Immunomodulation by Interleukin-10 Therapy Decreases the Incidence of Relapse and Prolongs the Relapse-free Interval in Psoriasis

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The ability of interleukin-10 therapy to reduce the severity of exacerbated psoriasis has been demonstrated recently. Considering the immunobiologic properties of this cytokine we investigated the effects of long-term interleukin-10 application on the immune system and duration of psoriasis remission. We performed a placebo-controlled, double-blind, phase II trial using interleukin-10 in patients with chronic plaque psoriasis in remission. Patients received subcutaneous injections with either interleukin-10 (10 μg per kg body weight; n = 7) or placebo (n = 10) three times per week until relapse or study termination after 4 months. The treatment was well tolerated. In the placebo group almost all patients (90%) showed a relapse during the observation period. In contrast to this, only two of seven patients (28.6%) relapsed in the interleukin-10-treated group. Kaplan–Meier analysis revealed a significantly lower relapse incidence in the interleukin-10 than in the placebo group ($p = 0.02$). The mean relapse-free interval time was 101.6 ± 12.6 d in the interleukin-10 group in comparison with 66.4 ± 10.4 d in the placebo group. Immunologic activity of interleukin-10 application was indicated by an increase in soluble interleukin-2 receptor plasma levels and higher *ex vivo* interleukin-4 secretion capacities. Remarkably, a significant negative correlation was demonstrated between the interleukin-4 secretion capacity and Psoriasis Area and Severity Index score ($r = -0.36$, $p < 0.01$). Our data suggest that interleukin-10 therapy is immunologic effective, decreases the incidence of relapse and prolongs the disease-free interval in psoriasis. Its value should be further determined in larger trials and for the prevention of re-exacerbation of other inflammatory disorders with a similar immunologic profile. ***Key words: immunotherapy/interleukin-10/psoriasis/relapse prevention. J Invest Dermatol 118:672–677, 2002***

Owing to its considerable anti-inflammatory and immunosuppressive capacities interleukin (IL)-10 became a candidate for the therapy of several immune diseases. The first administration of human recombinant IL (rhIL)-10 in humans was performed in healthy volunteers in 1995 (Chernoff *et al*, 1995). The first successful therapeutic IL-10 treatment was reported in patients with steroid-refractory Crohn's disease (Van Deventer *et al*, 1997). Soon thereafter, Wissing *et al* (1997) demonstrated anti-inflammatory effects of rhIL-10 application in kidney transplant recipients receiving induction therapy with the monoclonal anti-T cell antibody OKT3.

Psoriasis is a common, chronically relapsing, T cell dependent (auto)immune disease characterized by a type 1 cytokine pattern (Valdimarsson *et al*, 1986; Uyemura *et al*, 1993). Recently, we started to study the therapeutic effect of rhIL-10 in psoriatic patients in a pilot trial (Asadullah *et al*, 1998). Daily injections of 8 μg rhIL-10 per kg body weight directly under a psoriatic plaque over a 24 d period led to complete clearance of the plaque in one of two patients. Moreover, some systemic anti-psoriatic effects were observed in all patients treated in this pilot trial, including the third patient receiving subcutaneous injections under nonlesional skin. The immunosuppressive effects (decrease of monocytic human leukocyte antigen-DR expression, IL-12 plasma levels, and responsiveness to recall antigens) as well as a shift towards a type 2 cytokine pattern (increasing proportion of IL-4 producing T cells, increase in immunoglobulin E serum levels), which we observed in all three patients, might be the basis for the observed anti-psoriatic activity of IL-10. As these findings suggested that IL-10 treatment is safe and might be effective, its anti-psoriatic effect was further investigated. In an open label phase II clinical trial, 10 psoriatic patients received subcutaneously rhIL-10 over a 7 wk period in a daily dosage of 8 μg per kg (n = 5) or 20 μg per kg three times per week (n = 5), respectively (Asadullah *et al*, 1999a). Patients were followed up for an additional 7 wk. The treatment was well tolerated. Anti-psoriatic effects were found in nine of 10 patients resulting in a significant decrease of the psoriasis area and severity index (PASI) by over 50%. The anti-psoriatic effect was confirmed by histologic examination. A similar clinical effectiveness of IL-10 application was recently reported by Reich and coworkers (Reich *et al*, 1998; Asadullah *et al*, 2001a; Reich *et al*, 2001). These results suggest that IL-10 therapy in psoriasis over up to 7 wk is safe and clinically efficient to treat psoriasis exacerbation.

