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A controlled study of deflazacort in the treatment of idiopathic nephrotic syndrome

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Abstract. Forty patients with steroid-dependent idiopathic nephrotic syndrome (INS), a mean follow-up of 5.5 years, and a mean number of relapses of ten were blindly assigned to either deflazacort (DFZ) (n = 20) or prednisone (PDN) (n = 20) according to a ratio of equivalence of DFZ/PDN = 0.8. This treatment was given for 1 year. The number of relapses was significantly lower in patients receiving DFZ. After 1 year, 12 remained in remission with DFZ compared with 2 with PDN. Growth velocity was not different in the two groups. Bone mineral content, assessed by quantitative computed tomography of L1 L2 vertebrae, decreased after 1 year by 6% in the DFZ group versus 12% in the PDN group (NS). The mean body weight increase of $+3.9 \pm 4.1$ kg in the PDN group was higher than that of the DFZ group, $+1.7 \pm 2.8$ kg (P = 0.06). Cushingoid symptoms tended to be less after 12 months in the DFZ group. In conclusion, this study shows that DFZ was more effective than PDN in limiting relapses in steroid-dependent INS, and that cushingoid symptoms, weight gain, and decrease in bone mineral content tended to be less marked with this drug than with PDN.

Key words: Idiopathic nephrotic syndrome – Corticosteroid treatment – Deflazacort – Prednisone – Bone loss

Introduction

Side effects, including cushingoid symptoms, growth stunting, and osteoporosis, are the major drawbacks of long-term corticosteroid treatment, which is currently administered in a number of situations in pediatric nephrology. Deflazacort (DFZ), a synthetic heterocyclic oxazoline glucocorticoid, was shown to be as effective as prednisone (PDN) in diseases such as rheumatoid arthritis [1–3], juvenile chronic arthritis [4], adult nephrotic syndrome [5], perhaps asthma [6], and also in kidney [7] and heart [8] transplantation, with a lower overall incidence of adverse effects, as recently reviewed by Markham and Bryson [9]. Children with the nephrotic syndrome seemed to develop fewer side effects of steroid therapy under DFZ in an uncontrolled study [10], and it appeared important to go further. The present study was performed in children with steroid-dependent idiopathic nephrotic syndrome (INS) who were blindly assigned to DFZ or PDN for 1 year at the time of a relapse. The aim of this study was to assess the effectiveness of DFZ in this subgroup of nephrotic patients and to compare the metabolic effects of the two drugs mainly on bone and growth. Bone mineral density of the lumbar spine was assessed at the start of the study and after 1 year, as well as growth velocity and clinical signs of Cushing syndrome. This study has already been partially reported in abstract form [11].

Patients and methods

Forty children (32 boys, 8 girls) were included in the study. All had steroid-dependent INS. Corticosteroid dependency was defined as more than two relapses in the preceding 12 months despite the ingestion of PDN every other day, or within 2 months of stopping this treatment. At the end of the study it was confirmed (after unblinding) that the history of the disease and the number of patients just relapsing or already in remission at the start of the study were similar in the two groups. Age, gender, mean duration of the disease, and the mean number of relapses per patient at the time of the study were not different (Table 1). The administration of alkylating agents (chlorambucil 8 mg/kg body weight over 8–12 weeks or chlormethin, two series of four intravenous injections of 0.1 mg/kg body weight at 1-month intervals) before the study was also similar in the two groups.

A kidney biopsy had been performed in 6 patients of the DFZ group and in 5 of the PDN group. All had minimal changes; 3 patients from the DFZ group also had focal sclerosis. Six children in the DFZ group and 5 in the PDN group had received ciclosporine (4–6 mg/kg per day in two doses). The mean duration of this treatment before the study was 22.8 months for the DFZ group and 20 months for the PDN group. It is important to stress that despite these treatments all patients relapsed and remained corticosteroid dependent, according to the definition already given.

