Cyclosporin A Treatment in Psoriasis: Monitoring by Neopterin Concentrations in Serum and Urine

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Summary

Psoriasis is a hyperproliferative skin disorder in which immune mechanisms are thought to play a role. Recently, cyclosporin A has been found effective to treat psoriasis. However, mechanisms of action of cyclosporin A in patients are not well understood. We investigated seven patients (6 males, 1 female, aged 29-58 years) with severe psoriasis, three of them associated with arthropathy. The patients were treated with cyclosporin A given twice daily in gelatine capsules. Four patients were given 5 mg/kg, the others received 2.5 mg/kg initially. Two of them were put on 5 mg/kg (after 4 and 12 weeks of treatment). Clinical evaluation before and during therapy was carried out using the Psoriasis Area and Severity Index (PASI). Patients were followed up for 6 and 15 months. Their cyclosporin A blood levels were adjusted by a monoclonal radioimmunoassay. In parallel, serum and urine neopterin levels were quantified by HPLC. Mean neopterin concentrations in patients prior to therapy were found only slightly higher (serum 6.5 ± 0.8 mmol/l) than in healthy controls. There was no correlation of neopterin values and the degree of PASI-score. Onset of cyclosporin A was paralleled by decreasing neopterin concentrations and improvement of the skin status. Decrease of cyclosporin A doses was accompanied by an increase of PASI and significantly decreasing neopterin levels. In patients with severe relapses of psoriasis after withdrawal of cyclosporin A, neopterin rose higher than pretreatment levels. In 6/7 patients PASI and neopterin levels were closely correlated.

Key words: Psoriasis, Neopterin, Interferon-gamma, Psoriasis activity and severity index, Cyclosporin A

Introduction

Psoriasis is a common chronic, inflammatory skin disorder. There is evidence for an important role of immune mechanism in the pathogenesis of psoriasis (1). The recent introduction of cyclosporin A, which inhibits T-cell activation and cytokine release, as a highly effective treatment of psoriasis (2) had also an impact for the understanding of the immunological mechanisms of psoriasis.

Interferon-gamma (IFN-gamma) is detectable in psoriatic epidermis (3), and the intradermal administration of IFN-gamma to human individuals some-

times provokes clinical and histopathological changes comparable to psoriasis (4). Since neopterin is released by macrophages upon stimulation by IFN-gamma (5), we were interested whether the clinical response of psoriasis to cyclosporin A is accompanied by changes in the serum or urine neopterin levels.

Methods

We investigated seven patients (6 males, 1 female, aged 29-58 years) with severe psoriasis (Psoriasis Activity and Severity Index-PASI-score ≥ 20), three of them associated with arthropathy. The patients were

treated with cyclosporin A (Sandoz, Basle, Switzerland) given twice daily in gelatine capsules. Four patients were given 5 mg/kg body weight, the others received 2.5 mg/kg, initially. Two of the latter patients were put on 5 mg/kg later on (after 4 and 12 weeks of treatment) because of an unsatisfactory response on the lower dosage of cyclosporin A.

Clinical evaluation before, during and after therapy was carried out using the PASI score. Patients were followed up for 10 to 18 months. Determination of serum and urinary neopterin levels was performed. Serum neopterin concentrations were evaluated using radioimmunoassay (Henning-Berlin, Germany) (6). Neopterin in urine samples was assessed using high performance liquid chromatography (HPLC) as previously described (7). Neopterin concentrations were related to concomitantly determined creatinine levels to compensate for physiological variations of urine dilution.

Statistics

For comparison of paired data, Wilcoxon paired rank test was applied. Correlation analyses were performed using Spearman rank correlation test.

Results

Clinically all patients responded well after 6 weeks with the 5 mg/kg dosage. Pretreatment mean PASI-index of 24 ± 2.3 was reduced by 5 mg/kg cyclosporin A to mean values of 5 ± 3.9 ($p < 0.01$) after 6 weeks of treatment. Five patients tolerated therapy well. Side effects in two patients (herpes zoster, nephrotoxicity) led to discontinuation of therapy.

Mean neopterin concentrations in patients prior to therapy were found to be only slightly higher (mean $\pm$ S.D.: 6.5 ± 0.8 nmol/l) than in healthy controls (5.3 ± 2.7 ; not significant). Only one out of these patients had serum and neopterin levels before treatment with cyclosporin A above 8.7 nmol/l, which is the 9th percentile of healthy controls (6). There was no correlation of neopterin values and the degree of PASI-score (Table 1).

Onset of cyclosporin A with the higher dosage of 5 mg/kg body weight was paralleled by decreasing neopterin concentrations and improvement of the skin status. Decrease of cyclosporin A dosage was accompanied by an increase of PASI and neopterin (Fig. 1). Compared to pretreatment levels significantly decreased neopterin levels either in serum or in urine were observed during therapy ($p < 0.05$).

Table 1.

