



Review

Experimental Therapies for Psoriasis

KHUSRU ASADULLAH^{1*}, HANS-DIETER VOLK², MARKUS FRIEDRICH³ and WOLFRAM STERRY³

¹ Corporate Research Business Area Dermatology, Schering AG, D-13342 Berlin, Germany, ² Department of Immunology, ³ Department of Dermatology and Allergology, University Hospital Charité, Berlin Humboldt University, D-10098 Berlin, Germany

Abstract. There is a high medical need for better therapies for psoriasis. Based on new insight into the pathophysiology of this frequent immune disease, a number of novel systemic immunomodulatory therapies are currently in clinical development. These include approaches targeting antigen presentation and costimulation, T cell activation and leukocyte adhesion, action of proinflammatory mediators, and modulating the cytokine balance. Although mainly only preliminary data are available so far, these trials contribute to a further understanding of the disease and will eventually lead to new therapeutic options for psoriasis. Moreover, since psoriasis can be considered as a visible model disease for T cell-mediated disorders characterized by a type 1 cytokine pattern in general, such approaches may have impact for other immune disorders as well. Here we review the rationale and the initial clinical data of these important recent experimental therapies.

Key words: psoriasis; immunotherapy; cytokines; costimulation; biologicals.

Introduction

Tremendous progress in the understanding of the pathophysiology of psoriasis has been achieved during the last few decades. Psoriasis is now known to be a T cell-mediated (auto)immune disease in which cytokines play an essential part^{7, 9}. Arguments for considering psoriasis as a T cell-mediated dermatosis include:

- the presence of activated T cells in the skin lesions,
- cure of the disease by bone marrow transplantation from healthy persons and transfer of the disease by transplantation of bone marrow from psoriatic patients,
- the demonstration of the impact of immunocytes by SCID mice experiments,
- the therapeutic effects of immunosuppressants targeting T lymphocytes (e.g. cyclosporin A, anti-T cell antibodies).

This new pathophysiological understanding offers for the first time a chance of developing new and better-aimed therapeutic strategies⁷.

Remarkably, there are certain common features between psoriasis and immunological diseases that manifest themselves in other organ systems, such as rheumatoid arthritis, multiple sclerosis, Crohn's disease, ulcerous colitis and rejection of organ transplants. New immunomodulatory forms of therapy could therefore prove useful for various diseases in this group. The skin as an "outwardly visible immune organ" and psoriasis as an "outwardly visible immunological disease with a type 1 cytokine pattern" could thus serve as a model organ and model disease for the development of new therapeutic strategies. The validation of a therapeutic approach, i.e. the "proof of concept" in phase 2 clinical studies, is substantially easier in psoriasis than, for example, in transplantation medicine. Thus, the recent

* Correspondence to: Dr. Khusru Asadullah, M.D., Corporate Research Business Area Dermatology, Schering AG, D-13342 Berlin, Germany, e-mail: khusru.asadullah@schering.de

clinical trials in psoriasis may finally lead to novel therapeutic options for several entities, underlying a general impact of the early experimental therapies currently being investigated. The understanding of psoriasis as a model disease has practical implications for the development of new drugs for other indications as well. Whereas in the past new treatments were adapted for use in skin diseases after they had been used e.g. in transplantation medicine, movement in the opposite direction is now beginning to take place. Experimental dermatology could thus become the vanguard of medical progress⁷.

Practically all existing well-established methods for the treatment of psoriasis have been developed empirically and all existing treatment methods have distinct limitations. To this day there are no truly curative methods (and there are as yet none on the horizon). The available therapeutic approaches are ineffective in a significant proportion of the patients, or do not lead to complete regression, or do not prolong the remission intervals. They are often troublesome to the patients and/or require frequent visits to the doctor's office or

even hospitalization. Bearing in mind the high prevalence of psoriasis (approximately 2% of the population), the economic burden on society is considerable. The annual resulting costs in the US alone are estimated at some 3.2 billion dollars²⁴. The psycho-social stress on psoriasis sufferers due to their visible lesions is high. Surveys have revealed that patients would in principle prefer effective oral forms of treatment. However, the currently available systemic treatments have a considerable side-effect potential. Methotrexate, for instance, can cause hepatotoxicity, cyclosporin nephrotoxicity, and retinoids disturbances in fat metabolism. Therefore, they are generally used only in severe forms of psoriasis. All in all, there is a high medical need for better therapies, in particular therapies with an improved safety profile (fewer side effects, suitability for long-term treatment).

The novel experimental treatments essentially aim to regulate T cell activation, in some cases indirectly by acting on antigen-presenting cells (APC) and/or by inhibiting the action of proinflammatory mediators produced by activated immune cells, including T cells

