Acta Derm Venereol (Stockh) 1996; 76: 357–360

Soluble Interleukin-2 Receptor (sIL-2R) Is a Marker of Disease Activity in Psoriasis: A Comparison of sIL-2R, sCD27, sCD4, sCD8 and sICAM-1

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Psoriasis is a T-cell-mediated inflammatory skin disease which can be treated successfully with immunosuppressive drugs. Our purpose was to evaluate disease activity of psoriasis and the effect of immunosuppressive treatment by monitoring the soluble T-cell products sIL-2R, sCD27, sCD4, sCD8 and sICAM-1.

Twenty-two patients were treated orally with escalating dosages of cyclosporin A ($n=17$)(3–5 mg/kg/day) or FK506 ($n=5$)(0.05–0.15 mg/kg/day). The Psoriasis Area and Severity Index (PASI) was used to monitor clinical activity of psoriasis. Serum samples were analyzed by ELISA.

sIL-2R levels showed the highest correlation with psoriasis disease activity ($r_s=0.89$; $p<0.05$). The longitudinal part of this study showed that levels of sIL-2R and sCD27 decreased during immunosuppressive treatment but remained above normal even in patients successfully treated.

Our data indicate that sIL-2R levels are well correlated with disease activity in patients with psoriasis. sIL-2R levels closely follow the decrease of disease activity during immunosuppressive treatment. ***Key words: T-lymphocytes; immunodermatology; CD25.***

(Accepted March 18, 1996.)

Acta Derm Venereol (Stockh) 1996; 76: 357–360.

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Psoriasis is a chronic inflammatory skin disease, sometimes accompanied by manifestations of arthritis. The beneficial effect of immunosuppressive drugs (cyclosporin A, FK506, anti-CD4 monoclonal antibodies) together with immunohistological data support the hypothesis that psoriasis is a T-cell-mediated dermatosis (1–4). The disease activity can be scored by using the Psoriasis Area and Severity Index (PASI). Although the PASI is well documented and frequently applied in clinical studies, it is hampered by the lack of objectivity. It can therefore be anticipated that quantitation of soluble T-cell activation products can be an alternative useful tool to monitor disease-activity in patients with psoriasis.

The synthesis and expression of IL-2R represent an early sign of T-cell activation, which is accompanied by the release of a soluble product: sIL-2R (5). CD27 is a surface antigen found on T-cells and a small subset of B-cells. Activation of T-cells via the T-cell receptor-CD3 complex leads to a transient increase in the membrane expression of CD27 that peaks 3 to 4 days after activation (6, 7). Increased serum levels of a 32 kDa soluble form of CD27 have been found in patients suffering from various T-cell-mediated diseases, including psoriasis (8, 9).

In addition, analysis of levels of the soluble CD8 molecule was included in this study because evidence has been put forward that serum sCD8 levels are increased in psoriasis (10). Since we and others have shown that increased CD4/CD8 ratios can be found in psoriasis, sCD4 levels were studied as well (11, 12).

Increased levels of soluble adhesion molecule ICAM-1 have been found in various cancers and inflammatory conditions, including psoriasis (13–16). Longitudinal studies on sICAM-1 of psoriasis patients treated with FK506 and cyclosporin A are of potential interest, since sICAM-1 levels reflect the activation of various inflammatory cells including endothelium.

Treatment of psoriasis with the immunosuppressive drugs cyclosporin A and FK506 can lead to dose- and time-dependent side-effects (17, 18). For this reason assays are needed to monitor disease activity and objectively evaluate therapeutical response in order to optimize immunosuppressive treatment. We therefore performed a longitudinal study in psoriasis patients during immunosuppressive treatment with cyclosporin A and FK506. Serum samples were analyzed for levels of the T-cell activation products sIL-2R and sCD27. Our findings show that sIL-2R levels are well correlated with the clinical manifestation of psoriasis and that during immunosuppressive therapy the levels of sIL-2R closely follow the decrease of disease activity.

MATERIALS AND METHODS

Patients

Twenty-two patients (aged 18–70 years) with moderate and severe chronic plaque type psoriasis, who unsatisfactorily responded to conventional therapy, were included in this study. Patients participated in a multicentre trial designed for evaluation of guidelines for the use of cyclosporin A (19) and in a double-blind placebo-controlled study on the effectiveness of FK506 (18). Written informed consent was obtained from all patients. Exclusion criteria specified that patients should not have received systemic treatment for 4 weeks or any active topical treatment for 2 weeks prior to entering the study. Further exclusion criteria were: impaired liver, kidney or heart function, (drug-controlled) hypertension, arteritis, a history of pancreatitis or diabetes mellitus, malignant tumour, infection, serious hypersensitivity, epilepsy and pregnancy. Uncooperative patients who were unlikely to comply with medical prescriptions and who were not willing or otherwise uncapable to attend regular visits were excluded. Patients receiving drugs known to influence the course of psoriasis were not allowed to enter the study. Formal approval for these studies was given by the medical ethical committee of this hospital.