Patient	Age	PASI	Neopterin serum [*]	Concentration urine [*]
1	62	24.2	10.5*	215
2	49	27.4	5.6	145
3	42	23.7	4.8	177*
4	33	19.7	5.8	207*
5	42	30.7	6.4	101
6	38	23.6	6.2	214*
7	46	25.2	6.9	225*

*Neopterin increased compared to average of normal healthy controls of same age (serum in nmol/l, urine in μ mol/mol creatinine)

Figure 1. PASI-scores and serum and urine neopterin levels: 7 patients with severe psoriasis before (0), during (1; last measurement before withdrawal) and after (2) therapy with cyclosporin A. Median and 25th-75th percentiles are shown.

* $p < 0.05$, Wilcoxon paired rank test.

A correlation between urine and serum neopterin levels was observed during therapy ($r_s = 0.786$, $p = 0.05$). Serum and urine concentrations correlated moderately with PASI-score before therapy was stopped ($r_s = 0.600$, $p = 0.14$ and $r_s = 0.709$, $p = 0.08$). In two young patients, who suffered from severe relapses of psoriasis after withdrawal of cyclosporin A, serum and urine neopterin concentrations rose higher than pretreatment levels. In 6 of 7 patients, PASI and neopterin levels during follow-up were closely correlated, in one patient less so ($p = 0.018$). Two typical courses of PASI-scores and neopterin-levels during follow-up are shown in Figs. 2 and 3: In patient 3 increase of serum neopterin levels preceded the relapse of psoriasis (Fig. 2), whereas in patient 6 increase and decrease in serum neopterin levels correlated time-dependently with increase and decrease of PASI (Fig. 3). The increase of PASI-score and serum neopterin-levels after withdrawal of therapy was significant (Fig. 1); it was less so

Figure 2. Course of serum neopterin concentration (nmol/l) and PASI-scores in patient 3 during therapy: increase of neopterin preceded the relapse of psoriasis after withdrawal of cyclosporin A.

Figure 3. Course of serum neopterin concentrations (nmol/l) and PASI-scores in patient 6 during therapy: decrease and increase of serum neopterin concentrations correlated time-dependently with severity of psoriasis measured by PASI-scores.

for urinary neopterin levels ($z=1.16$, $p=0.11$). In contrast to neopterin levels PASI-score still stayed lower than pretreatment levels ($z=2.10$, $p=0.04$).

Discussion

Our results correspond to previous investigations which demonstrated IFN-gamma in the epidermis of psoriasis patients (3). Increase and decrease of neopterin concentrations in patients with psoriasis depend on the clinical status of the disease in individual patients but no association between neopterin levels and PASI was observed cross-sectionally. The data suggest an involvement of endogenously released IFN-gamma, which induces release of neopterin by human monocytes and macrophages in the pathogenesis of psoriasis. However, the pretreatment

value of serum neopterin was elevated in only one patient. This may be explained by the fact that, on the one hand, the neopterin molecule does not sufficiently diffuse from the periphery into the blood stream (9) and on the other hand, the release of IFN-gamma is more important for the neighbouring keratinocytes in loco.

The involvement of IFN-gamma in the pathogenesis of psoriasis would explain some of the clinical phenomena. Under normal conditions, IFN-levels in peripheral blood are not detectable in psoriasis patients (unpublished data). Also, neopterin levels are within the normal range in the majority of patients.

Infections with viruses, for example, with a massive production of IFN-gamma and neopterin are often accompanied by the occurrence or relapse of psoriasis. During virus infections highly increased neopterin-levels are observed (10) which indicate T-cell activation and production of IFN-gamma. In our study, a rebound phenomenon with a massive relapse of psoriasis was accompanied by dramatically increasing neopterin levels (Figs. 2, 3). Likewise amelioration of psoriasis is often observed after viral infections. Interestingly an increase of urinary neopterin levels was also described earlier in kidney allograft recipients after withdrawal of cyclosporin therapy (8). These data may indicate that cytokine pathways, like IFN-gamma release, which are inhibited by cyclosporin A, became reactivated after withdrawal of therapy.

In contrast to recent results of Harland *et al* (11), there was no significant correlation of PASI-index and urine neopterin levels in our study. However, the number of patients is certainly too small for a final conclusion. In addition to that, our study revealed generally normal neopterin levels of patients with severe chronic plaque psoriasis compared to healthy controls; however, during follow-up, increase and decrease of PASI was associated with increase and decrease of neopterin concentrations in all patients. Our findings and also the results of other studies (3, 4) may indicate that IFN-gamma plays an important pathogenetic role in the development of psoriatic lesions. This may also explain the clinical phenomenon of virus infection associated relapse of psoriasis as well as of the psoriasis associated with human immunodeficiency infection (12): In these patients significantly elevated serum IFN-gamma levels were found as well as elevated serum neopterin levels (10, 13). In psoriasis, probably activation of T-cells is followed by a release of IFN-gamma, which acts as a proinflammatory cytokine in skin and may also be important in the epi-

dermotropism of T-lymphocytes in psoriasis (14). Our data are in line with observations of others (1, 3, 4) suggesting an important role of IFN-gamma in the pathogenesis of psoriasis.

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