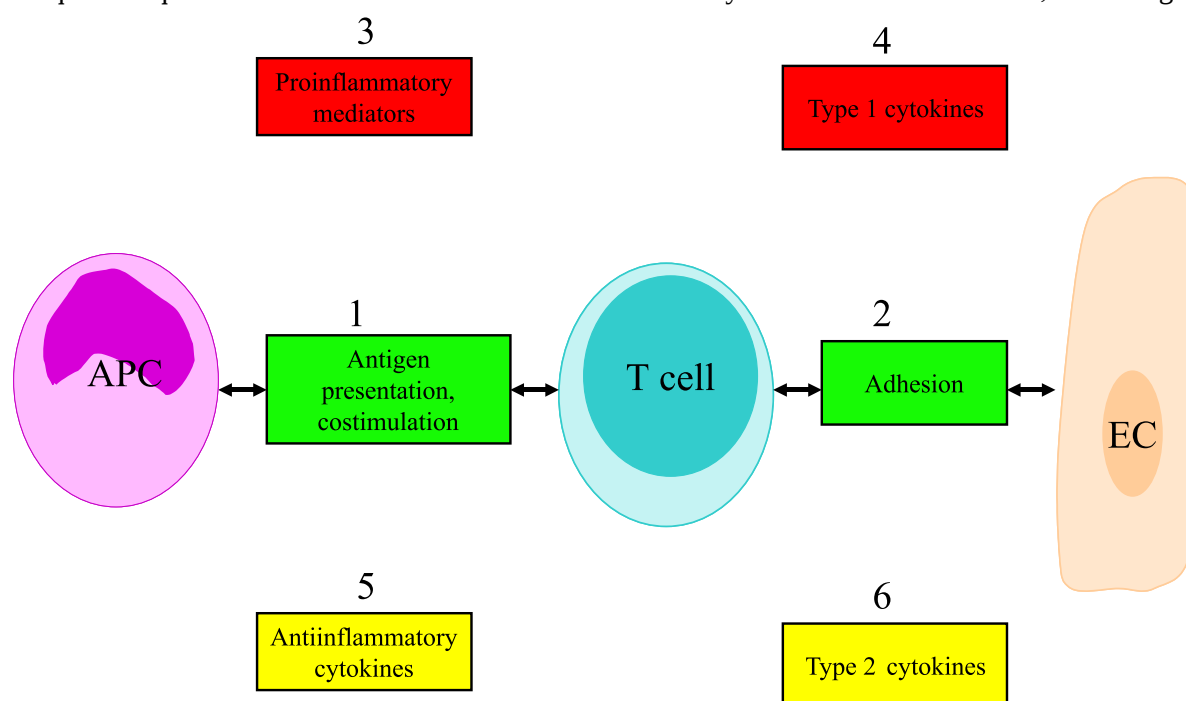


Fig. 1. Principal targets of new immunomodulatory antipsoriatics. Several cell populations, such as antigen-presenting cells (APC), T cells and endothelial cells, as well as their interactions, are promising targets for therapeutic intervention. The interaction between APC and T cells can be achieved by a blockade of antigen presentation and/or of costimulation (1). Specific action sites are indicated in Fig. 2, with examples in Table 1. After adhesion to endothelial cells, activated T cells migrate into skin, the target organ. Inhibition of this adhesion is thus another attractive option (2). Activated immune cells (including APC, T cells, and endothelial cells) produce excessive quantities of proinflammatory mediators and type 1 cytokines (red), such as $\text{TNF-}\alpha$, IL-2, IFN- γ , and IL-12, which, on their part, trigger the inflammatory reaction further and are therefore also of pathophysiological significance. In contrast to this, the antiinflammatory and type 2 cytokines are formed in insufficient amounts (yellow). The ratio of proinflammatory to antiinflammatory and of type 1 to type 2 cytokines determines the presence or absence of psoriatic inflammation. Neutralization or antagonization of the proinflammatory and type 1 cytokines (3 and 4) or replacement of antiinflammatory and type 2 cytokines (5 and 6) thus represent further new therapeutic possibilities (Asadullah et al.⁷)

Table 1. New immunomodulatory therapies for the treatment of psoriasis

Action on the function of antigen-presenting cells
CTLA-4 (BMS 188667)
LFA-3TIP (Amevive/Alefacept)
anti-CD80 antibodies (IDEC-114)
calcitriols (Rocaltrol)
fumaric acid esters (Fumaderm)
T cell inhibitors
macrolides (FK506, tacrolimus, Prograf, SDZASM981, pimecrolimus, sirolimus, Rapamycin)
anti-CD2 (MEDI507, sipilizumab)
anti-CD3 antibodies (OKT3, HuM291)
anti-CD4 antibodies (BB14)
mycophenolate mofetil (CellCept)
IL-2-coupled diphtheria toxin (DAB398IL-2)
anti-CD25 antibodies (basiliximab, daclizumab)
Inhibitors of adhesion
anti-CD11a antibodies (hu-1124, efalizumab)
anti-CD6 antibodies (ior-t1)
anti-selectin-antibodies, selectin-inhibitors
Inhibitors of proinflammatory cytokine/mediator action
anti-IL-8 antibodies (ABX-IL8)
anti-TNF-α antibodies (infliximab, Remicade)
soluble TNF-α receptors (Etanercept, Enbrel)
LTB4-receptor antagonist (VML 295)
anti-IFN-γ antibodies
Administration of antiinflammatory cytokines
IL-4
IL-10
IL-11

The listed therapies are in clinical development (phase 1–3). The classification is schematic, each therapy being mentioned only once, in the group where it fits best, but it must be noted that some of the strategies could be put in more that one group. For example, an administered cytokine (e.g. IL-10) could act as a T cell inhibitor and inhibit costimulation by antigen-presenting cells (modified table from ASADULLAH et al.⁷).

(Fig. 1). An overview of current clinical development projects is shown in Table 1.

Experimental Therapies

Inhibitors of costimulation

The processes of primary stimulation by T cell receptors alone are not sufficient for effective T cell activation. Adequate costimulation is required in addition. Various experimental therapies involving a targeted blockade of costimulation should therefore be effective.

- Thus (Fig. 2),
- LFA-3TIP (Amevive, Alefacept) blocks the interaction between LFA-3 and CD2,
 - a CTLA-4 fusion protein (CTLA-4 Ig BMS 188667) blocks the interaction of CD80 and CD86 with CD28,
 - an anti-CD80 antibody (IDEC-114) blocks the interaction of CD80 with CD28,
 - an anti-CD11a antibody (hu-1124) blocks the interaction of LFA-1 with ICAM.

The action of the anti-CD11a antibody seems to comprise not only an inhibition of the T cell/APC interaction, but also decisive inhibition of cutaneous infiltration.