 ISSN 0001-5555

Evaluation of patients and study medication

The severity of the psoriasis was evaluated at each consecutive visit by means of the Psoriasis Area and Severity Index (PASI) (20).

Patients received 3.0 mg/kg/day cyclosporin A at start. If, after 4 weeks, the PASI reduction was less than 25% of the baseline value, the dose was increased with 1 mg/kg/day to 4 mg/kg/day. At 8 weeks, a dose increase of 1 mg/kg/day was performed in case of a PASI reduction of less than 50%, resulting in a dose of 4 mg/kg/day for those who responded at week 4 and still were on 3 mg/kg/day, or in a dose of 5 mg/kg/day for those who had already had a dose increase. At week 12 the dose was increased with 1 mg/kg/day if the PASI reduction was less than 60%.

Patients treated with FK506 received an initial dose of 0.05 mg/kg/day. In the case of insufficient efficacy and the absence of adverse events, the dose was increased by 0.05 mg/kg/day to 0.10 mg/kg/day and 0.15 mg/kg/day at the end of weeks 3 and 6, respectively.

Quantitation of disease activity markers

Blood samples were taken at regular intervals and serum was stored at −20°C. All samples were collectively analysed. sIL-2R, sCD4, sCD8, and sICAM-1 levels were measured by enzyme-linked immunosorbent assay (ELISA) (T Cell Sciences, Cambridge, MA, USA) according to the manufacturer's instructions.

For sCD27 measurement an ELISA with a catching CLB-CD27/2 MoAb and biotinylated CLB-CD27/1 detecting MoAb was used (21). The detection limit is 5 U/ml. All samples were measured in duplicate.

Statistical analysis

The Spearman rank correlation (r_s) was used for calculation of the relation between the PASI and the data on the soluble serum factors.

RESULTS

Disease activity markers in patients with psoriasis before treatment

sIL-2R, sCD27, sCD4, sCD8 and sICAM levels were quantitated in 17 patients suffering from psoriasis before treatment with cyclosporin A (see Table I).

Soluble IL-2R levels were increased in 71% of the patients. The mean sIL-2R level was 784 U/ml (normal mean 444 U/ml). sCD27 levels were above the normal range in 35% of the patients but the mean sCD27 level was not increased. sCD8 levels were increased in 18% of the patients. The mean sCD8 level was 388 U/ml (normal mean 336 U/ml). sCD4 levels in all patients were normal. The mean sICAM-1 was 341 U/ml (normal mean 304). After calculation of the correlation between the PASI and these disease activity markers it was clear that serum levels of sIL-2R had the highest correlation ($r_s = 0.89$; $p < 0.05$) with the PASI. sICAM-1 levels gave a much lower correlation ($r_s = 0.62$; $p < 0.05$), while the correlation (r_s) between the soluble CD27 serum levels and the PASI was only 0.40 ($p < 0.05$).

Table I. *Serum levels of disease activity markers and Psoriasis Area and Severity Index (PASI) in patients (n=17) before treatment with cyclosporin A*

	PASI	sIL-2R U/ml	sCD27 U/ml	sCD4 U/ml	sCD8 U/ml	sICAM-1 ng/ml
Mean	16.2	784	211	26	388	341
Range	7.2–30.6	429–1214	129–330	7–50	129–678	221–630
s.d.	6.7	207	46	13	155	90
r_s		0.89	0.40	0.20	−0.01	0.62
NORMAL VALUES						
Mean		444	165	33	336	304
Range		268–620	112–217	4–62	138–533	183–585

Efficacy of cyclosporin A in psoriasis

Assessment of the PASI during cyclosporin A treatment showed a mean reduction of 78% after 16 weeks. Three patients (18%) showed a complete remission and 5 patients (29%) a PASI reduction of more than 75%. Eight patients (47%) showed a PASI reduction between 50 and 75%, and one patient showed a reduction of only 48%. No treatment failures were seen among these patients.

sIL-2R and sCD27 levels during cyclosporin A treatment

Because of the baseline results of sIL-2R and sCD27 levels in untreated patients, sIL-2R and sCD27 were monitored during cyclosporin A treatment. The mean level of sIL-2R dropped after 4 weeks from 784 U/ml to 603 U/ml (4 weeks), 480 U/ml (8 weeks) and 505 U/ml after 12 weeks (normal mean 444 U/ml). Three patients (18%) still showed high sIL-2R levels (1,081, 1,016 and 1,214 U/ml) after 4 weeks of cyclosporin A treatment. Two of these 3 patients suffered from very severe psoriasis, with little improvement after the first 4 weeks (baseline PASI 30.6 and 20.0; after 4 weeks 25.1 and 20.4, respectively). After 16 weeks of cyclosporin A treatment 15 of the 17 patients (88%) showed normal sIL-2R levels, although the mean level was above normal.

The mean sCD27 serum level was about 200 U/ml (normal 165 U/ml).

