NEW DEVELOPMENTS IN THE THERAPY OF NEPHRORTIC SYNDROME IN CHILDHOOD

Summary of PhD. Thesis

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SUMMARY

INTRODUCTION: Eighty to ninety percent of children with steroid-sensitive nephrotic syndrome (SSNS) have relapses. About half relapse frequently and are at risk of the adverse effects of corticosteroids. Non-corticosteroid immunosuppressive agents are used to prolong periods of remission; however these agents have significant potential adverse effects. Currently there is no consensus as to the most appropriate second line agent in steroid–unresponsive nephrotic syndrome (NS) in children.

OBJECTIVES: Our objective is to evaluate the benefits and harms of some non-corticosteroid immunosuppressive agents (i.e. levamisole, cyclophosphamide (CP), cyclosporine A (CSA)) in frequently relapsing (FRNS), steroid-dependent (SDNS) and steroid-resistant NS (SRNS) in children.

PATIENTS AND METHODS: A retrospective study was made on the medical records of 34 children (21 boys, 13 girls) with FRNS (15/34), SDNS (13/34), or SRNS (6/34), whom levamisole was introduced (2 mg/kg per day) after 4 weeks of daily corticosteroid treatment. A second retrospective study was made on the medical records of 37 children, where two groups of patients were identified. Group 1 consisted of 22 children (15 boys, 7 girls) who received CP first as a second-line immunosuppressive drug because of their nephrotic syndrome. Group 2 consisted of 15 children (10 boys, 5 girls) who received second-line treatment with CSA.

CONCLUSIONS: 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 akylating agents, and it may also have some benefit for the treatment of SRNS patients. CP and CSA are effective second-line therapies following steroid monotherapy in idiopathic NS patients, but the relapse rate is lower and the relapse-free period is significantly longer in our CP-treated group. A good remission rate still can be achieved after 5 years following the initial CP and CSA therapy, and the incidence of side effects is low. An important message of our study is that most children who have a difficult course of nephrotic syndrome after an initial remission induced by steroids do well 7-8 years after presentation. On the other hand, our study is finally not able to give a definitive answer to the question as to which is the better treatment in the examined patient population. This retrospective study works with non equal distribution of focal segmental glomerulosclerosis (FSGS) in the different treatment groups so the question can not be answered due to statistical restrictions. In addition, no accompanying genetic studies were performed, which means that about 10% of our patients are expected to have a genetic disorder.

Further research is still needed to elucidate the disorder’s molecular pathogenesis, identify new prognostic indicators, and to develop better approaches to treatment.

1. INTRODUCTION

Idiopathic nephrotic syndrome (NS) is the most frequent glomerular disease in children and is mainly due to minimal change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS). NS generally has a favourable long-term prognosis, about 90 % of affected children exhibit an excellent glucocorticoid responsiveness, but most suffer at least one relapse. According to the literature, about 40 % of the steroid-sensitive (SSNS) cases are frequently relapsing (FRNS) and they commonly become steroid-dependent (SDNS). Steroid resistance (SRNS) develops in 10 % of children and many of these exhibit FSGS.

Treatment of the FRNS, SDNS and SRNS patients is still challenging because they often require long-term immunosuppression, (i.e. steroids) with a greater prevalence of side effects and complications. The therapeutic aims are to induce complete remission, reduce the rate of relapses, the cumulative dose of corticosteroids, mortality, therapeutic side effects, and the incidence of serious complications. In the past two decades, alkylating agents such as cyclophosphamide (CP) and chlorambucil (Chl), the immunomodulatory drug levamisole and calcineurin inhibitors such as cyclosporine A (CSA), and recently mycophenolate mofetil (MMF), the inhibitor of purine biosynthesis, have been used as the main steroid-sparing agents. The effectiveness of cytotoxic therapy depends on the histology of the lesion, 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.

2. AIMS

The aims of our first study were

1. to investigate the effects of levamisole on the number of relapses in FRNS, SDNS, and SRNS patients in childhood.
2. to investigate the effects of levamisole on the cumulative steroid dose in FRNS, SDNS, and SRNS paediatric patients.
3. to investigate the side effects of the levamisole treatment.

The aims of the second study were

4. to compare the effect and
5. to compare the long-term outcome of CP and CSA therapy in those INS paediatric patients who were originally steroid sensitive but after several relapses became SRNS or SDNS.