Both tolerability and antipsoriatic effects have been demonstrated in early clinical studies with these “biologicals”. Thus, in therapy with LFA-3TIP more than half of the 24 patients showed a better than 50% improvement after 8 weeks of treatment. Intravenous administration of CTLA-4 Ig in an open phase 1/2 study led to a dose-dependent improvement, in 46% of the

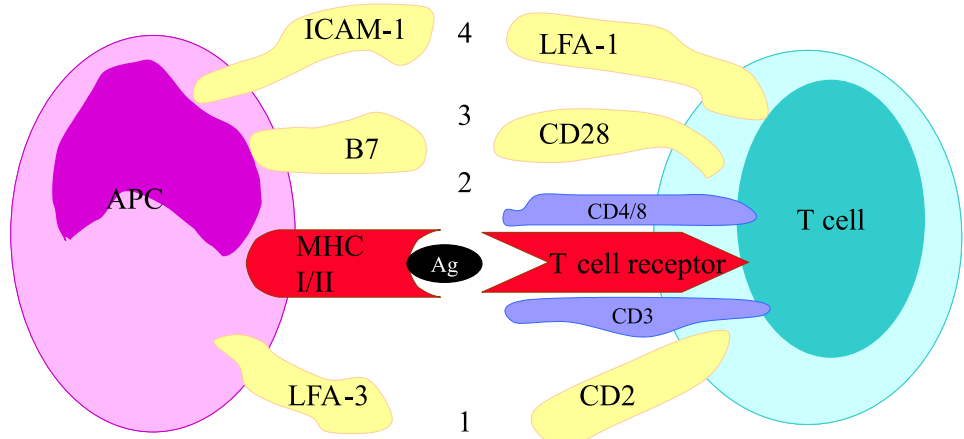


Fig. 2. Action sites for inhibition of APC/T cell interaction. APC/T cell communication seems to be an early, crucial step in the pathogenesis of psoriasis. Thus, inhibition of their interaction is one of the most attractive targets for the development of new antipsoriatics. T cell activation occurs via the T cell receptor/CD3 complex after contact with a specific antigen, which is presented embedded in the MHC complex of APC. MHC-I molecules also interact with CD8, while MHC-II molecules interact with CD4, defining the corresponding T cell subpopulations (signal 1). For effective T cell activation, these processes alone are insufficient and require adequate costimulation (signal 2). The action site of various experimental therapies for blocking this costimulation is shown⁷: 1 – LFA-3TIP, 2 – anti-CD80 and anti-CD86, 3 – CTLA-4 Ig, 4 – anti-CD11a

patients by over 50%. In 9 of the 10 patients in the highest-dose group, an at least 50% improvement was observed^{1,2}. Promising results from a phase 2 trial with an anti-CD80 monoclonal antibody were recently reported (GOTTLIEB et al. poster at the congress of the American Academy of Dermatology, 2001). Thirty-five patients received 4 intravenous infusions over a 3 to 6 week period, ranging from 2.5–15 mg/kg. Therapy was well tolerated and showed a considerable improvement of the skin lesions. A reduction of over 50% in the psoriasis area and severity index (PASI) was achieved in 40% of the patients.

Summarizing, the approaches are essentially characterized by good tolerability and a certain efficacy. Nevertheless, clearance is still quite rare, not all patients benefit from the therapy, and the desired effects generally appear only after several weeks.

Calcitriols

These vitamin D derivatives seem to exert their systemic antipsoriatic action mainly by suppressing the function of APCs. Thus, they reduce the expression of MHC-II and costimulating molecules and the TNF- α secretion capacity of the monocytes. In contrast to the effects after topical application of calcitriols, therefore, the action mechanism is not a direct inhibition of the keratinocyte proliferation. With the calcitriols available at the present time, oral administration is theoretically possible, but the therapy is problematic because it is still associated with risks of provoking hypercalcemias. Nevertheless, it has been demonstrated that this therapy is effective. Thus, in 85 patients calcitriol (Rocaltrol) led to a decrease in PASI from 18.4 to 9.7 after 6 months and to 7.0 after 36 months. Improvement has also been achieved in psoriatic arthritis. The calcitriol dose must be raised gradually, the patient's calcium intake must be limited by appropriate diet, and the calcium levels in serum and urine must be monitored to avoid hypercalcemia and hypercalciuria^{19,35}. The development of immunosuppressive calcitriols that do not provoke hypercalcemia could open new possibilities in this form of therapy. Indeed we recently discovered such vitamin D receptor binding molecules which display such a dissociation⁴⁶.

Fumaric acid esters

Since the biochemist SCHWECKENDIEK reported the successful treatment of his psoriasis with fumaric acid esters (FAEs) in 1959, this therapy and its side effects have been discussed. During recent years the im-

pressive antipsoriatic effectiveness of systemic treatment with a mixture of the FAEs (Fumaderm) has been proven in several multicenter trials. Today, FAEs are only approved in Germany, where they are frequently prescribed. In a recent multicenter trial with 101 patients, 69% reported adverse effects, mainly consisting of gastrointestinal complaints and flushing in the first weeks of FAEs treatment²⁹. However, they are usually mild and non-persisting.

The limited information available on the pharmacodynamics, pharmacokinetics, and safety profile and mode of action of these compounds has recently been reviewed³⁰. Methylhydrogenfumarate (MHF), which is formed by hydrolysis of dimethylfumarate, is believed to be the most potent metabolite of this drug, which is antiproliferative to keratinocytes. An effect on cytokine formation in peripheral blood lymphocytes and monocytes was demonstrated. An increase in IL-4 and IL-5, but not in IFN- γ and IL-2, production by stimulated mononuclear cells and T cells by MHF was reported. This augmentation of T helper 2 (Th2) cytokine response may provide a mechanistic explanation of the effects of MHF. Moreover, MHF enhances the secretion of proinflammatory (TNF- α) and antiinflammatory (IL-10, IL-1RA) cytokines in monocytes. Whereas the long-lasting induction of IL-10 may contribute to the antipsoriatic effects, the MHF-induced early TNF- α formation may be responsible for several side effects of FAEs. Very recently it was reported that Dimethylfumarate is an inhibitor of cytokine-induced nuclear translocation of NF- κ B1, giving a first insight into the molecular effects of FAEs⁴⁴.

Altogether, although FAEs have been used for decades and show promising efficacy, further clinical and experimental investigations are necessary. The complete clinical development of mono compounds seems essential before a global launch of such drugs could be expected.