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In contrast to treatment of an acute exacerbation of psoriasis the existing therapeutic options to prevent the reoccurrence of the disease are rather limited. Long-term applications of cyclosporine A, methotrexate or retinoids are frequently associated with partly severe side-effects, indicating the important medical need for novel long-term therapeutic options (Asadullah *et al*, 1999b). This would also reduce the cost-intensive morbidity and frequent hospitalization characteristic for patients with severe psoriasis.

Based on the promising results of IL-10 short/medium-term application and the observed long-lasting immunomodulatory effects of IL-10 treatment (Asadullah *et al*, 1998) it was hypothesized that low-dose long-term IL-10 maintenance treatment might represent a novel therapeutic regimen to prevent the rapid reoccurrence of lesions after successful conventional anti-psoriatic therapy in patients with severe remittent psoriasis. The aim of this trial was to collect initial data on the safety, immunologic effects and the clinical response to long-term low-dose subcutaneous IL-10 application after remission of psoriasis. We analyzed whether long-term IL-10 treatment is effective to extend the duration of remission or is even able to prevent the relapse of psoriasis at all. Such a secondary prophylactic approach is clearly different from the therapeutic approaches performed with IL-10 so far, all targeting on exacerbated established diseases. For the prolongation of the relapse-free interval in patients with psoriasis the long-term immunomodulatory effects of IL-10 rather than its direct anti-inflammatory activity should mainly determine the efficacy.

Table I. Criteria for inclusion and exclusion of psoriasis patients

Inclusion criteria
patients with known moderate to severe chronic plaque psoriasis
PASI > 10 before conventional anti-psoriatic treatment
preceding successful treatment with UV light, and/or topical anti-psoriatics
remission (PASI < 5)
no obvious need for further treatment
history of frequent relapses
older than 18 y
written informed consent.
Exclusion criteria
clinical evidence for infection during 1 wk prior to the study
patients with double-stranded anti-DNA antibodies
patients with chronic viral diseases
patients with presence of cancer
patients with presence of hematologic, hepatic, or renal disorder
Karnofsky index < 70
pregnancy
platelet count < 100,000 per μl
systemic treatment with steroids 3 wk preceding the study
treatment with medicine considered to exacerbate or trigger psoriasis (e.g., β-adrenoreceptor blockers, cyclooxygenase inhibitors, lithium)

MATERIALS AND METHODS

Study protocol and patients A placebo-controlled, randomized, double-blind, comparative early phase II clinical trial with recombinant human IL-10 (SCH 52000; kindly provided by Essex Pharma, Munich, Germany/Schering Plough Research Institute, Kenilworth, NJ) in patients with severe, remittent chronic plaque psoriasis in remission was performed. Remission was achieved by conventional, standard intensive anti-psoriatic therapy, including topical anti-psoriatics, such as anthralin and calcipotriol in combination with ultraviolet (UV) radiation during hospitalization (IL-10 pretreatment period). Including and excluding criteria for the IL-10 therapy are shown in **Table I**. Thirty-nine patients were screened for participation and 19 patients were included (**Fig 1**). Eleven patients were unable to take part in the study due to the stringent exclusion criteria. So evidence for an infection, mainly of the respiratory tract (n = 7), presence of a hematologic, hepatic, or renal disorder (n = 3), and pregnancy (n = 1) were found. Nine other patients refused to enter into the study and did not sign the informed consent, and the following reasons were specified: the worry to be treated with a placebo over a long period (n = 5), the wish to become pregnant (n = 1), and general concerns about being treated with an unapproved drug and the need for numerous investigations over a long period (n = 3).

Patients were randomized and received nonlesional subcutaneous injections with either IL-10 (10 μg per kg bodyweight; group A, n = 8) or placebo (group B, n = 11) three times a week. Before treatment no significant differences between the two groups were found with regard to age, sex, and PASI. The age of psoriasis onset, however, was lower in the placebo group (**Table II**). Besides IL-10 no other anti-psoriatic therapies were used. Bland emollients (up to 5% carbamid in eucerin cum aqua), however, could be applied topically.

Patients were treated for up to 4 mo (121 d). End-point beside the end of planned treatment period (4 mo) was occurrence of a relapse, which was defined as one of the following: (i) increase of the PASI to values > 8; (ii) request by patients for further additional treatment even if the degree of relapse was < 50% (according to the criteria by Levell *et al*, 1995); and (iii) other severe diseases, such as severe infections, development of cancer, and hematologic disorders.