3. PATIENTS AND METHODS

3.1. Levamisol study

A retrospective study was made on 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 Paediatrics 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 NS secondary to other systemic diseases or syndromes, and renal histology at onset or subsequently consistent with membranoproliferative or membranous nephropathy.

Renal biopsy was performed in 23 children and showed MCNS in 13, IgM nephropathy (IgM NP) 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. Prednisolone was restarted because we wanted to investigate whether these patients would become steroid sensitive with a combined administration with levamisole.

There were 19 patients that received other immunosuppressive therapy before levamisole [9 received CP (2-2.5 mg/kg per day for 8-12 weeks), 10 received Chl (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 (mean±SD; range: 5-36 months). Levamisole was discontinued for 6 months when leucopenia (white blood cell count $\leq 3x10^9$/l) occurred and was then restarted.

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

3.2. CP versus CSA study

A retrospective study was made of the medical records of 37 children (25 boys, 12 girls) with idiopathic NS (INS) who were admitted to the Department of Paediatrics between 1989 and 2000 (follow-up time 5-13 years, median 7.1 years). At the start of their disease, all were steroid sensitive, but following several relapses, they became steroid dependent or steroid resistant.

Two groups of patients were identified. Group 1 consisted of 22 children (15 boys, 7 girls) age range 2-14 (mean±SD: 7.4±3.6 years) who received CP first as a second-line immunosuppressive drug because of their NS. Group 2 consisted of 15 children (10 boys, 5 girls) who received second-line treatment with CSA. Their ages at the time of the diagnosis lay in the interval 5-16 (mean±SD: 11. 7±4.4) years.

Inclusion criteria were age at onset > 1 year and ≤ 18 years, SDNS or SRNS.

Renal biopsy was performed in all cases, and it was indicated because we wanted to see the histology before the change of steroid therapy to another immunosuppressant.

Biopsy revealed MCNS in 19 and FSGS in three patients in group 1. In group 2, FSGS was found in seven and MCNS in eight children.

CP was introduced at 2-2.5 mg/kg per day orally for 8-12 weeks. Mean duration of CP treatment was 2.5±0.5 months (2-3 months). CP therapy was associated with 1 mg/kg oral prednisolone every other day.

The mean proteinuria level at the time of diagnosis was 5.0±3.5 g/day (mean±SD), which became <0.5 g/day during the initial steroid therapy. Before the start of CP treatment, proteinuria level was 3.9±2.9 g/day (mean±SD), endogenous creatinine clearance was 100.4±50 ml/min per 1.73 m^2 (mean±SD), and the relapse rate was 3.4±2.8/year (mean±SD). The cumulative steroid dose before CP introduction was 6,941±2,891.2 mg/year (mean±SD).

CSA was introduced at 3-5 mg/kg per day. Mean CSA treatment duration was 28±15 (7-60) months. CSA serum drug level was monitored monthly; target concentration levels were 100-200 ng/ml at trough and 800-1000 ng/ml at peak. CSA therapy was associated with 1 mg/kg prednisolone every other day.

Proteinuria level at the time of diagnosis was 4.5±2.3 g/day (mean±SD) and became <0.5 g/day at the end of the first steroid course. Before the start of CSA treatment, the mean proteinuria level was 3.9±2.3 g/day (mean±SD), the endogenous creatinine clearance was 86.6±27.3 ml/min per 1.73 m^2 (mean±SD), and the relapse rate was 3.7±3.1/year (mean±SD). The cumulative steroid dose before CSA introduction was 7,656.4±3,517.2 mg/year (mean±SD).

3.3. Corticosteroid protocol

In both studies 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, with the dose then being tapered by 10 mg/week according to the recommendations of the International Study of Kidney Disease in Children (ISKDC) protocol. Relapses were treated by the same method in all patients. All patients were steroid sensitive at the first course of treatment, but they became FRNS, SDNS or SRNS later on. They received more than one steroid course; the median number was four.