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Table 1. Patient characteristics

	DFZ	PDN
n	20	20
Age (years)	9.2±2.7	8.5±4
Gender M/F	15/5	17/3
Duration of the disease (years)	5.6±3.1	5.4±4.3
Number of previous relapses	10.8±7.2	9.6±7.1
Kidney biopsy (*n*)	6	5
– minimal changes	3	5
– focal sclerosis	3	–
Patients who received alkylating agents (*n*)	7	8
– 1 course	5	6
– 2 courses	2	2
Patients given ciclosporine (*n*)	6	5
Dose of PDN at the time of the last relapse[b]	0.7±0.5	0.5±0.5

DFZ, Deflazacort; PDN, prednisone
[a] None are significantly different
[b] mg/kg every other day

The mean body height in the DFZ group was 125.9 cm (range 104.2–149 cm), or –1 SD (range –2.5 to +1.04 SD), and in the PDN group 125.6 cm (range 92.3–155 cm) or –0.2 SD (range –1.7 to +2.7 SD). The mean body weight in the DFZ group was 32.8 kg (range 20–59 kg) and in the PDN group 33.8 kg (range 13–56.9 kg). No significant differences were found in age or body weight between the two groups at the start of the study, but the body height standard deviation score (SDS) was significantly higher in the PDN group ($P = 0.02$).

Patients were blindly assigned to DFZ ($n = 20$) or PDN ($n = 20$), at the time of a relapse (29 cases) or after remission was attained shortly after a relapse (11 cases). This treatment was administered for 1 year. The method of randomization was as follows: new patients were given the next package of drug containing the quantity needed for a 1-year treatment. Packages were provided in blocks of 10. The packages were numbered from 1 to 10, 11 to 20 etc... They included an equal number of DFZ and of PDN in an order determined by a random code generator. The first patient received package no. 1 and so on. Therefore neither patients nor clinicians had any possibility of knowing the nature of the drug until the end of the study.

Both drugs were provided by Cassenne Laboratory (Puteaux, France) in identical bottles and as identical tablets, containing each either 6 mg of DFZ or 5 mg of PDN, according to a ratio of antiinflammatory equivalence of DFZ/PDN equal to 0.8 [12].

Corticosteroid treatment during the study was administered according to the current protocol of the French Society for Pediatric Nephrology [13]. In this protocol the treatment for a relapse, expressed in PDN equivalence, is 60 mg/m^2 administered daily until the 5th day of complete remission, then every other day for 6 weeks, then tapered to 15–20 mg/m^2 every other day over 6–8 weeks, and then continued at this dose for at least 1 year before attempting discontinuation. This protocol was often adapted to individual cases. For example, the steroid dose for treatment of a relapse was sometimes lower than 60 mg/m^2 if this dose was proven effective, or the maintenance dose on alternate days was different, according to the so-called threshold of corticosteroid dependence. The mean cumulative dose of steroid, expressed in PDN equivalent, during the study was 5,668 mg/m^2 in the DFZ group and 5,092 mg/m^2 in the PDN group (NS).

Six patients from the DFZ group and 5 from the PDN group who were started on ciclosporine 6–44 months before the study continued to receive it during the study at a mean dose of 5 mg/kg per day. Two patients withdrew from the study between 6 and 12 months: 1 was lost to follow-up in the PDN group and 1 who received ciclosporine had corticosteroids withdrawn by mistake in the DFZ group. Thus, 38 of the 40 patients who started the study completed 12 months of treatment, 19 in each group.

In addition to DFZ or PDN, all patients received calcium supplementation at a mean dose of 26±17 mg/kg per day and 25 hydroxycholecalciferol at a mean dose of 1±1.1 μg/kg per day. There was no statistically significant difference in the dose of these drugs in the two groups. Three patients in each group received antihypertensive treatment.

Cushing syndrome was clinically assessed at the start of the study and after 3, 6, 9, and 12 months, as absent, mild, or marked. Photographs of the face and the trunk were also taken at the start and the end of the study and after 6 months. All photographs were blindly assessed by two physicians working separately who did not follow the patients during the study. The date of the photographs was also not known. Each photograph was graded according to the severity of cushingoid symptoms from 1 to 4 (1 = absent, 2 = mild, 3 = moderate, 4 = severe).

Bone density was assessed at the start and after 12 months by quantitative computed tomography of two vertebrae, according to Kalender et al. [14]. The measurements were performed with a CGR and a General Electric scanner on the body of L1 and L2. The vertebral density was assessed on two cross-sections of 10 mm thick in the center of the vertebra after comparison with a phantom made with an increasing solution of dipotassium phosphate in water [14]. This measurement was performed in single-energy mode (120 kV) because of the lack or the very low level of fat in the bone marrow of children. The measurements were expressed in milligrams per square centimeter.

