Clinical study

LONG-TERM CYCLOSPORIN A FOR PSORIASIS

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ABSTRACT

We report on a randomized cyclosporin A (CyA) dose-finding trial: 1.25 mg versus 2.5. mg/kg/day. In context with the results of other trials, we favour a CyA-starting dose of 2.5 mg/kg/day. It is mandatory that all patients should undergo a careful dermatological, physical and laboratory examination before therapy, including a careful monitoring during treatment considering the up to now established guidelines of drug administration to minimize the risk of side-effects.

KEY WORDS

psoriasis, cyclosporin A, long-term treatment

INTRODUCTION:

Oral CyA has been widely used in controlled trials for treating different forms of psoriasis with impressive results.

Published data are available for short-term and long-term treatments lasting over a continuous period of at least 12 months up to more than 54 months. In those long-term trials the initial or intermittent administration of Cyclosporin A (CyA) doses vary between 1 to 8.4 mg. (8-11, 25). We conducted a randomized dose finding trial using 1.25 vs 2.5 mg/ CyA/kg over a period of 12 months. This was followed by a 3-month observation period during which no treatment was given.

PATIENTS AND METHODS

PATIENTS

A total of 22 patients suffering from severe psoriasis vulgaris were included in the study. The age of the patients at the commencement of treatment was between 28 and 69 years (average age 45.9 years). Four of the 22 patients were females and 18 were males. Patients considered for this type of treatment should suffer from severe psoriasis vulgaris and show insufficient response or resistance to conventional therapeutic schedules (cignolin, UVA, SUP, PUVA, etretinate). A PASI-Score > 16 had to be present in order to be included in this study.

* *Dedicated to the 70th birthday of Prof. Dr. S. Borelli*

Patients with severe kidney and liver illnesses, malignant diseases, acute infections of any type, extreme cardio-vascular and neurological illnesses, digestive disorders, drug or alcohol abusers, as well as pregnant or lactating women were excluded from this study. Use of any other conventional type of treatment for psoriasis was not allowed during this period.

METHODS

Evaluation of the severity of the disease was assessed by the Psoriasis-Area-Severity-Index (PASI), in which the parameters erythema, infiltration, desquamation as well as extension are included (4).

Patients enrolled in the study were randomized into two treatment groups. 10 patients received a daily CyA-Dosage of 1.25 mg/kg.

The other group in which the remaining 12 patients were included was given a daily dosage of 2.5 mg/kg CyA. The daily dosage was divided equally and given orally, mornings and evenings. The therapy should be continued for a period of 12 months for each patient.

In order to be able to judge the success of the therapy the PASI-Score was evaluated at the beginning of the treatment period, after 1, 2, 3, 4, 6, and 8 weeks and from then on at 6-weekly intervals over the entire treatment period. Blood pressure, blood count and urine samples as well as serum parameters were also obtained at the aforementioned intervals. The CyA-levels were also assessed at the same time, ensuring that the CyA intake took place 12 hours previously.

A reduction of the PASI-Scores to at least 90% of the initial PASI after 2 weeks, to at least 70% after 6 weeks and to at least 25% (PASI-Score < 8) after 12 weeks was considered to be a successful treatment result.

In cases where there was an insufficient response or where the condition deteriorated, i.e. increase of PASI > 50% over the initial PASI, the daily treatment dosage was increased. For these patients the daily dosage was increased from 1.25 mg to 2.5 mg and this dosage was maintained throughout the remainder of the treatment period. For patients receiving 2.5 mg it was planned that this dose should be increased over a period of between 6-12 weeks up to 5 mg. Following this, with the appropriate reduction in the PASI, a continuing of the treatment with 2.5 mg was planned. In cases where there was insufficient reduction of the PASI or where a continuous deterioration of the condition occurred (non responder) the treatment was discontinued. A 3-monthly phase of follow-up observations was made after regular completion (after 12 months) or discontinuation of the therapy.