Immunosuppressive macrolides

Cyclosporin has been well established for the systemic treatment of psoriasis for years. Recently, novel macrolides have been developed for topical use^{10,31}, but they could become significant in systemic therapy, too. In one double-blind study it was found that FK506 (tacrolimus, Prograf) used in a dose of 0.05–0.15 mg/kg/day in psoriasis patients led to an 83% improvement after 9 weeks⁴⁰. The results of a placebo-controlled double-blind study were recently reported in which an ascomycin derivative (pimecrolimus) was given orally in doses of 5–60 mg/day. Tolerability was very good

and higher doses gave good clinical efficacy, with a 60 to 75% reduction in the PASI score after 4 weeks³⁶. Little information is available on the use of sirolimus (Rapamycin), but the occurrence of severe side effects (capillary leak syndrome) has been reported²⁰. Further studies must be carried out to see whether the long-term safety profile of these substances is superior to that of cyclosporin. In particular, altered lipidemia and thrombocytopenia must be carefully monitored.

Anti-T cell antibodies/fusion proteins

In view of the key role played by T cells in psoriasis, it is easy to see that their depletion could also have a therapeutic effect. Antibody therapies of this kind have been tried since the early nineties. Monoclonal anti-CD2 (MEDI507, Siplizumab) and anti-CD3 antibodies (e.g. OKT3, HuM291), directed against all T cells, and anti-CD4 antibodies, directed predominantly against T helper cells, were tested. The treatments are reported to have produced impressive improvements rapidly. Maximum effects were observed 2–4 weeks after the beginning of the infusions, which had been given over 5–8 days^{15, 28, 39, 41, 45}. Whereas the first antibodies used were of murine origin, newer approaches are using humanized antibodies in order to achieve better tolerability and to avoid the formation of neutralizing antibodies.

Targeting T cells is also attempted by using DAB398IL-2, an IL-2-coupled diphtheria toxin. Since IL-2 is an important growth factor for T cells, such coupling with the toxin should result in an inhibition of the lymphocytes. Systemic therapy with this agent in fact proved to be very effective in around 40% of patients with severe psoriasis¹⁶. There were also appreciable side effects, which greatly restricts the use of this method⁸.

In principle, non-selective depletion of T cells or Th cells represents a very serious intervention in the immune system, with a considerable potential for the appearance of side effects. The use of monoclonal anti-CD25 antibodies (basiliximab, daclizumab) could be advantageous in this context, since here only the action of IL-2, important for lymphocytes, is inhibited by a blockade of binding to its receptors. Initial results do in fact indicate that the tolerability is good. In an open phase 2 study, 19 patients were given daclizumab infusions, initially 2 mg/kg and then 1 mg/kg every 2 weeks. However, the antipsoriatic action was at best moderate: only in a subgroup with low psoriasis activity prior to the therapy was there an approximately 30% reduction after 8 weeks²³. Case reports suggest that ba-

siliximab might be more effective and could lead to outstanding action in combination with cyclosporin^{32, 34}.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) (CellCept), a low-molecular, relatively lymphocyte-specific immunosuppressant, is used successfully in transplantation medicine. It exerts a non-competitive and reversible blockade of the neosynthesis of guanine nucleotides, which are essential for RNA and DNA synthesis in lymphocyte proliferation. Antipsoriatic effects of oral therapy with this substance have been described¹⁸. In one study, 5 patients with treatment-resistant psoriasis vulgaris and 6 patients with psoriatic arthritis received MMF monotherapy for a period of 10 weeks in a dose of 2 g/day. The treatment was well tolerated. A moderate improvement in the findings was observed, but only in the patients with moderate psoriasis and with psoriatic arthritis¹⁷. Recently, more promising data were reported¹³, describing a mean decrease of the PASI from 30.5 to 16.1 after 6 weeks of treatment in 11 patients with severe plaque psoriasis.

Inhibitors of leukocyte adhesion

The migration of activated immune cells into the skin constitutes another important point for pharmacological intervention; inhibition of the adhesion of immune cells to the endothelium seems to be particularly promising. In an open study of 31 patients, a humanized monoclonal anti-CD11a antibody (hu-1124, efalizumab) was infused once at concentrations of 0.03 to 10 mg/kg. This antibody inhibits the interaction of CD11a (LFA-1) with various ICAM molecules. ICAM-1 (CD54) is expressed on activated endothelial cells. The antibody therefore inhibits both the APC/T cell interaction (Fig. 2) and the adhesion to endothelial cells and, hence, transendothelial migration²². At doses above 1 mg/kg, a statistically significant, but only moderate, decrease in the PASI score was observed after 2–3 weeks¹⁴. A monoclonal anti-CD6 antibody (ior-t1) is also suggested to exert antipsoriatic effects by inhibiting lymphocyte migration into skin, but so far there has been only one preliminary report²⁷.

Anti-IL-8 antibodies

IL-8, a proinflammatory cytokine overexpressed in psoriasis, has potential pathophysiological significance, since it is mitogenic for keratinocytes, chemoattractive for granulocytes and T lymphocytes, and acts as an

angiogenesis-stimulating factor. In a phase 1–2 study of 43 patients, 4 infusions of a humanized anti-IL-8 antibody (ABX-IL8) were given, at intervals of 2–3 weeks, at various doses (0–3.0 mg/kg). The therapy was well tolerated, but the results were rather poor. A reduction in the PASI was observed only with the higher doses, and even then only by on average of around 20% (ABDULGHANI et al., presentation at the congress of American Academy of Dermatology, 2001). These results suggest that IL-8 plays no key role in the pathophysiology of psoriasis or that neutralizing its effects in the skin by systemic antibody therapy is difficult.

Anti-TNF- α strategies

Lesional and systemic elevated levels of the proinflammatory cytokine TNF- α have been found in psoriasis. Its proximal position in the effector cytokine cascade has made TNF- α an interesting candidate for inhibition of inflammatory reactions. Essentially, two different strategies are followed for inhibition of its action through a blockade of receptor binding: neutralization by monoclonal anti-TNF- α antibodies and soluble TNF- α receptors. They have already proved themselves successful in the treatment of rheumatoid arthritis and Crohn's disease.