3. 4. Clinical assessment

Patients were followed monthly. At each visit, besides the clinical assessment, the following were performed in every case: urinanalysis, 24-h urinary protein measurement, urinary protein:creatinine ratio, endogenous creatinine clearance was measured (based upon 24 hours urine collection), complete blood count, serum creatinine determination, liver function tests. In the second study estimated glomerular filtration rate (eGFR) was calculated with the Swartz formula: eGFR = *k x height[cm]/serum creatinine[mg/dL]* where *k=0.55*, and serum lipid profile and CSA blood concentration determinations were also performed. Genetic analysis of the patients was not performed. At the start of the study, all the patients had normal liver function tests and a normal blood count in the levamisole study. The endogenous creatinine clearance was initially not normal in 7/22 patients in the CP and in 5/15 patients in the CSA group.

3.5. Statistical analysis: The clinical data on the patients are reported as median, mean±standard deviations (SD). Statistical analyses included the Student's t-tests for the comparison of parametric data. The level of statistical significance was taken as $*p<0.05$.

4. RESULTS

4.1. Results of the levamisole study group

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.

The duration of levamisole treatment was 5-36 (median 17) month. There were 29 patients that received levamisole for at least 18 months, 5 received it for a shorter period because of leucopenia. 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 one child had two relapses per year. Following the levamisole treatment the relapse rate during the 24-month follow-up was 0.22/year; 28 of the 34 children remained in complete remission and only six of them relapsed.

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

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

The endogenous creatinine clearance did not change significantly during the follow-up period, being 108.2±45 ml/min per 1.73 m^2 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 serum electrolyte and liver functions.

During the follow-up period, 5 of our patients developed reversible neutropenia (white blood cell count $<3x10^9$/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. Side effects of glucocorticoid therapy disappeared during the observation period in all patients.

4.2. Results of the CP treated group

Twenty-two INS patients received CP for 2.5±0.5 months in the first course as a second immunosuppressive drug after a remission with steroids was achieved. The average time from the onset of NS to the start of CP therapy was 2.5±2.0 years. Fifteen of the 22 patients also received methylprednisolone (MP) pulse therapy before administration of CP. Fifteen children had SDNS and seven had SRNS. Nineteen had MCNS and three had FSGS.

Proteinuria decreased from 3.9±2.9 to 0.5±1.4 g/day ($p<0.01$) and remained at 0.9±1.7, 5 years later. One patient with FSGS, who had heavy proteinuria (12.8 g/day) at the start of CP, still had 6.2 g/day at the end of the 5-year follow-up. There were three patients with MCNS who developed increasing proteinuria, 1.8, 5.2 and 3.0 g/day, respectively, by this time.

Nine patients had a reduced creatinine clearance and were ranged into National Kidney Foundation Kidney Disease Quality Outcomes Initiative stages for chronic kidney disease (NKF K/DOQI CKD) stage III-V at the end of CP therapy; one normalized by the time of the 5-year follow-up. One patient needed renal replacement therapy at the end of the 5-year follow-up. Eight of 22 patients had an elevated systolic blood pressure (≥120 mmHg) at the end of the 5-year follow-up period.

The relapse-free period was 30±21.5 months (29.9±21.5 months in SDNS and 30.3±23.3 months in SRNS patients). The relapse rates decreased significantly from 3.4±2.8 to 0.5±0.6/year during the first course of CP therapy and remained at this level (0.1±0.2/year)

during the 5-year follow-up ($p<0.001$). At the end of follow-up, five patients were in remission with immunosuppressive therapy. In the CP group, CSA was introduced when CP results were not sufficient (6/22). Four of 22 patients received prednisolone/MMF therapy as immunosuppression after CP.

In relation to CP therapy, 3/22 children had nausea, 2/22 patients had reversible hair loss, 1/22 had leucopenia and 1/22 alopecia.

4.3. Results of the CSA treated group

Fifteen patients received CSA for an average of 28±15 months in the first course as a second immunosuppressive drug after a remission with steroids had been achieved. Twelve of the 15 patients also received MP pulse therapy before administering CSA. Time from diagnosis to the start of CSA treatment was 3.5±3 years. Eight children had SDNS and 7 SRNS. Seven of them had FSGS and 8 MCNS.

Proteinuria decreased significantly (at the start of CSA treatment, it was 3.9±2.3 g/day, whereas at the end of CSA treatment, it was 0.9±1.4 g/day, $p<0.01$, 5 years later, it was 0.7±1.6 g/day).