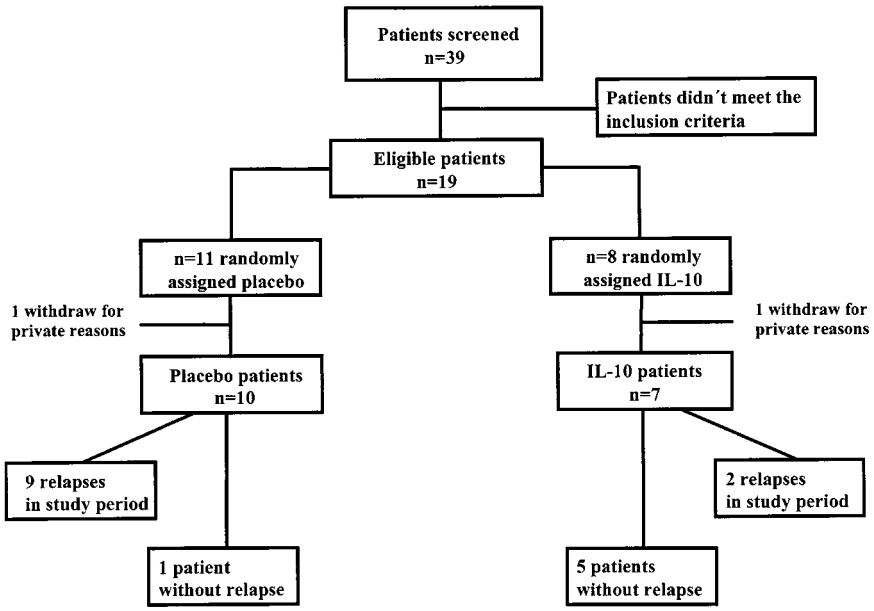

Figure 1. Study population.

Table II. Baseline profiles of psoriatic patients

	Patients receiving IL-10	Patients receiving placebo
Patient number	8	11
Age (y)[a]	46.6 ± 5.3	35.1 ± 3.6
Sex ratio (male/female)	3:5	7:4
Age of onset (y)[a]	30.6 ± 4.7	15.6 ± 4.0[b]
PASI score[a]	1.61 ± 0.23	1.85 ± 0.27
Prestudy treatment		
UV phototherapy	8	10
Anthralin	4	6
Vitamin D analoga	2	1
Topical glucocorticoids	1	1
Methotrexate	1	1
Fumaric acid esters	0	1

[a]Data are mean ± SEM.
[b]$p < 0.05$, Mann–Whitney U test.

The study was approved by the Institutional Review Board of the Medical Faculty, and written informed consent was obtained from all patients.

Investigations Clinical examination was performed before therapy, at 1 wk after start of IL-10 treatment and at least twice a month subsequently. The patients were interviewed with regard to side-effects. An adverse event was defined as any change in the patient's baseline condition, which occurred during the course of the study, regardless of whether or not the event was related to treatment. Efficacy was measured at baseline and every 14 d by the PASI scoring system (Fredriksson and Pettersson, 1978). Relapse incidence and mean duration of remission (time until occurrence of relapse) were determined in the IL-10 and placebo groups to assess the clinical value of IL-10 long-term treatment.

Blood samples were obtained before therapy, after 1 wk and thereafter every 14 d for laboratory investigations. Paraclinical parameters to assess safety of IL-10 treatment included the determination of hemoglobin, hematocrit, red and white blood cell count, differential blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, thrombocyte count, coagulation parameters, albumin, total protein, bilirubin, transaminases, alkaline phosphatase, electrolytes (Na, Ca, and K), creatinine, urea, urea acid, and glucose.

Investigations to assess the immunologic activity of IL-10 treatment were performed at monthly intervals (before and on days 30, 60, 91, and 121) in all patients until study termination or relapse of psoriatic disease. Plasma concentration of the soluble IL-2 receptor (sIL-2R), a parameter that we have found to increase during IL-10 treatment in previous studies (unpublished data), was determined by the semiautomatic Immulite system (DPC Biermann, Bad Nauheim, Germany). For assessing the impact of IL-10 on the T helper (Th)1/Th2 balance, interferon (IFN)-γ and IL-4 secretion was determined after 24 h concanavalin A stimulation (100 μg per ml, Serva Feinbiochemica, Heidelberg, Germany) in 1:5 prediluted heparinized whole blood. Cytokine levels in pooled supernatants of duplicated tests were determined by IFN-γ enzyme-linked immunosorbent assay (Medgenix, Ratingen, Germany) and Cytoscreen ultrasensitive IL-4 enzyme-linked immunosorbent assay (Laboserv, Giessen, Germany) with the upper detection limits of 150 IU per ml and 50 pg per ml, respectively.