The humanized monoclonal anti-TNF- α antibody (infliximab, Remicade) was initially used in a psoriatic patient who was also suffering from an inflammatory intestinal disease. A dramatic improvement in the skin lesions was observed as soon as 2 weeks after a single infusion³³. Good activity has also been reported in combination with methotrexate²¹. Very recently, the efficacy and safety of infliximab monotherapy was demonstrated in a controlled randomized trial. Eleven patients with moderate to severe plaque psoriasis each received placebo or the antibody at 2 dosages (5 mg/kg or 10 mg/kg) intravenously at weeks 0, 2, and 6. Eighty-two percent in the infliximab 5 mg/kg group and 73% of the 10 mg/kg group had at least 75% improvement in the PASI (18% of patients in the placebo group). The mean PASI decreased from 22.1 to 3.8 (5 mg/kg) and 26.6 to 5.9 (10 mg/kg) by week 10. The mean time to response was 4 weeks¹¹.

Similarly promising data were reported on the soluble TNF- α receptor Etanercept (Enbrel) in the treatment of psoriatic arthritis. Sixty patients were included in a placebo-controlled study. The treatment (25 mg by subcutaneous injection twice weekly for 12 weeks) was well tolerated. A distinct improvement of the joint involvement was observed in 73% of the patients treated, compared with 13% of the patients in the placebo

group. In addition to this, the PASI fell by over 75 in 25% of the actively treated patients. In all, a 46% reduction in PASI was achieved²⁵.

These results indicate that inhibition of TNF- α could become a highly promising option in the treatment of psoriasis and psoriatic arthritis. However, severe infections in some of the patients treated with Etanercept underline the need for careful control until further experience with this treatment has been accumulated.

Anti-IFN- γ

Since this proinflammatory type 1 cytokine is overexpressed in psoriasis and considered to be mainly responsible for the Th 1 immune deviation, its neutralizing represents another therapeutic approach. A humanized monoclonal antibody has recently been generated and is currently used in a phase 1–2 trial. Clinical data should become available soon.

LTB4-receptor antagonists

Cutaneous infiltration of leukocytes, due to the production of chemoattractants, is a typical phenomenon in psoriasis. One of the most potent chemoattractive proteins is leukotriene B₄ (LTB₄), a proinflammatory mediator formed from arachidonic acid by a 5-lipoxygenase-dependent metabolism. Elevated levels of LTB₄ have been reported in psoriasis.

Inhibition of LTB₄ activity was investigated as a therapeutic strategy, but treatment with pharmacologically active doses of an oral LTB₄-receptor antagonist (VML 295) did not have any relevant antipsoriatic effect⁴³. In a further study it was recently demonstrated that LTB₄-antagonist therapy also does not prevent a relapse of previously cleared psoriasis²⁶. It may be concluded that LTB₄ does not have any central pathophysiological significance in psoriasis.

IL-4 administration

IL-4 is a type 2 cytokine of decisive significance in regulating Th1/Th2 cytokine balance. In animal studies it has been found that deviation of an existing type 1 cytokine pattern into an IL-4-dominated type 2 pattern can suppress inflammatory T cell-mediated autoimmune processes. Since IL-4 itself is a highly potent factor for the induction of IL-4 in T cells, it was recently tried in the therapy of psoriasis. In an open study, 22 patients received injections of IL-4 in various doses over 6 weeks. Side effects appeared only after the highest dosage. Twenty patients completed the study. In

18 of them the PASI fell by 60–80% within the 6-week period. Particularly impressive effects were achieved with higher doses⁴². These results indicate that IL-4 might have considerable clinical potential.

IL-10 administration

IL-10 possesses antiinflammatory properties and is a suppressor of cellular immunity. Its action on APCs appears to be of particular importance. Here, IL-10 inhibits antigen presentation, the production of inflammatory mediators (e.g. TNF- α), and stimulates the production of antiinflammatory mediators. IL-10 is also of major significance for APC-controlled regulation of the Th1/Th2 balance, promoting a type 2 response⁵. Cutaneous IL-10 mRNA expression is significantly lower in psoriasis than in other T cell-mediated dermatoses, despite the overexpression of proinflammatory cytokines, indicating a relative IL-10 deficiency⁶.

After a pilot study with IL-10 (8 μ g/kg/day for 24 days in 3 patients) had shown that the treatment is well tolerated and an improvement had occurred⁶, two phase 2 studies were performed, each with 10 patients^{3,37}. Good clinical efficacy (PASI reduction by 50–60%) was achieved after a 6–7-week subcutaneous therapy with 4 or 8 μ g/kg/day or 20 μ g/kg 3 times a week. Figure 3 shows a clinical example. The clinical improvement was accompanied by general normalization of the histological and immunohistological findings typical of psoriasis. Interestingly, IL-10 therapy led to a decrease in cutaneous IL-8 and an increase in IL-4 expression,

both of which might contribute to the antipsoriatic effect^{4, 38}. Recently we analyzed the long term effects of IL-10 in a placebo-controlled, double-blind, phase 2 trial in patients with chronic plaque psoriasis in remission. Patients received subcutaneous injections with either IL-10 (10 μ g/kg body weight; n=7) or placebo (n=10) 3 times per week until relapse or study termination after 4 month. 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 2 out of 7 patients (28.6%) relapsed in the IL-10-treated group. Kaplan-Meier analysis revealed a significantly lower relapse incidence in the IL-10 than in the placebo group. The mean relapse-free time interval was 101.6 ± 12.6 days in the IL-10 group in comparison with 66.4 ± 10.4 days in the placebo group. The immunological activity of IL-10 application was indicated by an increase in soluble IL-2 receptor plasma levels and higher *ex vivo* IL-4 secretion capacities. Remarkably, a significant negative correlation was demonstrated between the IL-4 secretion capacity and PASI score¹². Overall these data suggest that IL-10 therapy is immunologically effective in both improving psoriatic disease activity and decreasing the incidence of relapse and prolonging the disease-free interval in psoriasis. Its value should be further determined in larger trials.