Creatinine clearance and eGFR did not significantly change during the 2-year follow-up but increased at the end of the study. After 5-years of follow-up, eGFR deceased <15 ml/min per 1.73m^2 in two FSGS patients. In these patients, marked hypertension had also developed. One patient needed renal replacement therapy at the end of the 5-year follow-up.

Two patients with FSGS and one with MCNS did not respond to this CSA course. Proteinuria increased further in an FSGS case 5 years after the first CSA period, whereas in the other FSGS and the MCNS patient, a further course of CSA treatment resulted in a decrease in proteinuria.

The relapse-free period was 26.2±18 months (28.1±22.4 months in SDNS and 24±12.7 months in SRNS patients). Relapse rates significantly decreased, from 3.7±3.1 to 0.9±0.5/year during the first CSA course and remained at this lower level (0.6±0.8/year) during the follow-up ($p<0.001$). At the end of follow-up in the CSA group, four patients were in with immunosuppressant therapy. In the CSA group 5/15 patients received more than one CSA course, and 4/15 needed other immunosuppressive therapy.

During CSA treatment 3/15 patients exhibited hirsutism, 2/15 tremor, 2/15 gingival hyperplasia, and 1/15 had nausea and appetite loss.

5. DISCUSSION

5.1. Levamisole study

The immunomodulatory agent levamisole has been used as an adjunctive therapy in FRNS patients as a good alternative to major immunosuppressives. This treatment leads to decreases in the number of relapses and the amount of prednisolone required.

We used approximately double the dose that used in the British Association for Paediatric Nephrology study, because they reported a number of relapses after the treatment was stopped. 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 has one, and one 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,

six among the 13 SDNS children, and three 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 unknown histology (indicating a clinical presentation that corresponds to MCNS) exhibited a better response to levamisole than those with IgM NP and FSGS. Genetic analysis of the patients was not available in our centre at the time of the study.

The cumulative steroid dose was significantly lower following the introduction of levamisole treatment (i.e.1468±1766/year). The positive effect of reducing the steroid dosage may be secondary to the previously given alkylating agents. To investigate this, a prospective study is necessary either with 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 five patients, but no other side effects.

5.2. CP versus CSA study

This retrospective study documents that the long-term results of CP treatment in SDNS and SRNS in childhood are at least as effective as those for CSA.

5.2.1. Clinical course of nephrotic syndrome

In our study, CP treatment duration was 2.5±0.5 months, and the relapse-free period was 30.05±21.5 months (in 5/22 patients $\geq$60 months). Eighteen of the 22 patients (82%) had a relapse-free period of more than a year following CP therapy without other immunosuppressive treatment. Altogether, 10/22 patients (48%) did not need further immunosuppressive therapy until the end of the fifth year. Of the CP-treated patients, 45.5% were in complete and 36.3 % in partial remission after the 5-year follow-up (81.8% altogether). Further immunosuppressive therapy was needed in 12/22 patients because of relapses.

In our CSA-treated group, CSA treatment duration was 28±15 months (7-60 months). The relapse-free period following the start of CSA therapy was 26.2±18 months (in 2/15 patients it was $\geq$60 months). Of the CSA-treated patients, 46.6 % of the patients were in complete and 46.6 % in partial remission (altogether 93.2%) at the end of the 5-year follow-up, and 33% (5/15 patients) did not need therapy. Since many patients relapsed, their treatment was resumed or changed. Nevertheless, 9/15 patients still needed maintenance immunosuppressant therapy from the beginning until the end of the 5-year follow-up.

At the end of the 5th year, 10/15 patients were in remission (66.6%) in the CSA group and 15/22 (66.2%) in the CP group. The difference between the relapse-free period and the relapse rates after the first CP or CSA period was significant in the 2-year and 5-year follow-up period, with much rarer relapses following CP therapy ($p<0.05$). When estimating our results, we found that partial remission did not equal complete remission and might finally not turn out beneficial for the patients.

5.2.2. Renal function, proteinuria and hypertension

Compared with the CSA group, a significant decrease in creatinine clearance was seen in patients who were treated with CP first after steroids, at the end of CP treatment, and 2-years after the CP therapy, but this change was reversible, and disappeared after 5 years. Endogenous creatinine clearance and eGFR also showed a significant increase in the CSA-treated group after the 5 years of follow-up. In the CP-treated group, a significantly higher proportion of patients had <0.4 g/day proteinuria (16/22 patients, 72.7%) than those in CSA therapy (9/15 patients, 60 %) at the end of the 5-year follow-up. At this time, the blood pressure was significantly lower after CP than following CSA therapy.