RESULTS

In this 12 months lasting treatment 22 patients were enrolled. The initial dose for 10 patients was 1.25 CyA. Two exclusions because of hypertension, one failure, two treatments up to month 12 with PASI-reduction between 60% and 87%. Five patients were switched from 1.25 mg to 2.5 mg CyA. In this group three were non responders, one exclusion because of diarrhoea and only one efficient treatment up to month 12. Out of 12 patients treated initially with 2.5 mg CyA, 7 patients improved with PASI-reduction between 74% and 88% during the 12 months lasting therapy. Two exclusions because of serum creatinine rises, 3 because of non compliance. A transitory increase in uric acid level (5 pat.), triglyceride level (3 pat.), cholesterol and bilirubin (1 pat.) was not long lasting (Figure 2). No tachyphylaxia, no rebounds during a 3 months lasting follow up but relapse in all patients with increase ≥PASI to 50% of the initial PASI were observed (Fig. 1).

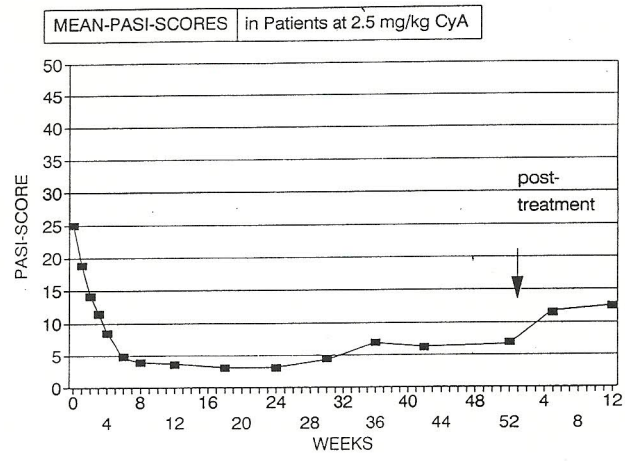


Figure 1: Mean PASI-Scores in patients on 2,5 mg/kg CyA during a 52 weeks lasting treatment and a 12 weeks lasting follow-up.

DISCUSSION

In the course of our dose-finding study CyA 1.25 mg/kg versus 2.5 mg/kg daily, the 2.5 mg dosage proved to be definitely superior. A continuous reduction of the PASI-Scores during the first six months of therapy was followed by instability and in some cases a tendency to become worse was ascertained. The fact that 2 of the patients successfully responded to a dosage of only 1.25 mg over the twelve-months period reconfirms the dosage spectrum and response behaviour as shown in the appropriate literature (8-11, 19, 25).

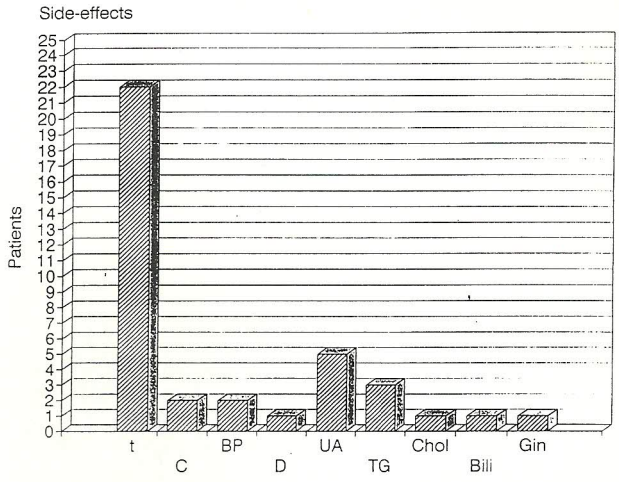
None of our patients showed any signs of tachyphylaxia or rebounds during the entire treatment period as was the case in the above mentioned long-term studies. After cessation of therapy a gradual increase in the PASI-Scores of up to 60% of the final values was noted in the 1.25 mg group, and of up to 50% in the 2.5 mg group during the three months post-treatment observation phase.

