 SRNS were treated under a protocol of

methypredisone pulse in conjunction with orally administered predisone were included. If a relapse was noted after the frequency of pulse had been diminished, oral treatment with cyclophosphamide was added together with weekly pulse. Total INS, remission was achieved in 22 patients (73.3%), ten patients only with methypredisone pulse and 12 by the addition of cyclophosphamide in 3 children and no response in five.[8]

Cyclophosphamide for FRNS/SDNS

A prospective study was conducted with total of 51 children with FRNS(22) or SDNS(29). The patients were given oral prednisolone 60mg/m2/day for 2 weeks or until they had been in remission for 3 days, and they were then given 40 mg/m2 on alterday for 4 weeks tapering off over the next 4 weeks. Introvenous cyclophosphamide(IVCP) was started in a dose of 500mg/m2/month for 6 months after achieving a steroid induced remission. FRNS group 15(67.5%) patients achieved a prolonged remission. 4(18%) improved and became FRNS, while another 3(13.6%) patients remission FRNS, despite IVCP therapy. In the SDNS group, 12(41%) patients achieved a prolonged remission, 9(31%) improved to FRNS, 5(17%) turn FRNS and 3(10%) remained SDNS despite IVCP. After a mean follow up to 27 months after the last dose of IVCP, of the 51 patients, 27(51%) achieved sustained remission, 13(25%) became FRNS, 8(16%) were FR while 3(6%) remained SDNS. The number of children in FRNS group who achieved a sustained remission(15/22) was similar to that in the SDNS group(12/29).[9]

Side effects of cyclophosphamide

The incidence of side effects was higher with oral than IVCP. Alopecia was more common in the oral group and reversed on completion of therapy in both group. Leutopenia was also more common in the oral group.[10] Minor side effects included weight gain, hypertension, abdominal pain, mild hair loss and bluish discoloration of the nails were also noted during treatment more serious adverse effects, possibly related to treatment, including severe infections, septicaemia and chickpox, bone marrow suppression.[11,12], gonodal toxicity and possibly oncogenicity seen to be dose related.

3. Cyclosporine A

Cyclosporine A(CsA) is efficient in decreasing proteinuria in both SDNS and SRNS.[13] Unfortunately, NS usually relapses soon after the drug is stopped and may be more difficult to control.[14] A second major concern is the potential for nephrotoxicity induced by CsA therapy. Sheashaa et al.[15] conducted a retrospective analysis. In this study, 197 pediatric patients (103 SDNS and 94 SRNS) received CsA therapy, the mean period was 22.16 months. The results showed that 132 (67%) complete remission and 13(6.6%) partial remission. Discontinuation of the drug in 40 patients maintained remission. Renal dysfunction developed in 18 patients of whom 12 recovered completely on drug discontinuation. Thirty-seven patients developed hypertension. All side effects were significantly more prevalent in CsA-resistant patients. So the another consider that CsA is effective and well tolerated in long term treatment in INS children, but two-thirds of cases showed relapse after CsA discontinuation. Plank et al.[16] found a significantly higher response to CsA therapy in complete remission at 6 months. The rate of complete remission and partial remission in CsA patients was significantly higher than in cyclophosphamide patients. Higher dose of CsA may be helpful in patients not responding to the usual dosage of CsA therapy. The short-term safety profile of both therapies was comparable. CsA therapy is superior to cyclophosphamide therapy in inducing at least partial remission in children with primary SRNS secondary to minimal change disease or FSGS. As such, CsA is indicated as first line therapy in children with SRNS. Klaassen et al.[17] reported that children with SRNS treated successfully with cyclosporine for a median of 3 years. They found that 73% of children who stopped CsA had no further relapse of NS over a median follow-up of 9.7 years.

The side effects of cyclosporine is hypertension(10%), gingival hypertrophy(32%), elevated creatinine(6%), hypertrichosis(70%).[18]

4. Tacrolimus

Some studies concluded that tacrolimus is more effective and safe for treating children with refractory case of CsA-resistant with no any serious toxicities.[19,20] Choudary et al.[21] conducted RCT where significantly high relapse was observed in those receiving CsA with side effects such as nephrotoxicity, hypertrichosis and gum hyperplasis compared to tacrolimus. Tacrolimus can be a promising alternative to CsA in view of the low risk of relapses and lack of cosmetic side effects. Gulati et al.[22] concluded the first prospective, randomized, multicenter trial of intravenous cyclophosphamide versus tacrolimus in 131 children with SRNS. Consecutive patients aged 2-16 years with biopsy confirmed minimal change NS, FSGS, or mesangio-proliferative glomerulonephritis were strectified by early and late steroid resistance and randomized to 12 months of tacrolimus or 6 monthly infusions of cyclophosphamide. Each group received alternate day predisolone. The primary and point was the proportion of patients with complete or partial remission on the basis of first-morning urine protein to creatinine ratios at 6 months. Complete or partial remission rates were higher in patients receiving tacrolimus (82.5%) versus cyclophosphamide (45.9%) and sustained remission or steroid sensitive disease was higher in the tacrolimus group at 12 months (52.4% vs 14.8%). In contrast, treatment withdrawal due to drug toxicity was higher among patients on cyclophosphamide. The authors concluded that prescription of tacrolimus and prednisolone is effective, safe, and superior to intravenous cyclophosphamide as the initial therapy for children with SRNS. The largest study by Gulati et al[23]

to evaluate the safety and efficacy of tacrolimus in SRNS suggested that tacrolimus is an effective therapy who does not response to cyclophosphamide and CsA.