Data were recorded on each patient at baseline and every 3 months thereafter, including any relapse, body height and weight, presence of edema, diastolic and systolic blood pressure, cushingoid symptoms, and routine biochemistry, including proteinuria, blood count and hemoglobin, plasma electrolytes, protein, albumin, and creatinine, blood urea and glucose, glycosylated hemoglobin, transaminases, ionized and total calcium, phosphorus, alkaline phosphatases, cholesterol, and triglycerides.

This study was approved by the Necker Hospital ethics committee. All patients and parents were carefully informed about the study and gave signed informed consent.

Statistical analysis. The statistical methods used were: Student's t-test, variance analysis, Fischer's exact test, and the Mann-Whitney test. The actuarial remission curve was calculated according to Kaplan Meier and the two curves were compared by the Mantel Cox and the Breslow Wilcoxon tests.

Results

Efficacy of DFZ

The mean time for attaining remission when the treatment was started at the time of a new relapse was 8 days in the DFZ group (range 3–24 days) and in the PDN group (range 4–69 days). The mean number of new relapses per patient during the study was significantly higher in the PDN than the DFZ group: 2.8±1.8 versus 0.9±1.4 ($P < 0.002$). Conversely the number of patients free of relapse during the study was significantly higher in the DFZ group (12/20, 60%) than the PDN group (2/20, 10%) ($P = 0.002$).

The actuarial proportion of patients remaining in remission after the start of the study, taking the end point as the first relapse, was significantly higher in the DFZ group (Mantel Cox $P = 0.015$; Wilcoxon Breslow $P = 0.0086$) (Fig. 1). At the end of the study, this proportion was 58% in the DFZ group versus 12% in the PDN group.

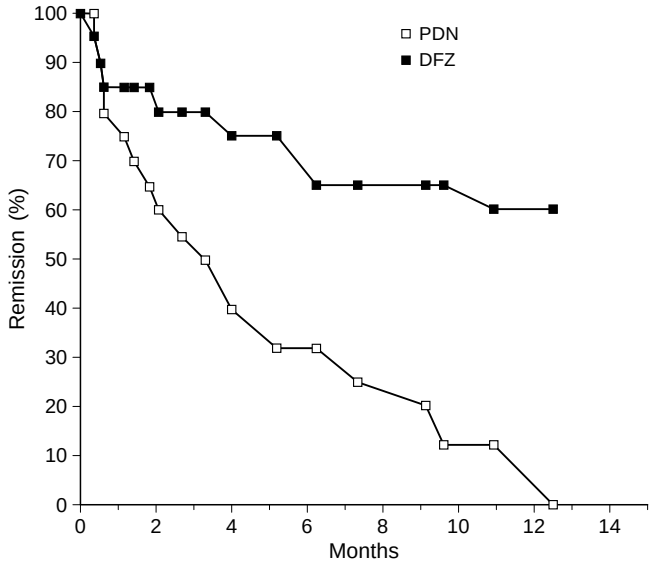

Fig. 1. Actuarial remission curve for the two groups of patients, *PDN*, Prednisone; *DFZ*, deflazacort

Change in height

After 1 year, the mean growth velocity was similar in the DFZ and PDN groups: 4.1 ± 1.2 cm/year and 4.4 ± 1.4 cm/year, respectively. Hence the change in statural height was not different in the two groups: from –1 to –1.2 SDS in the DFZ group and from –0.2 to –0.6 SDS in the PDN group. The height SDS, significantly higher in the PDN group at the start, was not significantly different at the end of the study.

Bone mineral content

The mean bone mineral content of the spine (L1+L2) decreased in both groups from 129 ± 30 mg/m² to 121 ± 35 mg/m² in the DFZ group and from 142 ± 26 mg/m² to 125 ± 26 mg/m² in the PDN group, but only the decrease observed in the latter group was of borderline significance (P = 0.05). Over the study period, the mean decrease in bone density was –6% in the DFZ group and –12% in the PDN group. These changes were not significantly different, even after correction for body surface area, and the mean bone mineral density was the same in both groups at the end of the study.

