Cyclosporine in the treatment of steroid-resistant and steroid-dependent idiopathic nephrotic syndrome

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Abstract

Introduction
Cyclosporine A is effective in treating steroid-dependent (SD) and steroid-resistant nephrotic syndrome (SRNS), despite its potential chronic nephrotoxicity. This study reports the results of a CsA (cyclosporine microemulsion, Sigma Pharma / Nature’s Plus, Brazil) treatment of 33 children with idiopathic nephrotic syndrome (INS), 17 of which were SRNS, and 16 showed signs of steroid toxicity. The histological diagnosis leading to the INS showed minimal changes in the disease (MCD) on 21 children, focal segmental glomerulosclerosis (FSGS) on 11 patients and membranous nephropathy (MN) on one. Only those children whose histological analyses showed a maximum of 30% of interstitial fibrosis, with normal renal and liver function, were included in the group.

Method
CsA was administered at a dose of 5 mg/kg twice a day, in combination with alternate-day prednisone. The dose was adjusted to maintain moderate levels between 50 and 150 ng/ml, as measured on whole blood by monoclonal radioimmunoassay (RIA), for a period of 3 to 12 months.

Results
In SRNS, CsA therapy in association with prednisone induced complete remission in 53% of the patients (9 children), incomplete or partial remission in 30% of the patients (5 children), and 29.4% of the patients (5) were only maintained on CsA. CsA therapy in association with prednisone induced complete remission in 100% of the patients (16 children) and, 81.2% of the patients (13 children), were only maintained on CsA in SD cases. Only one patient developed CsA nephrotoxicity.

Conclusion
The association of alternate-day prednisone was highly effective in inducing complete remission in patients with SRNS and in tapering off the corticoids among those with signs of steroid toxicity.
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Introduction

The idiopathic nephrotic syndrome (INS) is one of the most frequent glomerulopathies with pediatric patients. Patients are treated with prednisone according to the classical schedules suggested by the International Study of Kidney Diseases in Children (ISKDC). Approximately 70 to 90% of the treated patients are steroid-sensitive (SS) and more than 50% of them relapse when the corticoid is reduced or withdrawn, i.e., they become steroid-dependent (SD). 10 to 20% of INS cases are resistant to steroid therapy, and 50% of the steroid-resistant (SR) and a substantial percentage of SD patients tend to evolve towards kidney failure in ten years.

Presently, although pathogenetic mechanisms of INS are not yet fully clarified, it is believed that T cells, sensitized by specific antigens, release lymphokines such as IL-2, heparitinase or vascular permeability factor, which would determine the loss of negativity of the basal glomerular membrane, altering its permeability to plasmatic proteins.

Based on studies since 1985 cyclosporine A has been used as an alternative treatment in cases of poor response to traditional therapy. As an inhibitor of calcineurine, cyclosporine A yields alteration of the expression of T cells activating genes, including those implied in the transcription of mRNA to IL-2.

In most cases Cyclosporine A provides a high level of INS remission, both on SR and SD patients. Even though the microemulsion formulation improves bioavailability in comparison to the conventional form, absorption, is variable.

It must be emphasized that with short-term treatments (for less than one year) a medication dependency with early relapses following drug withdrawal can be observed. Nonetheless, if the patient remains in complete remission for one year or more and the immunosuppressant is withdrawn slowly, the risk of relapse decreases and the sensitivity to corticoids increases in SR patients.

The potential nephrotoxicity of the drug, histologically characterized by hyaline degeneration of the afferent arteriole, followed by interstitial fibrosis and tubular atrophy must not be ignored. These findings may precede kidney functions alterations. Therefore, the safest method to evaluate renal risk is histological analysis. Other side effects are arterial hypertension, hyperlipidemia, hypertrichosis, gingival hypertrophy and hyperuricemia.

The purpose of using CsA was to induce remission in INS - SR patients and to reduce or even suspend the corticoid in SD patients. The study has already completed 18 months and is still going on, so that the data herein presented refer to a determined period. We intend to prolong our observations until the whole SD group completes one year treatment at least. Regarding SR patients, the drug will be maintained for a period longer than one year, in low and controlled doses, performing serial biopsies.