Side effects of tacrolimus

Some studies suggest that tacrolimus is well tolerate in children. The most common side effects are diarrhea and hyperglycemia.[23,24] Few children have new onset hypertension, seizure and sepsis.[25,26]

5. Mycophenolate mofitil

Mycophenolate mofitil (MMF) is an inhibitor of the de novo purine pathway with preferential inhibitory effects on T and B lymphocyte proliferating[27] as well as on immunoglobulin production.[28] Some studies results showed that the success of MMF to treat SDNS relies on the efficiency to limit the exposure to predisone as well as to lack of irreversible side effects.[29-31] It can decrease the relapse rate and cumulate predisone dose, and had a similar efficacy as cyclosporine, but with less side effects, and especially no risk of nephrotoxicity and no cosmetic adverse events.[32] Dehoux et al.[33] reported 96 cases of SDNS treated with MMF, and follow up 4.7 years. This study confirmed the efficacy of prolonged treatment with MMF in patients with SDNS and found that MMF is more efficient when patients are treated at a younger age and early in the course of the disease. However, MMF showed no remnant effect, since nearly all patients relapsed after the withdrawal of the drug. MMF is also used in some children with CsA dependent NS. Fujinage et al.[34] reported that 12 cases with CsA dependent nephrotic syndrome treated with MMF. It demonstrated that MMF may be an alternative treatment for children with INS after long-term CsA therapy without serious side effects, increase in relapsing rate and higher steroid requirements.

The side effects of MMF, including digestive troubles, infectious events, as well as anemia, lymphopenia or thrombocytopenia, are mild and transient. MMF is teratogenic, so caution must be used when recommending this agent to women and girls of childbearing age.[35]

6. Rituximab

Rituximab for SRNS

Immunosuppresive agents above are useful for the most of FRNS children, but about 1-3% of them are unresponse. These children have a high risk of end-stage renal failure. Rituximab, a chimeric anti-CD20 monoclonal antibody, has been shown to be effective for patients with complicated FRNS or SDNS.

Bagga et al.[36] firstly reported that rituximab was effective for the refractory SRNS. Five children with refractory SRNS induced complete remission in 3 patients and partial remission in two. Other reports are showed that rituximab is an effective therapy for some INS children with refractory SRNS.[37-39] However, Magnasco et al.[40] reported an open-label, randomized trial of 31children with refractory SRNS compared response in 16children who received calcineuria inhibitors, prednisolone and two infusion of rituximab, and in 15 who received calcineuria inhibitors and prednisolone alone. However, proteinuria remained unchanged in rituximab-treated patients and none achieved partial or complete remission. The results showed that no evidence is available for rituximab as an effective therapy for patients with refractory SRNS.

Rituximab for FRNS/SDNS

Rituximab is a promising treatment for complicated FRNS/SDNS in children. A multi-center trial was reported by Ruggenti et al.[41] showed that one or two doses of rituximab followed by withdrawal of immunosuppression on disease recurrence in 10 children and 20 adults with complicated FRNS/SDNS found all patients in remission after 1 year. Furthermore, an open-labed, randomized, controlled trial showed that rituximab plus lower doses of predisone and calcineurin inhibitors were no inferior to standard dose of these agent in maintaining short-term remission in children with steroid- and calcineuria inhibitor-dependent nephrotic syndrome.[42] Iijima et al.[43] reported a multicenter, double-blind, randomized, placebo-controlled trial of rituximab therapy for childhood-onset complicated FRNS/SDNS. The results showed that the time to treatment failure were significantly longer. The relapse rate was significantly lower in rituximab than in the placebo group. In this trial, no death was reported and the majority of adverse events were mild. These finding indicated that rituximab was safe and effective, at least for 1 year in the treatment of childhood-onset, complicated FRNS/SDNS.

Adverse effects of rituximab

Rituximab is safe and well tolerated in most patients. However, some rare serious adverse events had been reported in children, including pulmonary fibrosis[44], fulminant myocarditis[45], pneumocystic pneumonia[46], immune mediated ulcerative colitis[46] and agranulocytosis[47], even hypersensitivity reactions during a second course of rituximab infusion.[48]

7. Mizoribine

Few reports indicated the effects about mizoribine treating nephrotic syndrome of children. Fujinaga et al;[49] reported that the efficacy of single daily high dose mizoribine therapy was assessed in 10 children with SDNS who had never been treated with CsA previously. Mizoribine was started at 5mg/kg, administered as a single daily dose after breakfast, and the dose was adjusted to achieve 2-h post dose mic levels of approximately 3ug/ml. In 9 of the 10 patients, treatment with a single daily dose of MIR (mean dose 8.4mg/kg/day) over a period 0f 22 months resulted in significant reduction of the mean prednisolone dose from 0.29 to 0.15 mg/kg/day and meadian 12-month relapse rate from 3.0-0.4 episodes/12 months. These data indicated that single daily high-dose MZR therapy is

possibly useful in treating children with SDNS and it may also eliminate the need of CsA in some patients. More clinical controlled studies are needed for mizoribine treating childhood nephrotic syndrome.

8. Summary

Many therapeutic methods are available for the treatment of children with SDNS/RFNS, or SRNS. The drugs potential complications should be consider with patients families prior to prescribing treatment. Furthermore, randomized controlled trials are indicated to determine which agents are most effective and to determine methods to predict medication response in individual children.

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