Table 2. Cushingoid symptoms, clinical assessment. Number of patients with no, mild, or marked symptoms

			Months of treatment			
		Baseline	3	6	9	12
PDN	Absent	10	9	9	8	8
	Mild	8	9	9	9	9
	Marked	2	2	2	1	2
DFZ	Absent	6	7	6	9	12
	Mild	10	10	12	7	5
	Marked	4	3	2	2	2

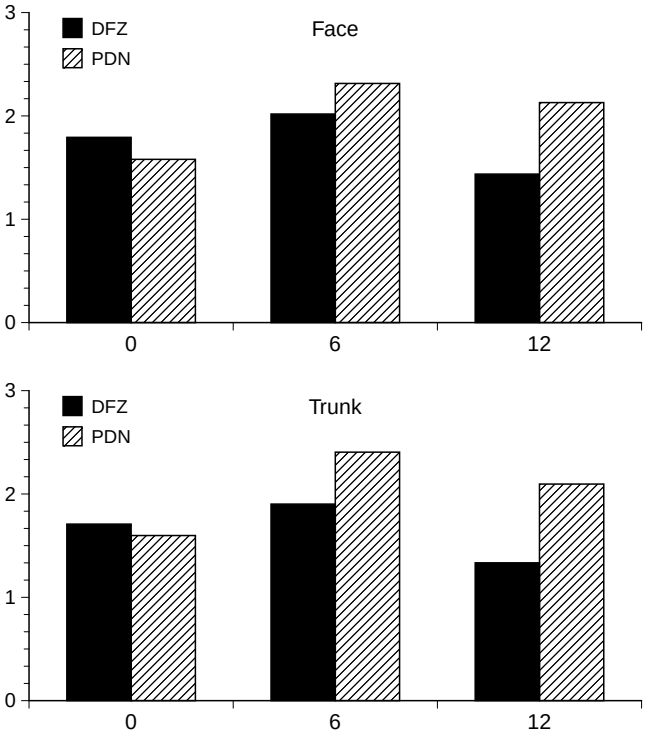

Fig. 2. Evolution of the mean index of cushingoid symptoms in the two groups of patients according to the blind examination of photographs of face and trunk taken at the start of the study and after 6 and 12 months

Change in body weight

The mean body weight was higher at the end of the study in both groups: from 32.8 ± 10.7 kg to 34.2 ± 10.1 kg in the DFZ group and from 33.8 ± 14.4 kg to 38.3 ± 15.8 kg in the PDN group. The individual change in body weight was higher in the PDN group (3.9 ± 4.1 kg vs. 1.7 ± 2.8 in the DFZ group). This difference was close to significance (P = 0.06). Almost all patients were overweight. This was more obvious when weight was expressed as a mean SDS for height: it was +3.9 and +4 SD above the mean normal at the start of the study and after 12 months for DFZ and +4.4 and +5.1 for PDN.

Evolution of cushingoid symptoms

Clinically assessed cushingoid symptoms were similar at the start of the study in both groups and tended to be lesser after 12 months in the DFZ group. At the start, 6 patients from the DFZ group and 10 from the PDN group had no cushingoid symptoms. After 1 year, 12 patients from the DFZ group had no symptoms compared with 8 from the PDN group (Table 2). The blind assessment of face and trunk photographs at the start of the study and after 6 and 12 months also tended to show less cushingoid symptoms (Fig. 2), but with both methods the difference did not reach statistical significance.

Adverse events

Mean blood pressure, both systolic and diastolic, at the start, and at 3, 6, 9, and 12 months was not different in the two groups. Three patients in each group received antihypertensive drugs. This treatment was started during the study in the DFZ group, but was already prescribed in the PDN group. Two patients in the DFZ group had gastralgia and 1 patient in the PDN group had hematemesis. Finally, 1 patient in the PDN group exhibited necrosis of the femoral head.

Biochemistry

No difference was found between the two groups for all the biochemical parameters at the start and at 3, 6, 9, and 12 months of the study, i.e., hemoglobin, blood count, including polymorphonuclear leukocytes, eosinophils, and platelets, plasma creatinine, blood urea, fasting blood glucose and glycosylated hemoglobin, plasma sodium, potassium, chloride, bicarbonate, bilirubin, serum glutamate/oxalate and glutamate/pyruvate transaminases, alkaline phosphatases, ionized and total plasma calcium, phosphorus, total proteins, albumin, cholesterol, and triglycerides. Urinary calcium excretion was also similar with both treatments: 2.3 mmol/day at 6 and 12 months, respectively with DFZ, 2.5 and 2.3 mmol/day with PDN.

Discussion

The present study, already partially reported in abstract form [11], is the first controlled trial of DFZ in children with INS.