Methods

Initially, all patients received a classical corticotherapy and those who did not respond, were submitted to a kidney biopsy. Moreover, 35% of the patients (n=12) received pulse therapy with methylprednisolone, according to an adaptation of Mendoza's schedule and 60% of the patients (n=20) received cyclophosphamide, v.o., at a dose of 2.5 mg/kg/day for 60 to 90 days.

We used CsA in a group of 33 INS patients, classified as steroid-resistant (SR) or steroid-dependent (SD). SR were defined as those who did not remit or presented partial remission from the beginning of the corticoid treatment SD were those who presented complete remission after initial treatment with daily corticoid intake, but relapsed when put on medication on alternate days, becoming dependent even at low doses. All SD patients showed signs of steroid intoxication to some degree. None of them presented alterations of kidney or liver functions. The renal biopsy was carried out or repeated immediately before the introduction of CsA to discard possible anatomo-pathological alterations that could be attributed to the drug in case of prolonged treatment. According to literature, it is reported that cyclosporine A potential nephrotoxicity is influenced by pre-existent renal lesions. These include chronic cases with long-term follow-ups that might present interstitial fibrosis as an evolvement of the glomerulopathy. We established 30% of interstitial fibrosis as the cut point to receive CSA, with the purpose of excluding cases of low probability of response to the medication and a higher risk of intoxication.

The dose of CsA used was 5 mg/kg/day, in 2 intakes (12/12 hours), with periodic blood level determinations by monoclonal RIA, trying to maintain mo-
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derate levels, between 50 and 150 ng/ml. With all patients, an initial association with prednisone on alternate days was used (35 mg/m² each 48 hours).

In the SR group (n=17), 7 patients were female and 10 male, with ages varying between 2 and 16 years (mean=9.3 years). With regard to the histopathological diagnosis, 8 patients presented segmental and focal glomerulosclerosis (SFGS), 8 patients a minimum histological lesion (MHL) and 1 membrane glomerulonephritis (MGN). The duration of the medication varied from 3 to 12 months (mean=7.9 months).

In the SD group (n=16), 7 patients were female and 9 male. Ages varied from 3 to 16 years (mean=10.9 years). As for the histopathological diagnosis, 3 patients presented SFGS and 13 MHL. The period during which medications was administered varied from 3 to 12 months (mean=7.1 months).

Complete remission was considered to have occurred when serum albumin was normal and protein in 24 hour urine was absent, whereas partial remission was considered acceptable when albuminemia was partially normalized, with within non-nephrotic levels.

Results

Of the SR patients, 53% (n=9) presented complete remission after treatment with CsA and 30% (n=5) evolved towards partial remission. Another 17% (n=3) did not present remission and showed gradual worsening of the renal function, resulting in the withdrawal of the medication around the 3rd month. Corticoid withdrawal was possible in 23.5% of the patients (n=4) who presented remission.

In SD patients, remission occurred in 100% of the cases (n=16). In these cases it was possible to withdraw the corticoid in 82.3% (n=14) and the dose was reduced in the remaining cases.

Overall, in both groups, we observed that 76% (n=25) obtained total remission, where 54.9% (n=18) remained without corticoid. There was a partial response in 15% (n=15) of the cases, in 9% of the cases (n=3) there was no response and 2 patients presented an increase in urea and creatinine levels (Table 1).

During the treatment, 6 SR patients relapsed during infectious processes, with 3 SFGS and 3 MHL. There were 4 MHL cases of relapse and none SFGS cases among SD patients. (Table 2).

As for the side effects, 73% (n=24) presented mild to moderate gingival hyperplasia and 79% (n=26) mild to moderate hypertrichosis. With regard to blood pressure, 33% (n=10) of the children were hypertensive at the beginning of the treatment with CsA, either due to the pathology per se or because of the prolonged use of corticoids. In SR patients, there was an exacerbation of pressure levels in 11% (n=2) of the cases and an improvement in 18.7% (n=3). Among SD patients, blood pressure was normal on 1 patient (6.2%) during therapy, due to improvement of NS or corticoid withdrawal.