Statistical analyses The mean duration of remission (i.e., time until occurrence of relapse or if reaching the end-point of the study 121 d) were determined and compared between the groups using the Mann–Whitney test. The incidence of relapse was determined and compared between the groups using the Chi-square assay. To determine the risk of relapse, Kaplan–Meier analysis with the Log Rank Test was performed. Moreover, for the early study period (day 7 and day 14, before drop out of patients due to relapse) the PASI scores were compared with the pretreatment values (Wilcoxon test) and between the two groups (Mann–Whitney test). Differences were considered to be significant at $p < 0.05$. Pearson Product Moment Correlation was used for correlation analyses. Data are presented as mean ± SEM.

RESULTS

Tolerability Overall the treatment was well tolerated. Three of eight patients in the IL-10 group and four of 11 patients in the placebo group developed flu-like symptoms (rhinorrhea in six patients, cough, hoarseness, mild headache). All these symptoms were of minor severity and did not require interruption of the IL-10/placebo therapy. It seems unlikely that their occurrence during the long treatment period (4 mo) was related to the IL-10 administration as they were similarly observed in the IL-10 and placebo groups and they disappeared within 1–2 wk despite continuation of the treatment. Moreover, at the same time relatives of the patients had similar symptoms, suggesting an infectious origin. There was even a tendency for more frequent side-effects in the placebo group as only in the placebo group one single patient developed mild angina tonsillitis, another hypertension, and a third patient nausea and vomiting.

In contrast to our findings in the short-term IL-10 trial (Asadullah *et al*, 1999c) none of the patients showed mild local inflammation in the injection area.

When analyzing the safety laboratory parameters moderate effects on the hematopoietic system were found. In the IL-10-treated group leukocytes transiently decreased up to day 60 of the treatment when they recovered. In the differential blood count a decrease of the neutrophils (from 66.9 ± 4.2% to 58.1 ± 2.8% on day 91 and 61.4 ± 2.3% on day 121) was notable, whereas the lymphocytes increased from 23.5 ± 2.1% to 29.5 ± 2.6%. Hemoglobin, hematocrit, and erythrocyte counts did not change significantly during IL-10 therapy. There was no evidence for significant effects on electrolytes Na, K, and Ca. Renal and hepatotoxicity were excluded. The value of urea decreased from the beginning till day 121 from 24.6 ± 2.7 to 16.7 ± 3.4 mg per dl, and creatinine values also went down. Albumin was slightly reduced from 4.89 ± 0.09 g per dl to 4.51 ± 0.15 g per dl. Of the transaminases only alanine aminotransferase showed a difference to the placebo group. It decreased continuously during treatment period (from 17.1 ± 4.1 U per liter before to 9.44 ± 1.5 U per liter on day 91 and 10.3 ± 1.68 U per liter on day 121).

Taken together constitutional symptoms and laboratory safety parameters suggest a good tolerability of long-term low-dose IL-10 therapy.

One patient in each group withdrew from the study for private reasons, without signs for adverse effects and without a relapse of psoriatic disease; this was on day 91 for a patient of the placebo group and on day 46 for a patient of the IL-10 group (**Fig 1**). These two patients, who were included for the assessment of adverse effects and tolerability, were excluded from the analysis of the clinical and immunologic effects of IL-10 treatment.

Anti-psoriatic effects The individual courses of the patients are shown in **Fig 2(*A*)**. Five of seven patients in the IL-10 treatment group and one of 10 patients in the placebo group reached the 4 mo (121 d) end-point without psoriasis relapse. The other patients (two of seven in the IL-10 group and nine of 10 in the placebo group) fulfilled at least one criteria for relapse. Consequently, the relapse incidence was significantly lower in the IL-10-treated group (28.6%) than in the placebo group (90%) during this 4 mo treatment period ($p < 0.05$ chi-square test). In Kaplan–Meier analysis the risk of relapse was significantly different between the IL-10 and the placebo group ($p = 0.022$ Log Rank test) as could be seen in **Fig 2(*B*)**. Moreover, the mean duration of remission (time until the occurrence of relapse) in the IL-10 group was significantly longer than in the placebo group (101.6 ± 12.6 d *vs* 66.4 ± 10.4 d).