Cumulative data from multiple studies in more than 1000 patients and the results of our own studies favour an initial CyA dosage of 2.5 mg with the advise that, when favourable results occur, the lowest effective CyA dosage (LED) should always be looked for (26). If after one month there is no sign of response to the treatment an increase (about 1 mg every 2 weeks) of up to a maximum of 5 mg/kg limited to 6 weeks is recommended (6, 17, 26). If good improvement occurs, the dose should be reduced in steps of 0.5 - 1 mg to LED.

A total clearing of the psoriasis lesions should not be attempted. If a clinical improvement of 3/4 PASI compared to the original PASI occurred, every attempt should be made to attain to a maintenance therapy with the lowest effective dosage. Local corticosteroids could also be administered in limited quantities (7). More recently we had good success using calcipotriol. Similarly a combination with retinoids (10) or fish oil is worth considering (24).

Before starting a CyA therapy it is recommended that after clinical examinations all laboratory values (serum creatinine, uric acid, serum potassium-magnesium, liver enzymes, bilirubin, fasting lipids, differential blood count, urinary protein) as well as blood pressure measurements should be undertaken on 2 - 3 different occasions in order to establish or to exclude the presence of any malfunctions (6, 7). With a rise in serum creatinine (SK) it is advisable to test the glomerular filtration rate (GFR) and control it after 1/4 to 1 year as an additional safeguard (6, 16, 17). Increased creatinine > 30% of baseline value affords reduction of CyA dosage by 25 - 50% for 1 month (17). Should the SK remain high, then the CyA dosage should be completely withheld for one month. Should the SK return to 10 % over the baseline values then a continuation of the therapy is possible. Blood pressure measurements and laboratory checks should be made every 14 days up to 3 months and thereafter on a monthly basis. It has been proved that the risk of untoward reactions, especially nephropathy, depends upon the CyA dosage. This risk shows a marked increase when the limit of 5 mg/kg body weight is exceeded (5, 6, 12, 25).

Beside this careful monitoring it is mandatory to discuss the reports of non-melanoma skin cancer in



Legends

t	total of patients
C	Elevated plasma creatinine/exclusion
BP	Elevated blood pressure/exclusion
D	Diarrhoea/exclusion
Gin	Gingival hyperplasia

Above upper normal limit

Chol	Cholesterol
Bili	Bilirubin
UA	Uric Acid
TG	Triglycerides

Figure 2: Observed side-effects in all 22 treated patients. Exclusion of further CyA treatment because of: elevated plasma creatinine in 2 patients, elevated blood pressure in another 2 patients and diarrhoea in one patient. Only temporary elevation of uric acid, triglycerides, cholesterol and bilirubin returning to normal values during treatment. Gingival hyperplasia persisted.

patients suffering from psoriasis who were treated with CyA (14). It is striking that both PUVA and methotrexate (MTX) have been used prior to the CyA treatment. We have since learned from numerous reports that there is a marked increase in non-melanoma skin cancer after long-term PUVA-therapy (2, 13, 18, 23, 27). There seems to be a close relation to the number of treatments and the cumulative UVA dosage (1, 2, 13, 18).

The male genital area has proven to be the area which is especially endangered (13, 18, 22), although this is open to discussion how often a PUVA therapy is preceded by a tar treatment (18).

In the course of previous examinations MTX was not considered to be a risk factor for the development of skin malignancies (21). However, concerning the data of 227 patients suffering from psoriasis it could be proved that PUVA, MTX and their combined use most certainly increase the risk of skin carcinomas in connection with the prior exposure to cocarcinogens (14).

Up to now there have been no reports of mutagenous characteristics from CyA (15, 20). The incidence rate of carcinomas from CyA are not considered to be of any significance (3).

Because of the selective immunosuppression of CyA it is to be recommended that no additional immunosuppressive or PUVA or UV should be administered when psoriatic patients are treated with CyA (17). Patients who have previously undergone treatments with PUVA or with MTX require regular dermal examinations over short intervals.

Previously MTX treated patients with persistent malfunctions of the liver tend towards increased CyA-blood levels (7).

In order not to bring this valuable medicament unnecessarily into discredit there must be a control of both the exclusion and inclusion criteria in addition to a strict monitoring of all patients during treatment.

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