IL-11 administration

IL-11 is a multifunctional cytokine which exerts a range of effects on hematopoietic and nonhemato-



Fig. 3. Example of the clinical effects of IL-10. The situation before (A), during (B) [day15], and the end of IL-10 therapy (C) [day 50] are shown. The patient received IL-10, 20 μ g/kg of body weight, 3 times per week. (ASADULLAH et al.³, reproduction with permission of the American Medical Association)

poietic cells. Because of its stimulant action on megakaryocytopoiesis and thrombocytopoiesis, it has already been approved for the treatment of thrombocytopenia induced by chemotherapy. In addition to this, IL-11 also possesses considerable immunosuppressant and antiinflammatory activity. *In vitro* IL-11 reduces the production of TNF- α , IL-1 β , and IL-12, and in various animal models it alleviates inflammatory activity.

In a recent open phase 1–2 study, psoriasis patients were treated with recombinant IL-11: 12 patients were given daily subcutaneous injections for a period of 8 weeks. In 7 of the 12 patients antipsoriatic effects were observed, with PASI falling by 20–80%. The response to therapy was accompanied by a reduction in the gene expressions of IFN- γ , IL-8, IL-12, TNF- α , IL-1 β , and CD8⁷.

Conclusions

The data from the recent clinical trials with experimental therapies for psoriasis allows predicting some general upcoming possibilities and critical issues involving these novel immunotherapies (Table 2).

Table 2. Conclusions and expectations for novel antipsoriatic approaches based on the results from first clinical trials

Chances:	
well-targeted therapeutic interactions might have a favorable effect/side-effect profile	
approval for some compounds leading to new therapeutic options	
better pathophysiological understanding	
Critical issues (for biologicals):	
high costs	
administration usually by injection	
potential of neutralizing antibody induction	
limited efficacy	
To be addressed:	
which patients might be suitable for a particular therapy and why?	
chances for individual tailored therapy?	
which combinations yield synergistic effects?	
could small molecules suited to oral application mimic the effect?	

Some of the approaches currently under investigation will actually lead to the registration of new drugs for the treatment of psoriasis and to supplementation of existing therapeutic options, which is considerable progress. The majority of the novel immunological therapies currently in early clinical development are biologicals: fusion proteins, antibodies, and recombinant cytokines. Therefore, they must be administered by injection, which is quite inconvenient for the patients, they are expensive, and the induction of neutralizing

antibodies has to be excluded. Side by side with these biologicals, however, new immunosuppressants are being developed, which are also suitable for oral administration. The overall results of the first clinical trials have been variable and are partly preliminary. Data from controlled phase 2 and phase 3 studies are highly needed and will allow a better evaluation of the potential of the individual treatments. However, the picture already emerging that for the majority of the specifically acting biologicals, each individual treatment generally achieves a complete remission in only a small number of patients (usually less than 40%). Therefore, it must be identified which patients are suitable for which therapy. The crucial question will be how to do this. Perhaps analyses of cytokine receptor expression or polymorphisms may help. Only if this can be done effective immunotherapies with few side effects conceivably be tailored to suit individual patients. Moreover, it also has to be established which combinations of the various approaches will yield synergistic effects, improving the often still insufficient efficacy. Finally, the results of clinical trials are contributing significantly to our further understanding of the disease, indicating which mechanisms play a greater or lesser part in its development. This in turn will generate momentum for still better targeted pharmacological action in the future.

Acknowledgment. We would like to thank Dr. Doecke for critical reading; and Ms. Schoepe, Ms. Goerlich, Mr. Willett (Berlin) for editing the manuscript as well as Dr. Giesen (Berlin) for helpful discussion.

References

1. ABRAMS J. R., KELLEY S. L., HAYES E., KIKUCHI T., BROWN M. J., KANG S., LEBWOHL M. G., GUZZO C. A., JEGASOTHY B. V., LINSLEY P. S. and KRUEGER J. G. (2000): Blockade of T lymphocyte costimulation with cytotoxic T lymphocyte-associated antigen 4-immunoglobulin (CTLA4Ig) reverses the cellular pathology of psoriatic plaques, including the activation of keratinocytes, dendritic cells, and endothelial cells. *J. Exp. Med.*, **192**, 681–694.
2. ABRAMS J. R., LEBWOHL M. G., GUZZO C. A., JEGASOTHY B. V., GOLDFARB M. T., GOFFE B. S., MENTER A., LOWE N. J., KRUEGER G., BROWN M. J., WEINER R. S., BIRKHOFFER M. J., WARNER G. L., BERRY K. K., LINSLEY P. S., KRUEGER J. G., OCHS H. D., KELLEY S. L. and KANG S. (1999): CTLA4Ig-mediated blockade of T cell costimulation in patients with psoriasis vulgaris. *J. Clin. Invest.*, **103**, 1243–1252.
3. ASADULLAH K., DÖCKE W.-D., EBELING M., FRIEDRICH M., BELBE G., AUDRING H., VOLK H.-D. and STERRY W. (1999): Interleukin-10 treatment of psoriasis: clinical results of a phase 2 trial. *Arch. Dermatol. Res.*, **135**, 187–192.