When analyzing the psoriatic disease activity in the early treatment period (before drop-out of patients due to relapse), a significant increase in PASI score was observed in the placebo group (before 1.85 ± 0.27, 1 wk 2.48 ± 0.4, 2 wk 361 ± 0.8; $p < 0.05$ *vs* before for both). The PASI also slightly increased in the IL-10 group but the rise did not reach significance level (before 1.16 ± 0.2, 1 wk 1.74 ± 0.2, 2 wk 1.9 ± 0.3; $p > 0.05$). When

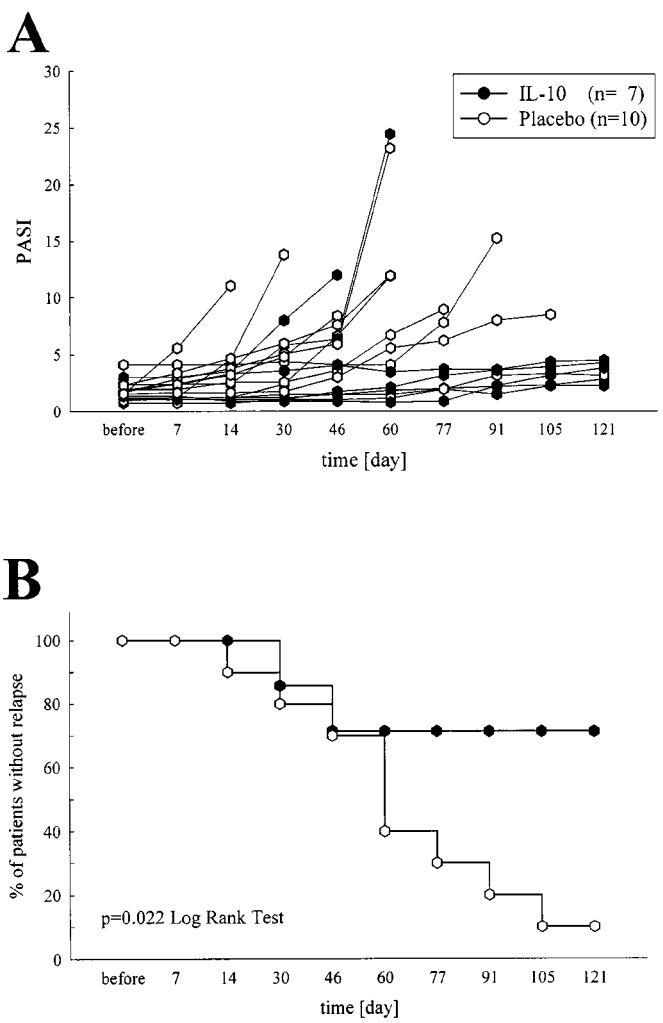

Figure 2. Clinical effects of IL-10 therapy. (*A*) Individual courses of psoriatic disease. The patients dropped out of the analysis when fulfilling the criteria for psoriasis relapse. (*B*) Kaplan–Meier analysis of relapse-risk.

comparing the PASI values of both treatment groups, the p-values were 0.3 and 0.06 for day 7 and day 14, respectively.

Taken together IL-10 therapy decreased the incidence of relapse and prolonged the disease-free interval in patients with chronic plaque psoriasis in remission.

Immunologic effects Based on our previous IL-10 trials in psoriatic patients we selected three parameters for monitoring immunologic effects: the plasma concentration of sIL-2R and the *ex-vivo* secretion of the Th1 cytokine IFN-γ and the Th2 cytokine IL-4.

We observed a strong, significant increase of the sIL-2R plasma levels in the IL-10 group (**Fig 3*A***). Remarkably, the two IL-10-treated patients, who developed a psoriasis relapse, almost completely lacked this sign for IL-10 *in vivo* activity.