5.2.3. Renal histology

FSGS is an indicator for poor prognosis: 6/10 patients relapsed, 2/10 patients developed end-stage renal failure and needed renal replacement therapy, and only 1/10 patient was in remission at the end of the fifth year with FSGS histology. In FSGS, the likelihood of remission is much lower than in MCNS, which should make a mixture of these two groups obsolete. The low number of the FSGS patients in the CP-treated group (3/25) compared to the 7/15 patients in the CSA group makes it difficult to determine the statistical significance of our results. Furthermore, we cannot be sure about the homogeneity of these two patient groups due to the lack of genetic analysis reviling the exact source of their symptoms. Although our patients had documented steroid sensitivity at the onset, the histology and the refractory course ending in end-stage renal disease in some patients suggests that a subgroup might have had a resistant or very poor response to steroids initially.

5.2.4. Adverse events

The types of side-effects during CP and CSA therapy were different. CP therapy applied for less than 3 months was not associated with more side-effects than CSA treatment. Any complications in the two treatment groups proved to be reversible, though none of our patients received more than one course of CP therapy. There were no patients who needed hospitalization because of severe infections during the administration of oral CP or CSA.
The known side-effects of CSA in the long term should be taken into account in the treatment decision. Its use for more than a year can result in chronic nephrotoxicity in 17-60% of patients (i.e. CSA-associated arteriolopathy, tubulointerstitial lesions, and focal glomerular lesions) or other side-effects, such as hypertension, gingival hyperplasia, and hirsutism. Lijima et al. reported that CSA treatment duration and duration of heavy proteinuria during CSA treatment were independent risk factors for the development of CSA-induced tubulointerstitial lesions in children with MCNS who had been treated with long-term moderate-dose CSA. Also, when using cyclophosphamide, the physician also must take into account the potential risk of infertility, cardiac disease and late cancer.

5.2.5. The possible use of cyclophosphamide or cyclosporine for treatment

Although a correct evaluation of the relative effectiveness of CP and CSA has not been possible because of the lack of a head-to-head randomised trial, studies in which alkylating agents and CSA have been compared have led to the conclusion that a course of cytotoxic drug leads to a higher rate of cumulative sustained remission compared with CSA. Pena et al. achieved high remission rates (73.3%) in histologically proven MCNS and FSGS SRNS patients using MP pulses and alkylating agents (CP, Chl) together. They also concluded that initial steroid resistance is a poor prognostic factor compared with late-onset

steroid resistance. Our patients were steroid sensitive at the beginning, which may explain our better results.

The efficiency of CP and Chl in patients with SDNS, SRNS, and FRNS is defined by remission duration. The effect of cytotoxic drug therapy in SSNS depends on several factors, such as the underlying glomerular disorder, e.g. MCNS, mild mesangial proliferation, IgM NP, FSGS, steroid sensitivity, FRNS or SDNS course of NS, type of cytotoxic drug, drug dose, treatment duration and concomitant drug therapy.

The reported remission rates after cytotoxic therapy vary from 0% after 12 months to about 30% after 5 years. In approximately 10% of the patients, however, NS may relapse during the cytotoxic treatment. The applied CP dose varies from 105 to 588 mg/kg body weight cumulatively. Higher dosages are associated with a higher chance of relapsing–free intervals, although the risk of side-effects increases. According to the meta-analysis of cytotoxic treatment in FRNS children published by Latta et al., the remission lasted for a maximum of 57 months after the first course of cytotoxic therapy, and the overall relapse-free survival after 4 years is <50%. On average, studies on FRNS result in remission rates of 72% after 2 years and 36% after 5 years; rates for SDNS are 40% and 24%, respectively [30]. Second courses of cytotoxic therapy are reported to increase the rate of long-lasting remissions. We gave a CP dose of 112-168 mg/kg cumulatively in one course, and we did not apply a second CP course in any of the NS patients. Our better results may partially be explained by the fact that our patients had SSNS at the start of the disease.