4. ASADULLAH K., FRIEDRICH M., HANNEKEN S., ROHRBACH C., AUDRING H., VERGOPOULOS A., EBELING M., DÖCKE W.-D., VOLK H.-D. and STERRY W. (2001): Effects of systemic interleukin 10 therapy on psoriatic skin lesions: histologic, immunohistologic, and molecular biology findings. *J. Invest. Dermatol.*, **116**, 721–727.
5. ASADULLAH K., SABAT R., WIESE A., DÖCKE W.-D., VOLK H.-D. and STERRY W. (1999): Interleukin-10 in cutaneous disorders: implications for its pathophysiological importance and therapeutic use. *Arch. Dermatol. Res.*, **291**, 628–636.
6. ASADULLAH K., STERRY W., STEPHANEK K., JASULAITIS D., LEUPOLD M., AUDRING H., VOLK H.-D. and DÖCKE W.-D. (1998): IL-10 is a key cytokine in psoriasis. Proof of principle by IL-10 therapy: a new therapeutic approach. *J. Clin. Invest.*, **101**, 783–794.
7. ASADULLAH K., VOLK H.-D. and STERRY W. (2002): Novel immunotherapies for psoriasis. *Trends Immunol.*, **23**, 47–53.
8. BAGEL J., GARLAND W. T., BRENNEMAN D., HOLICK M., LITTLEJOHN T. W., CROSBY D., FAUST H., FIVENSON D. and NICHOLS J. (1998): Administration of DAB389IL-2 to patients with recalcitrant psoriasis: a double-blind, phase II multicenter trial. *J. Am. Acad. Dermatol.*, **38**, 938–944.
9. BAKER B. S. and FRY L. (1992): The immunology of psoriasis. *Br. J. Dermatol.*, **126**, 1–9.
10. BORNHOVD E. C., SCHULLER E., BIEBER T. and WOLLENBERG A. (2000): Immunosuppressive macrolides and their use in dermatology. *Hautarzt*, **51**, 646–654.
11. CHAUDHARI U., ROMANO P., MULCAHY L. D., DOOLEY L. T., BAKER D. G. and GOTTLIEB A. B. (2001): Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomized trial. *Lancet*, **357**, 1842–1847.
12. FRIEDRICH M., DÖCKE W.-D., KLEIN A., PHILIPP S., VOLK H.-D., STERRY W. and ASADULLAH K. (2002): Immunomodulation by IL-10 therapy decreases the incidence of relapse and prolongs the relapse-free interval in psoriasis. *J. Invest. Dermatol.*, **118**, 672–677.
13. GEILEN C. C., ARNOLD M. and ORFANOS C. E. (2001): Mycophenolate mofetil as a systemic antipsoriatic agent: positive experience in 11 patients. *Br. J. Dermatol.*, **144**, 583–586.
14. GOTTLIEB A., KRUEGER J. G., BRIGHT R., LING M., LEBWOHL M., KANG S., FELDMAN S., SPELLMAN M., WITTKOWSKI K., OCHS H. D., JARDIEU P., BAUER R., WHITE M., DEDRICK R. and GAROVOY M. (2000): Effects of administration of a single dose of a humanized monoclonal antibody to CD11a on the immunobiology and clinical activity of psoriasis. *J. Am. Acad. Dermatol.*, **42**, 428–435.
15. GOTTLIEB A. B., LEBWOHL M., SHIRIN S., SHERR A., GILLEAUDEAU P., SINGER G., SOLODKINA G., GROSSMAN R., GISOLDI E., PHILLIPS S., NEISLER H. M. and KRUEGER J. G. (2000): Anti-CD4 monoclonal antibody treatment of moderate to severe psoriasis vulgaris: results of a pilot, multicenter, multiple-dose, placebo-controlled study. *J. Am. Acad. Dermatol.*, **43**, 595–604.
16. GOTTLIEB S. L., GILLEAUDEAU P., JOHNSON R., ESTES L., WOODWORTH T. G., GOTTLIEB A. B. and KRUEGER J. G. (1995): Response of psoriasis to a lymphocyte-selective toxin (DAB389IL-2) suggests a primary immune, but not keratinocyte, pathogenic basis. *Nat. Med.*, **1**, 442–447.
17. GRUNDMANN-KOLLMANN M., MOOSER G., SCHRAEDER P., ZOLLNER T., KASKEL P., OCHSENDORF F., BOEHNCKE W. H., KERSCHER M., KAUFMANN R. and PETER R. U. (2000): Treatment of chronic plaque-stage psoriasis and psoriatic arthritis with mycophenolate mofetil. *J. Am. Acad. Dermatol.*, **42**, 835–837.
18. HAUF M. G., BEISSERT S., GRABBE S., SCHUTTE B. and LUGER T. A. (1998): Psoriasis vulgaris treated successfully with mycophenolate mofetil. *Br. J. Dermatol.*, **138**, 179–181.
19. HOLICK M. (1998): Clinical use of oral 1,25-dihydroxyvitamin D3 (calcitriol) for the treatment of psoriasis and psoriatic arthritis. In MAIBACH H. and ROENIGK H.: *Psoriasis*. Marcel Dekker Inc., New York, 749–757.
20. KAPLAN M. J., ELLIS C. N., BATA-CSORGO Z., KAPLAN R. S., ENDRES J. L. and FOX D. A. (1999): Systemic toxicity following administration of sirolimus (formerly rapamycin) for psoriasis: association of capillary leak syndrome with apoptosis of lesional lymphocytes. *Arch. Dermatol.*, **135**, 553–557.
21. KIRBY B., MARSLAND A. M., CARMICHAEL A. J. and GRIFFITHS C. E. (2001): Successful treatment of severe recalcitrant psoriasis with combination infliximab and methotrexate. *Clin. Exp. Dermatol.*, **26**, 27–29.
22. KRUEGER J., GOTTLIEB A., MILLER B., DEDRICK R., GAROVOY M. and WALICKE P. (2000): Anti-CD11a treatment for psoriasis concurrently increases circulating T cells and decreases plaque T cells, consistent with inhibition of cutaneous T cell trafficking. *J. Invest. Dermatol.*, **115**, 333.
23. KRUEGER J. G., WALTERS I. B., MIYAZAWA M., GILLEAUDEAU P., HAKIMI J., LIGHT S., SHERR A. and GOTTLIEB A. B. (2000): Successful *in vivo* blockade of CD25 (high-affinity Interleukin-2 receptor) on T cells by administration of humanized anti-Tac antibody to patients with psoriasis. *J. Am. Acad. Dermatol.*, **43**, 448–458.
24. MARCHETTI A., LAPENSEE K. and AN P. (1998): A pharmacoeconomic analysis of topical therapies for patients with mild-to-moderate stable plaque psoriasis: a US study. *Clin. Ther.*, **20**, 851–869.
25. MEASE P. J., GOFFE B. S., METZ J., VAN DER STOEP A., FINCK B. and BURGE D. J. (2000): Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. *Lancet*, **356**, 385–390.
26. MOMMERS J. M., VAN ROSSUM M. M., KOOLMANS-OTERO M. E., PARKER G. L. and VAN DE KERKHOF P. C. (2000): VML 295 (LY-293111), a novel LTB4 antagonist, is not effective in the prevention of relapse in psoriasis. *Br. J. Dermatol.*, **142**, 259–266.
27. MONTERO E., FALCON L., MORERA Y., DELGADO J., AMADOR J. F. and PEREZ R. (1999): CD6 molecule may be important in the pathological mechanisms of lymphocytes adhesion to human skin in psoriasis and for t1 MAb a possible new approach to treat this disease. *Autoimmunity*, **29**, 155–156.
28. MOREL P., REVILLARD J. P., NICOLAS J. F., WIJENES J., RIZOVA H. and THIVOLET J. (1992): Anti-CD4 monoclonal antibody therapy in severe psoriasis. *J. Autoimmun.*, **5**, 465–477.
29. MROWIETZ U., CHRISTOPHERS E. and ALTMAYER P. (1998): Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. German Multicentre Study. *Br. J. Dermatol.*, **138**, 456–460.
30. MROWIETZ U., CHRISTOPHERS E. and ALTMAYER P. (1999): Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use. The German Fumaric Acid Ester Consensus Conference. *Br. J. Dermatol.*, **141**, 424–429.
31. MROWIETZ U., GRAEBER M., BRAUTIGAM M., THURSTON M., WAGENAAR A., WEIDINGER G. and CHRISTOPHERS E. (1998): The novel ascomycin derivative SDZ ASM 981 is effective for