When investigating the *ex vivo* mitogen-induced Th1/Th2 lymphokine secretion, a tendency for increasing IFN-γ and decreasing IL-4 secretion capacities paralleled the high relapse incidence in the placebo group. In contrast, in the IL-10-treated patients the sustained remission in five of seven patients was associated with an even slightly increasing mitogen-triggered IL-4 secretion up to 3 mo (**Fig 3*B***, ***C***). As a consequence the IFN-γ/IL-4 ratio increased in the placebo but not in the IL-10-treated group (**Fig 3*D***), due to a decreasing IL-4 secretion capacity in patients without IL-10 and an increasing IL-4 production in IL-10-treated patients. Likely due to the escalating drop-out of relapsing patients from the investigations none of the alterations reached significance level between the groups. The relation between a high *ex vivo* IL-4 secretion capacity and the failing activity of the psoriatic disease became even more clear, when we looked for the correlation between IL-4 secretion and PASI score. In both groups a negative correlation was found (placebo group $r = -0.284$, $p = 0.11$; IL-10 group $r = -0.454$, $p = 0.007$) resulting in a highly significant negative correlation between IL-4 secretion capacity and PASI score for the entire study population ($r = -0.364$, $p < 0.006$) (**Fig 4**). This supports that the parameter chosen is indeed of pathophysiologic relevance for the disease.

DISCUSSION

Psoriasis is a chronic self-perpetuating immune disease in which a relative IL-10 deficiency seems to be of crucial importance (Asadullah *et al*, 1998). Recent analyses of the IL-10 promoter polymorphism in psoriasis suggested that this IL-10 deficiency might have a genetic background (Asadullah *et al*, 2001b). Here we show clinical safety and therapeutic efficiency of IL-10 long-term treatment. Low-dose IL-10 application inhibited the rapid reoccurrence of the skin lesions in patients with severe psoriasis in remission. This suggests that IL-10 therapy may be a novel approach for the prevention of relapses and the prolongation of the disease-free interval in psoriasis. To our knowledge this is one of the first reports on IL-10 long-term therapy, and the capabilities of IL-10 administration to inhibit the relapse of an immune disease.

It is unlikely that other factors than IL-10 application itself are responsible for the different clinical courses between the IL-10 and the placebo group. It is well known that established anti-psoriatic therapies differ in their remission duration (Koo and Lebwohl, 1999). Analyses of the pretreatment before entry into the study, however, excluded a significant difference between the two groups (**Table II**). Another important factor with impact on the relapse rate is the age of onset. So, patients with an earlier onset of the disease have a shorter remission duration. Although a significant difference in the age of onset between the groups was found, the average age is rather low in both of them. Both groups mainly consisted of patients with early onset of the disease; therefore, six of eight IL-10-treated and 10 of 11 placebo-treated patients showed an onset before the age of 40, resulting in a median age of 24 y for the IL-10-treated patients and of 15 y for the placebo-treated patients. Correlation analyses between the time until relapse and the age of onset for the entire population ($r = 0.297$, $p = 0.25$, $n = 17$) as well as for the two treatment groups (placebo: $r = 0.297$, $p = 0.40$, $n = 10$; IL-10: $r = -0.24$, $p = 0.60$, $n = 7$) excluded a significant correlation between the exacerbation during the observation period and an earlier onset of psoriatic disease. The high relapse rate in the placebo group reflects that only patients with moderate to severe psoriasis and a history of frequent exacerbations were included into the study.

It is likely that IL-10 exerts its anti-psoriatic activity by effects on different cell populations, including T cells, antigen-presenting cells, and perhaps keratinocytes as well as their mutual interactions. Psoriasis is a T cell dependent (auto)immune disease, probably initiated by presentation of so far unknown "psoriasis-related antigens" by specialized cutaneous antigen-presenting cells (Valdimarsson *et al*, 1986; Asadullah *et al*, 1999c). IL-10 is able to suppress the antigen-presenting cell activity of monocytes, macrophages, and dendritic cells (Asadullah *et al*, 1999c). In fact, depressed monocytic HLA-DR expression as well as tumor necrosis factor-α and IL-12 secretion led to a lasting shift to a type 2 cytokine profile (increasing proportion of the IL-4, -5, and -10 producing T cells, selective increase in IgE serum levels, depressed delayed type hypersensitivity reaction to recall antigens). In agreement with this it was observed during this trial that IL-10 may enhance the IL-4 secretion capacity. Recently, it was reported that successful UV therapy of psoriasis is associated with a

