Experimental Therapies for Psoriasis

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Abstract. There is a high medical need for better therapies for psoriasis. Based on new insight into the pathophiology 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 pathophiology 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 part⁷.⁹. 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 strategies⁴.

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

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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 progress.

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 dollars. 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...
Table 1. New immunomodulatory therapies for the treatment of psoriasis

<table>
<thead>
<tr>
<th>Action on the function of antigen-presenting cells</th>
<th>Inhibitors of costimulation</th>
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<tbody>
<tr>
<td>CTLA-4 (BMS 188667)</td>
<td>LFA-3TIP (Amevine/Alefacept)</td>
</tr>
<tr>
<td>LFA-3TIP antibodies (IgG)</td>
<td>anti-CD80 antibodies (IDE-114)</td>
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<tr>
<td>anti-CD2 (anti-CD11a, 3–CTLA-4 Ig)</td>
<td>anti-CD11a antibodies (hu-1124, efalizumab)</td>
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<tr>
<td>anti-CD2 (MED1507, sipilizumab)</td>
<td>anti-CD6 antibodies (ior-t1)</td>
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<tr>
<td>anti-CD3 antibodies (OKT3, HuM291)</td>
<td>anti-selectin-antibodies, selectin-inhibitors</td>
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<tr>
<td>anti-CD4 antibodies (BB14)</td>
<td>Inhibitors of adhesion</td>
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<tr>
<td>anti-CD45 (CD11a, CD11b)</td>
<td>anti-CD11a antibodies (hu-1124, efalizumab)</td>
</tr>
<tr>
<td>anti-CD80 antibodies (IgG)</td>
<td>anti-selectin-antibodies, selectin-inhibitors</td>
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<tr>
<td>anti-CD86 antibodies (anti-CD86 antibodies)</td>
<td>Inhibitors of proinflammatory cytokine/mediator action</td>
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<tr>
<td>anti-IL-8 antibodies (ABX-IL8)</td>
<td>anti-IL-8 antibodies (ABX-IL8)</td>
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<td>anti-TNF-α antibodies (aniflizumab, Remicade)</td>
<td>anti-TNF-α antibodies (aniflizumab, Remicade)</td>
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<tr>
<td>soluble TNF-α receptors (Enanercept, Enbrel)</td>
<td>LTB4-receptor antagonist (VML 295)</td>
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<td>LTB4-receptor antagonist (VML 295)</td>
<td>anti-IFN-γ antibodies</td>
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<tr>
<td>Administration of antiinflammatory cytokines</td>
<td>Inhibitors of adhesion</td>
</tr>
<tr>
<td>IL-4</td>
<td>anti-CD11a antibodies (hu-1124, efalizumab)</td>
</tr>
<tr>
<td>IL-10</td>
<td>anti-CD6 antibodies (ior-t1)</td>
</tr>
<tr>
<td>IL-11</td>
<td>anti-selectin-antibodies, selectin-inhibitors</td>
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</table>

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.2).

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 (Amevine, 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 (IDE-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...
patients by over 50%. In 9 of the 10 patients in the highest-dose group, an at least 50% improvement was observed. 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.

Calcitrions

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 calcitrions, therefore, the action mechanism is not a direct inhibition of the keratinocyte proliferation. With the calcitrions 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. The development of immunosuppressive calcitrions 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 displayed such a dissociation.

Fumaric acid esters

Since the biochemist Schwickendiek 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 impressive 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 treatment. 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 reviewed. 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 mechanism 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-xB1, giving a first insight into the molecular effects of FAEs.

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, 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 weeks. 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 weeks\textsuperscript{36}. Little information is available on the use of sirolimus (Rapamycin), but the occurrence of severe side effects (capillary leak syndrome) has been reported\textsuperscript{29}. 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\textsuperscript{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 psoriasis\textsuperscript{16}. There were also appreciable side effects, which greatly restricts the use of this method\textsuperscript{6}.

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 weeks\textsuperscript{23}. Case reports suggest that basiliximab might be more effective and could lead to outstanding action in combination with cyclosporin\textsuperscript{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 described\textsuperscript{18}. 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 arthritis\textsuperscript{17}. Recently, more promising data were reported\textsuperscript{23}, 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 migration\textsuperscript{22}. At doses above 1 mg/kg, a statistically significant, but only moderate, decrease in the PASI score was observed after 2–3 weeks\textsuperscript{14}. 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 report\textsuperscript{27}.

**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
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 infusion. Good activity has also been reported in combination with methotrexate. 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 doses (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 weeks.

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 achieved.

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 Th1 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 effect. In a further study it was recently demonstrated that LTB4-antagonist therapy also does not prevent a relapse of previously cleared psoriasis. 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 doses\(^2\). 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 response\(^3\). 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 deficiency\(^4\).

After a pilot study with IL-10 (8 µg/kg/day for 24 days in 3 patients) had shown that the treatment is well tolerated and an improvement had occurred\(^5\), two phase 2 studies were performed, each with 10 patients\(^6,7\). Good clinical efficacy (PASI reduction by 50–60%) was achieved after a 6–7-week subcutaneous therapy with 4 or 8 µg/kg/day or 20 µg/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\(^8\). 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 µg/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 \textit{ex vivo} IL-4 secretion capacities. Remarkably, a significant negative correlation was demonstrated between the IL-4 secretion capacity and PASI score\(^9\). 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-

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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 µg/kg of body weight, 3 times per week. (Asadhullah et al.\(^2\), reproduction with permission of the American Medical Association)
poietic cells. Because of its stimulant action on megakaryocytopenesis and thrombocytopenesis, 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. \textit{In vitro} IL-11 reduces the production of TNF-\(\alpha\), IL-\(\beta\), 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-\(\gamma\), IL-8, IL-12, TNF-\(\alpha\), IL-\(\beta\), and CD8\(^+\).

\textbf{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).

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

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

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, is 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.

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\textbf{References}


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