In the study by Cattran et al., 49 SRNS FSGS patients were treated with CSA+low-dose prednisolone and compared with low-dose prednisolone+placebo and followed for 200 weeks. They found 70% of the treatment group vs. 4% of the placebo group had a partial or complete remission by 26 weeks. Relapse occurred in 40% of patients by week 52 and in 60% by week 78, but the remainder stayed in remission to the end of 200 weeks. There was a decrease of 50% in the baseline creatinine clearance in 25% of the treated group compared with 52% of the controls.

Ehrich et al examined 86 children with SRNS due to FSGS and MCNS in a retrospective, non-randomized study, and they concluded that prolonged and intensified treatment with combined prednisolone+CSA therapy including intravenous MP pulses resulted in higher rate of remission when compared to CSA monotherapy or other immunosuppressive therapies. Because of a lack of efficacy and the risk of severe side effects of cytotoxic drugs including gonadal toxicity, their experience does not indicate that children should be treated for steroid-resistant MCNS with CP.

Planck et al conducted a controlled multicentre randomized open label trial to test the efficacy and safety of CSA (n=15) versus CP (n=17) pulses in the initial therapy of children with newly diagnosed primary SRNS and histologically proven MCNS, FSGS or mesangial hypercellularity. At week 12, nine of the 15 (60%) CSA patients showed at least partial remission. In contrast, three of the 17 (17%) CP patients responded ($p < 0.05$). After 24 weeks, complete remission was reached by two of the 15 (13%) CSA and one of the 17 (5%) CP patients (p = n.s.). Partial remission was achieved by seven of the 15 (46%) CSA and two of the 15 (11%) CP patients ($p < 0.05$). They concluded that CSA is more effective than CP in inducing at least partial remission in SRNS in children.

Based on the data of the above mentioned trial Hodson et al concludes that although there was no difference in the number of patients achieving complete remission, those patients receiving CSA treatment were significantly more likely to achieve partial remission than

those receiving intravenous CP. They also suggest that CSA rather than CP should be used as first line therapy for children with SRNS.

In the Cochrane Review, 26 trials involving 1173 children were identified. CP and Chl significantly reduced the relapse risk at 6-12 months compared with prednisolone alone. In the single Chl vs. CP trial, no difference in relapse risk was observed at 2 years. There was no difference at one year between intravenous and oral CP. CSA was as effective as CP and Chl, and levamisole was more effective than steroids alone but the effects were not sustained once CSA treatment was stopped. There was no difference in the risk for relapse between MMF and CSA. Mizoribine and azathioprine were no more effective than placebo or prednisone alone in maintaining remission. The reviewers concluded that 8-week courses of CP or Chl and prolonged courses of CSA and levamisole reduce the risk of relapse in children with relapsing SSNS compared with corticosteroids alone. Meanwhile the choice of agent depends on the physician and patient preferences related to therapy duration and the type and frequency of complications.

Kemper et al. reported that SDNS can recur in patients despite CSA maintenance therapy, and despite its efficacy, the majority of patients relapse if CSA is stopped.

6. CONCLUSIONS

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 (1)

Levamisole may have a place in preventing relapse even after courses of akylating agents, and it may also have some benefit for the treatment of SRNS patients (2).

The confirmation of the favourable effects of levamisole on the reduction of the frequency of relapses and on sparing steroids in an adequately powered, double-blind, placebo-controlled, randomized, multicenter clinical trial will promote consensus on the place of levamisole in the treatment of FRNS in childhood.

In the long term, both CP and CSA are effective second-line therapies following steroid monotherapy in INS patients (3).

However, the relapse rate is lower and the relapse-free period significantly longer in the CP-treated group (4).

An important message of our study is that most children who have a difficult course of NS after an initial remission induced by steroids do well 7-8 years after presentation (5).

A good remission rate can be achieved after 5 years following the initial CP and CSA therapy, and the incidence of side effects is low (6).

On the other hand, our study is finally not able to give an answer to the question as to which is the better treatment in the examined patient population because it is a retrospective study with unequal distribution of FSGS in the different treatment groups. In addition, no supplementary genetic studies were performed; therefore about 10% of our patients are expected to have a genetic disorder.

Further research is needed to elucidate the disorder’s molecular pathogenesis, identify new prognostic indicators, and to develop better approaches to treatment.

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