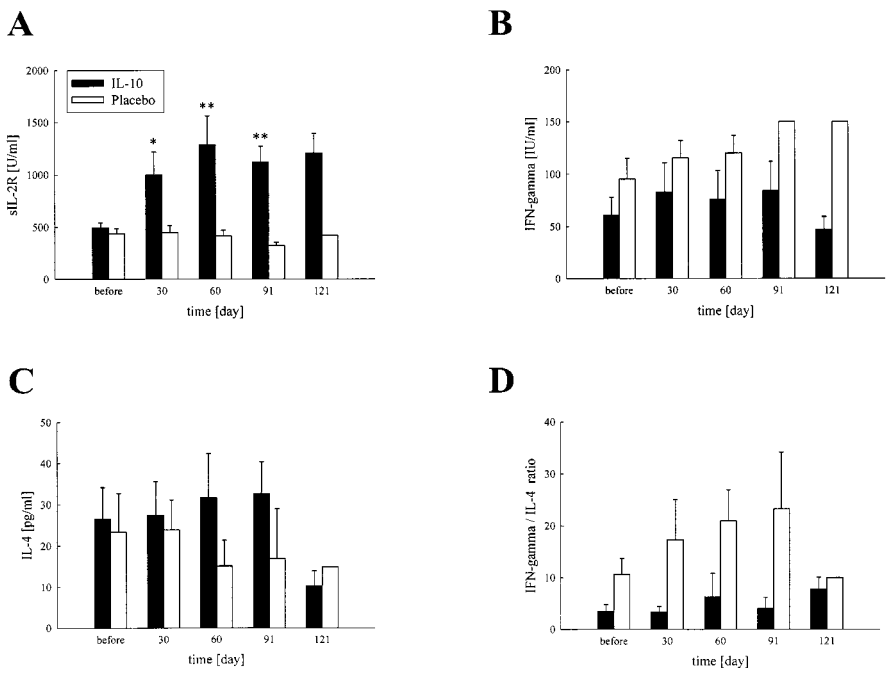

Figure 3. Immunologic effects of IL-10 therapy. The plasma levels of soluble IL-2 receptor (*A*), the *ex vivo* secretion of IFN-γ (*B*) and IL-4 (*C*), and the resulting IFN-γ/IL-4 secretion ratio (*D*) were determined in monthly intervals during the observation period. Sample numbers for the different time points are: before 7/9 (IL-10/placebo); 30 d 7/9; 60 d 5/7; 91 d 5/2; 121 d 5/1. The sIL-2R plasma concentrations were assessed by semiautomatic Immulite™ system (DPC Biermann). IFN-γ and IL-4 secretion was determined in cultures of 1 : 5 with RPMI prediluted heparinized whole blood stimulated for 24 h (37°C, 5% CO_2) with concanavalin A (100 μg per ml). The tests run in duplicate. In the pooled supernatants cytokine concentrations were determined by Interferon-γ ELISA (Medgenix) and IL-4 ultrasensitive enzyme-linked immunosorbent assay (Cytoscreen) with upper detection limits of 150 IU per ml and 50 pg per ml, respectively. The IFN-γ and IL-4 secretion pattern was quite similar after correction by lymphocyte count (data not shown).**$p < 0.01$, *$p < 0.05$ *vs* placebo group in Mann–Whitney test.

considerable increase of cutaneous IL-4 expression.[1] Moreover, preliminary data suggested efficacy of IL-4 application itself.[2] This may point to a key role of this cytokine in psoriasis. Our finding of a strong negative correlation between the IL-4 secretion capacity and the psoriatic disease activity, reported here, further supports such a hypothesis. Finally, direct effects of IL-10 on keratinocytes may have contributed to the clinical response. So, it has been shown that the IL-10 receptor is expressed on keratinocytes and that IL-10 in high concentrations inhibits the proinflammatory cytokine synthesis and proliferation of keratinocytes *in vitro* (Bécherel *et al*, 1995; Michel *et al*, 1997). Our recent *in vitro* results, however, using corresponding concentrations of rhIL-10 as detectable in plasma during therapy, suggest that the anti-psoriatic activity of IL-10 is rather caused by modulatory effects on circulating immune cells, which subsequently might infiltrate the skin, than by direct effects on human keratinocytes (Seifert *et al*, 2000).