After cyclosporin A treatment sCD27 serum levels were increased in 5 patients (29%), although the mean PASI of these patients showed an 80% improvement of the psoriasis (11.3 to 1.3). The 2 patients with increased sIL-2R serum levels after cyclosporin A treatment also showed elevated sCD27 serum levels.

sIL-2R serum levels during FK506 treatment

Five patients were treated with escalating dosages of FK506 for 9 weeks. The mean initial PASI dropped from 19.8 to 9.1 (54% improvement). sIL-2R levels were measured at 3-week intervals. The mean baseline sIL-2R serum level was elevated (901 U/ml; normal mean value 444 U/ml; range 268–620 U/ml). During treatment with FK506 the mean sIL-2R serum level decreased to 634 U/ml. As an example, one patient who suffered from very severe psoriasis (PASI 43.4) also showed very high levels of sIL-2R (2,267 U/ml). The psoriasis of this patient decreased after 3 weeks of FK506 treatment by 37% (PASI reduction) and parallel to this improvement the serum sIL-2R levels showed a 47% decrease.

DISCUSSION

Our findings indicate that the soluble T-cell factors sIL-2R and sCD27 are elevated in psoriasis, while sCD4 is not and sCD8 is only marginally increased. Moreover, the soluble product of ICAM-1, which is expressed by leukocytes, endothelial cells, fibroblasts, macrophages and keratinocytes, was also increased (22). For quantification of psoriasis sIL-2R

seems to be superior to sICAM-1 and sCD8, since the best correlation was found between sIL-2R and the PASI ($r = 0.89$). Psoriasis patients treated with optimal dosages of cyclosporin A and FK506 showed a decrease of sIL-2R, although the mean sIL-2R levels remained elevated.

T-lymphocytes are thought to be pivotal in the pathogenesis of psoriasis (1). Parallel to other T-cell-mediated diseases, increased levels of the T-cell activation product sIL-2R could therefore be anticipated (23) and were indeed found in psoriasis (9, 10, 24–26). Since cyclosporin A and FK506 are both immunosuppressive drugs that inhibit T-cell activation, a decrease of T-cell activation products during treatment is not surprising. Cyclosporin A and FK506 inhibit the biosynthesis and gene expression of IL2 (27, 28). Although there was a significant decrease of sIL-2R during treatment with cyclosporin A, a small but persistent elevation of sIL-2R, as compared to baseline, remained detectable. This finding is in agreement with others who found that clearing of psoriasis by using tar did not have any effect on elevated sIL-2R levels (25).

Our data on the T-cell activation product sCD27 also clearly demonstrate that there is increased T-cell activation in untreated psoriasis patients. Moreover, increased levels of sCD27 were seen even during treatment with effective dosages of cyclosporin A, parallel to the sIL-2R data, thus suggesting that T-cell activation remained even during immunosuppressive treatment. The mechanisms controlling the shedding and excretion of sCD27 are at present not well understood (21). The lack of any significant decrease of serum sCD27 levels could be related to the fact that lesional skin T-cells are predominantly CD27-negative (12). Alternatively, sCD27 could be partly derived from a recently identified subset of B-cells (29). Quantitative and qualitative studies regarding these B-cells in psoriasis and their contribution to sCD27 serum levels are lacking.

sICAM-1 is not derived from one single celltype; ICAM-1 is inducible on several types of cells involved in inflammation in general (13) and psoriasis (22). Indeed, several groups showed that increased levels of sICAM-1 are present in psoriasis (14–16). Our data support these findings and also show that the disease activity according to the PASI is correlated ($r_s = 0.62$) with sICAM-1 levels.

sICAM-1 contains most of the extracellular region of ICAM-1 and has retained the ability to bind to LFA-1 (13). We previously demonstrated that binding of ligand to LFA-1 results in the transduction of regulatory signals in T-cells (30). sICAM-1 can therefore interfere with T-cell activation.

sICAM-1 can function as a rhinovirus receptor (31). However, the contribution of elevated levels of sICAM-1 in psoriasis patients in relation to rhinovirus infections remains elusive.

Previous studies published by Kapp (32) indicate that elevated levels of sCD8 can be found in psoriasis patients. Our data partly support these findings; sCD8 serum levels were only marginally increased. Moreover, sCD8 serum levels were not correlated with psoriasis disease activity (PASI) and are therefore not suitable for monitoring of immunosuppressive treatment.

Our findings indicate that there is increased T-cell activation in psoriasis. Moreover, even during and after successful immunosuppressive treatment, indications of activation of the immune system are present. This suggests that there is a discrepancy between the inflammatory process and the disease activity in psoriasis. Comparison of levels of several soluble T-cell activation markers (sIL-2R, sCD27, sCD4 and sCD8) indicates that sIL-2R can be used to monitor disease activity and therapeutic responses.

ACKNOWLEDGEMENTS

We thank Mr. Robert Rodenburg for preparing the illustrations, Mrs. Monique de Nooijer for technical assistance and Dr. Rogier Hintzen for measuring sCD27 serum levels.

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