Discussion

In this study, we have evaluated the response to CsA in 33 children with INS, its side effects and the possibility of reducing or even suspending the use of corticoid in steroid-dependent patients. The mean period of observation varied from 3 to 12 months; the patients remained under evaluation and it is our intent to maintain the medication for one year in SD and longer in SR patients, performing serial biopsies for control.

Steroid-resistant

In our study, considering the SR group (n=17), there was total remission in 53% (n=9) of the patients, 30% (n=5) of the patients had partial remission, 17% (n=3) remained with unbalanced nephrotic syndrome,
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Steroid-dependent

In the SD group (n=16), where the patients presented symptoms of corticoid intoxication, we observed that 100% presented good response to CsA. In 68.7% (n=11) it was possible to reduce or interrupt the steroid therapy and only 25% (n=4) relapsed within the period. Inoue and co-workers,\textsuperscript{19} treating ISN-SD patients for 2 years by using moderate doses of cyclosporine A, considered the drug effective in preventing relapses and in reducing the symptoms of steroid iatrogenesis with results and doses similar to ours.

The patient T.F.S. completed a one-year-therapy, during which she remained on remission and without corticoid intake, then relapsed during a common infectious process, with increased urea and creatinine levels and gaining considerable weight. There was no response to the increase of CsA dose and to corticoid reintroduction. The kidney biopsy was repeated and did not show worsening of the histological pattern.

Side effects

The most important cyclosporine A side effect, nephrotoxicity, occurred only in one SD case, where control renal biopsy, performed after 12 months follow-up, demonstrated the presence of hyaline stores in arterioles. The biopsy was due to hypertensive peaks. The corticoid had been withdrawn the 2\textsuperscript{nd} month after CsA introduction, there were no relapses during the follow-up period and urea and creatinine remained normal during the entire follow-up period. After the anatomo-pathological exam we withdrew medication.

The presence of nephrotoxicity characterized histologically by hyaline degeneration of afferent arteriole followed by interstitial fibrosis and tubular atrophy may precede the reduction of renal functions as happened in our case.\textsuperscript{19}

Niaudet and collaborators considered that the risk of developing chronic nephrotoxicity is higher in SR patients and is not related to the length of treatment; it may even appear during normal renal functions.\textsuperscript{9}

In a prospective study of 12 children with SD nephrotic syndrome for 2 years, Inoue and co-workers found lesions in control biopsies suggestive of nephrotoxicity in 7 cases.\textsuperscript{19} Therefore, they considered that the renal function alone is not a reliable indicator of iatrogenesis.

Hypertrichosis and gingival hyperplasia were frequent, as reported in the literature.\textsuperscript{12}

Hypertension was not a problem during the clini-
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In our study we observed a drop in blood pressure in 12% (n=4) of the previously hypertensive patients. In addition, loss of weight loss and growth restart were observed since corticoids were reduced or withdrawn, while children were kept in remission only with CsA.

In agreement with our observations this was also reported by Hino S. and collaborators, with a 23-month mean period treatment with moderate doses of cyclosporine A (50 ng/ml to 120 ng/ml), and also showed a structural gain, decrease of relapses and reduction of the prednisolone dose.12 Kano K. and co-workers mention the increase of children's height during the period in which they received cyclosporine A.20 Growth continued and there was a loss of the Cushing aspect in most of the children.

In regard with the incidence of early relapse after cyclosporine withdrawal,21 the withdrawal of the medication has recently been initiated.

We conclude that CsA represents a valid alternative to SD patients with signs of corticoid intoxication. The literature suggests that relapses after withdrawal may be reduced by using moderate doses for long periods of time. However, caution is recommended as the risk of nephrotoxicity is emphasized.2 In SR patients, the drug, although less effective, also represents a valid therapy, but in these cases occurrences of nephrotoxicity may be higher.

References

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