During the 1-year period of this study, 12 of 20 patients remained in remission with DFZ compared with only 2 of 20 with PDN. Considering the first relapse occurring during the study as an end point, these data unequivocally showed that DFZ given in an equipotent dose was more effective than PDN. It is unclear why the mean cumulative dose of both drugs was similar in the two groups and why the DFZ group, who had few relapses and were given steroid according to the same protocol, did not receive a lower dose. One hypothesis is that the patients in this group had a slightly higher level of corticosteroid dependency, as indicated by the slightly higher dose of PDN they received at the time of the last relapse before the study. However, although the cumulative dose of steroid was not significantly different, there was a significant difference in the relapse rate.

Two studies of DFZ in nephrotic syndrome have been reported in adult patients. Olgaard et al. [5] found a similar efficacy of high doses of both drugs in terms of reduction of proteinuria. Piccoli et al. [15], using the same equipotent ratio as in the present study, found a greater efficacy of DFZ in a short-term (2×5 weeks) crossover study. In both studies, however, the underlying renal disease was predominantly membranoproliferative or membranous glomerulonephritis, with only a few cases of supposed INS, and no information was given in terms of relapse in these cases.

Cushing syndrome, blindly assessed from serial photographs in the present study, appeared less marked in patients receiving DFZ, but the difference did not reach significance; the change in body weight was close to significance. Therefore, this study only showed a tendency for fewer adverse effects of DFZ than PDN, but the small number of patients precludes any conclusion. A recent study in adult patients with rheumatoid arthritis showed a clear difference in terms of Cushing syndrome after 1 year of DFZ treatment [1]. Moreover, pooled data from 46 clinical studies involving more than 1,000 patients revealed an overall incidence of adverse events in DFZ recipients of 16.5% versus 20.5% in PDN recipients [9].

Height SDS was significantly higher in the PDN group at the start of the study, but there was no significant difference at the end of the study, as the patients of the PDN group had a greater decrease in their mean SDS. This could be interpreted as a greater adverse effect of PDN on growth than DFZ. However, the mean growth velocity was not different and the change in height SDS was also not different in the two groups. Some studies have shown that growth velocity was less affected in children treated with DFZ than those receiving PDN [7, 16, 17], but this was not so in the present study. This may be due to an excessive dose of corticosteroid in these patients.

Regarding cushingoid symptoms, the present study showed only a tendency for a smaller bone density decrease in patients receiving DFZ. Such an effect was first suspected in a clinical uncontrolled study [18], then proven in an animal study which showed less hypercalciuria with DFZ [19]. It was also observed in controlled studies in adult patients with the nephrotic syndrome receiving DFZ for 12 months [5], in premenopausal women with rheumatoid arthritis [3], and in 12 adult patients with different diseases blindly allocated to DFZ or PDN [20].

A difficult problem when comparing two corticosteroids is to determine their equipotency. This is usually estimated from the antiinflammatory activity either in vitro or in vivo. Since the results of animal studies may be misleading, it is best to compare the drugs in man, considering a good control of symptoms as the end point. Such control could differ among diseases. On the basis of studies in adults with rheumatoid arthritis, DFZ is less potent than PDN, and the equivalence ratio between DFZ and PDN is most likely to be 1.2 : 1 [2]. This was the ratio used in the present study. A more recent estimation based on the results of seven trials involving 160 patients gives a potency ratio of DFZ versus PDN of 1.3: 1 [9, 21]. According to these data, it is possible that DFZ was underused in the present study, but this would tend to reinforce the conclusion of the better activity of this drug in INS.

Although the pathogenesis of INS is still unclear, dysfunction of T lymphocytes is highly suspected. The present results may thus be explained by a difference in the immunomodulatory effect of DFZ and PDN. A single oral dose of DFZ induces T cell depletion and affects the ratio of helper, inducer/suppressor, cytotoxic T cells for up to 72 h, while they return to baseline levels within 24 h following PDN [22, 23]. This change in the OKT4/OKT8 cell ratio

has been consistently found in patients treated daily with DFZ, while it is inconsistent during PDN treatment. These changes in T lymphocyte subsets were confirmed in another study of patients after kidney transplantation [24].

In conclusion, this study showed that DFZ was more effective in limiting relapses in children with corticosteroid-dependent INS and that the side effects had a tendency to be less marked with this drug than with PDN. This drug certainly deserves further study on a larger scale to reach definitive conclusions.

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