Although the effectiveness of IL-10 application for the therapy of established exacerbated immune diseases (psoriasis, inflammatory bowel diseases, rheumatoid arthritis) has been suggested by early phase 2 trials, the potency of this treatment seems to be overall below that of other promising approaches such as the anti-tumor necrosis factor-α strategies. So, a complete disease clearance is a very rare event after IL-10 application, suggesting a relatively low anti-inflammatory potential of this therapy. Moreover, a recent report (Lauw *et al*, 2000) and our own recent unpublished observations suggest even pro-inflammatory properties of IL-10. In agreement with this it was observed that there was an increase of the sIL-2R levels in IL-10-treated patients. Therefore, we conclude that the impressive effects with regard to prevention of disease relapse described here, reflect long-term immunomodulatory rather than anti-inflammatory properties of IL-10. These immunomodulatory effects might be primarily responsible for the prolongation of the disease-free interval that was observed. Such a hypothesis is supported by recent data from animal and *in vitro* experiments,

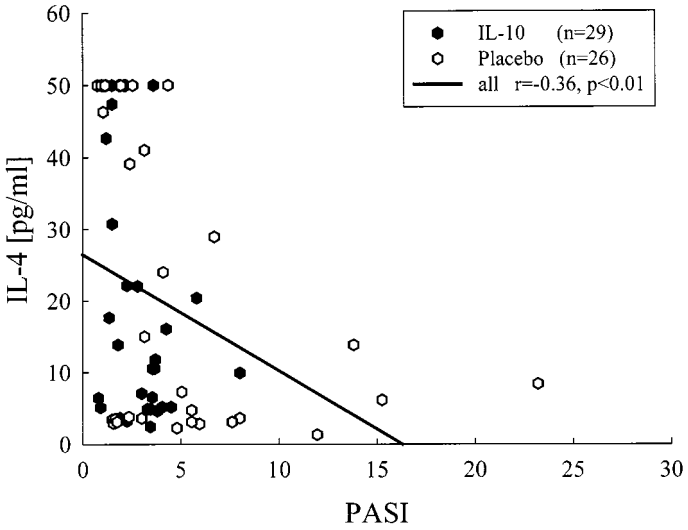

Figure 4. Correlation of IL-4 secretion capacity with the disease activity. The concanavalin A-triggered IL-4 secretion in whole blood was monthly determined (for time points and method see legend for **Fig 3**) in all patients until exacerbation or study termination. Overall 55 samples were available. Correlation analyses (Pearson) between psoriatic disease activity (PASI) and the *ex vivo* IL-4 secretion capacity yielded a negative correlation in both treatment groups (placebo $r = -0.28$, $p = 0.11$; IL-10 $r = -0.45$, $p = 0.007$) resulting in a highly significant negative correlation for the entire study population ($r = -0.36$, $p = 0.006$). The single values for each group and the regression line for all patients are shown.

demonstrating that IL-10 can induce the formation of regulatory T cells with a major impact on the immunoregulation (Cottrez *et al*, 2000; Levings *et al*, 2001). Taken together, both clinical and immunologic data suggest that IL-10 application seems to be more attractive in a secondary prophylactic (prevention of relapse) than in a therapeutic approach.

Our finding, that low-dose long-term IL-10 maintenance treatment seems to be able to prevent the frequent relapse of skin lesions in patients with severe psoriasis after intensive anti-psoriatic

[1]Walters I, Ozawa M, Trepicchio W, *et al*: Narrow band UVB suppresses γ-IFN and IL-12 and increases IL-4 production: in vivo evidence of immune deviation in psoriatic patients. *J Invest Dermatol* 114:792, 1999 (abstr.)

[2]Thomas P, Ghoreschi K, Breit S, *et al*: IL-4-induced immune deviation as therapy of psoriasis. *Arch Dermatol Res* 293:39, 2001 (abstr.)

therapy, might be of importance as it may offer a new option to reduce cost-intensive morbidity and hospitalization. It might be speculated, that IL-10 could be equally effective in other entities, such as rheumatoid arthritis, and transplantation, where the beneficial effects of IL-10 short-term application have been observed already. Corresponding trials should be considered. To investigate further the effect of IL-10 long-term treatment in psoriasis as a new therapeutic concept, might be of particular interest, as psoriasis may serve as a model for hyperinflammatory autoimmune diseases. Moreover, in contrast to several other disorders such as the above mentioned, disease activity is clearly visible and therapeutic effects can be monitored easily. It has to be determined whether the long-term safety profile of IL-10 is superior to other alternatives currently in use such as cyclosporine A or methotrexate. Although our preliminary data, obtained from a rather small study population, are quite promising, additional information based on data from larger populations are essential.

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