- psoriasis when used topically under occlusion. *Br. J. Dermatol.*, **139**, 992–996.
32. MROWIEZ U., ZHU K. and CHRISTOPHERS E. (2000): Treatment of severe psoriasis with anti-CD25 monoclonal antibodies. *Arch. Dermatol.*, **136**, 675–676.
 33. OH C. J., DAS K. M. and GOTTLIEB A. B. (2000): Treatment with anti-tumor necrosis factor α (TNF- α) monoclonal antibody dramatically decreases the clinical activity of psoriasis lesions. *J. Am. Acad. Dermatol.*, **42**, 829–830.
 34. OWEN C. M. and HARRISON P. V. (2000): Successful treatment of severe psoriasis with basiliximab, an interleukin-2 receptor monoclonal antibody. *Clin. Exp. Dermatol.*, **25**, 195–197.
 35. PEREZ A., RAAB R., CHEN T. C., TURNER A. and HOLICK M. F. (1996): Safety and efficacy of oral calcitriol (1,25-dihydroxyvitamin D3) for the treatment of psoriasis. *Br. J. Dermatol.*, **134**, 1070–1078.
 36. RAPPERSBERGER K. (2000): Oral SDZ ASM 981: safety, pharmacokinetics and efficacy in patients with moderate to severe chronic plaque psoriasis. *Br. J. Dermatol.*, **143**, 161.
 37. REICH K., BRUCK M., GRAFE A., VENTE C., NEUMANN C. and GARBE C. (1998): Treatment of psoriasis with interleukin-10. *J. Invest. Dermatol.*, **111**, 1235–1236.
 38. REICH K., GARBE C., BLASCHKE V., MAURER C., MIDDEL P., WESTPHAL G., LIPPERT U. and NEUMANN C. (2001): Response of psoriasis to interleukin-10 is associated with suppression of cutaneous type 1 inflammation, downregulation of the epidermal interleukin-8/CXCR2 pathway and normalization of keratinocyte maturation. *J. Invest. Dermatol.*, **116**, 319–329.
 39. RIZOVA H., NICOLAS J. F., MOREL P., KANITAKIS J., DEMIDEM A., REVILLARD J. P., WIJDENES J., THIVOLET J. and SCHMITT D. (1994): The effect of anti-CD4 monoclonal antibody treatment on immunopathological changes in psoriatic skin. *J. Dermatol. Sci.*, **7**, 1–13.
 40. The European FK 506 Multicentre Psoriasis Study Group (1996): Systemic tacrolimus (FK 506) is effective for the treatment of psoriasis in a double-blind, placebo-controlled study. *Arch. Dermatol.*, **132**, 419–423.
 41. THIVOLET J. and NICOLAS J. F. (1994): Immunointervention in psoriasis with anti-CD4 antibodies. *Int. J. Dermatol.*, **33**, 327–332.
 42. THOMAS P. (2001): IL-4-induced immune deviation as therapy of psoriasis. *Arch. Dermatol. Res.*, **293**, 39.
 43. VAN PELT J. P., DE JONG E. M., SEIJGER M. M., VAN HOOIJDONK C. A., DE BAKKER E. S., VAN VLIJMEN I. M., PARKER G. L., VAN ERP P. E. and VAN DE KERKHOF P. C. (1998): Investigation on a novel and specific leukotriene B4 receptor antagonist in the treatment of stable plaque psoriasis. *Br. J. Dermatol.*, **139**, 396–402.
 44. VANDERMEEREN M., JANSSENS S., WOUTERS H., BORGHMANS I., BORGERS M., BEYAERT R. and GEYSEN J. (2001): Dimethylfumarate is an inhibitor of cytokine-induced nuclear translocation of NF- κ B1, but not RelA in normal human dermal fibroblast cells. *J. Invest. Dermatol.*, **116**, 124–130.
 45. WEINSHENKER B. G., BASS B. H., EBERS G. C. and RICE G. P. (1989): Remission of psoriatic lesions with muromonab-CD3 (orthoclone OKT3) treatment. *J. Am. Acad. Dermatol.*, **20**, 1132–1133.
 46. ZÜGEL U., STEINMEYER A., GIESEN C. and ASADULLAH K. (2002): Novel immunosuppressive 1 α , 25-dihydroxyvitamin D3 analog with reduced hypercalcemic activity. *J. Invest. Dermatol.* (in press).

Received in June 2002

Accepted in August 2002