Standard and innovative therapy of psoriasis

C.C. Geilen, C.E. Orfanos

Christoph C. Geilen and Constantin E. Orfanos, Department of Dermatology, University Medical Center Benjamin Franklin, The Free University of Berlin, Berlin-Dahlem, Germany.

Please address correspondence and reprint requests to: Prof. Dr. Dr. Christoph C. Geilen, Klinik und Poliklinik für Dermatologie, Universitätsklinikum Benjamin Franklin, Faberstrasse 60-62, 14195 Berlin-Dahlem, Germany.
E-mail ccgeilen@zedat.fu-berlin.de

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ABSTRACT
Psoriasis is one of the most common skin diseases. A variety of molecular alterations has been identified in the active, lesional epidermis and dermis of psoriasis, but the pathogenesis still remains unexplained. Therefore, all antipsoriatic therapeutic regimens are symptomatic. Although there is no cure for psoriasis, a variety of therapeutic modalities is available to reduce the severity and increase the life quality of the patient. In cases with mild to moderate psoriasis, topical therapy (tars, dithranol, topical corticosteroids, and vitamin D derivatives) is the most appropriate choice for initial treatment. For patients with more severe, recalcitrant psoriasis, application of UV-radiation and systemic therapies (e.g. retinoids, methotrexate, cyclosporine A) are available. These modalities are more effective than topical therapy but they are also associated with significant cutaneous and/or systemic adverse effects and a risk-benefit ratio must be taken into account. In recent years, a variety of new approaches and substances has been developed. Their efficacy and safety should be proven in the future.

Introduction
Psoriasis is a common, chronic, genetically determined skin disease affecting 1-3% of European and American population. Men and women are equally affected. The mean age at onset of psoriasis skin lesions is 28 years, but initial lesions may appear in very early childhood or as late as 90 years (1,2). The initial lesion is an erythematous papule topped by a silvery scale. These papules form plaques of varying shapes and patterns. Areas of the skin most commonly affected include the elbows, knees, groin, scalp, and nails. Beside the classical plaque-type psoriasis different clinical forms have to be taken into consideration: (i) psoriasis guttata, small erythematous, fine-scaled papules frequently generalized and developing after upper respiratory infections, e.g. viral flu or streptococcal pharyngitis, (ii) psoriasis pustulosa, which may develop in patients with or without pre-existing psoriasis. Withdrawal of systemic corticosteroids is one of the main reasons of this clinical form of psoriasis but other associations include infections and drugs (e.g. lithium, β-blockers, ACE-inhibitors), (iii) psoriatic erythroderma, a rare form of psoriasis with no typical plaque or guttate lesions resulting from a progressive worsening of psoriasis in either an acute or chronic fashion, and (iv) psoriasis arthropathica. This clinical form affects approximately 5-7% of psoriatic patients. The most common type is a monoarticular, nonsymmetrical arthritis affecting mainly joints of the hands. HLA-B27 histocompatibility antigen is strongly associated with psoriatic arthritis, Reiter’s disease, and ankylosing spondylitis (3).

A variety of cell biological, biochemical, and molecular biological alterations have been identified in the active, lesional epidermis and dermis in psoriasis, but the pathogenesis of psoriasis is still unexplained (4-6). Therapeutic regimen may clear the skin lesions but relapses occur regularly and most of the patients need once a year sufficient therapy over several weeks. Without therapy the spontaneous remission rate in psoriasis is approximately 30%, whereas, the therapeutic strategies available can induce remission in 90-100% of the patients. But in the absence of a cure we do have to keep in mind the possible side effects of effective drugs. Therefore, a broad therapeutic repertoire is necessary to maintain patients in remission and to reduce side effects.

Before initiation of all types of treatment factors that may provoke psoriasis such as alcohol intakes, infections, drugs or local mechanical irritations have to be excluded. Furthermore, all psoriasis patients need sufficient and regular skin care with emollients and
moisturizers.
For patients with mild to moderate psoriasis, topical therapies are generally used. This includes tars, dithranol, topical corticosteroids, and vitamin D derivatives. However, for approximately one-third of psoriasis patients these treatments are insufficient and systemic therapies including photochemotherapy are required to be applied alone or in addition. Most types of drugs used for moderate to severe psoriasis (e.g. psoralens, retinoids, methotrexate, cyclosporine A) have varying degrees of long-term toxicities. To minimize organ damage combination and/or rotational therapy may be considered for the management of psoriasis in a series of patients (7).

Topical therapy
Tars
Tars are mainly used in combination with UV phototherapy. In 1925 W. Goekerman introduced this therapy schedule consisting daily application of crude coal tar followed by UVB irradiation in patients with generalized psoriasis (8). Particularly in the USA, this treatment became a standard management procedure for psoriasis for half a century. Nowadays liquid tars are mainly used, such as liquor carbonis detergens (10-20% in petrolatum) (9).

Dithranol (Anthralin, Cignolin)
Hydroxyanthracene derivatives have held an important place in the treatment of psoriasis since in 1877 Squire reported the beneficial effect of Goa powder, an extract of the plant Ara arabo. The active compound of this natural product is chrysarobin and its synthetic substitute dithranol (1,8-dihydroxy-9-anthrone) was introduced into the therapy of psoriasis by Unna in Germany in 1916. Up to now the topical treatment of psoriasis by increasing concentrations of dithranol (0.05% to 2%) serves as a “golden standard” in many European studies (10, 11). The best results are seen in patients with chronic plaque-type psoriasis. In contrast, dithranol is not recommended for pustular or acute, exudative forms of the disease. Dithranol penetrates faster and in greater amounts into lesional as compared to non-lesional skin. Therefore, a short-contact therapy has been proposed to reduce irritancy. This form of dithranol application is recommended particularly for use in outpatients (12). In order to reduce side effects and to increase the efficacy many dithranol-containing combination therapies have been proposed. In our department a combination of tar plus selective UV phototherapy (310-330 nm) combined with low but increasing levels of topical dithranol in petrolatum (0.125 – 0.5%) is successfully used. Recently, dithranol embedded in crystalline monoglycerides (Micanol®) has become available and its efficacy in the treatment of psoriasis has been shown. Less irritation and staining are the main advantages of this new galenic preparation (13, 14).

Topical corticosteroids
Topical treatment of psoriasis with corticosteroids shows fast remission of the psoriatic plaques and leads to cosmetically acceptable results for the patients. This advantage, however, does not outweigh the well known disadvantages of corticosteroids such as skin atrophy, striae, purpura, bacterial and fungal infections, steroid acne, rebound phenomena, unresponsiveness for other antipsoriatic therapies, and shortening of the remission free interval. Also, the potential for topical fluorinated glucocorticosteroids to cause significant systemic effects has been reported (15). Nevertheless, topical corticosteroids are still useful in psoriasis in three particular indications: (i) eczematous psoriasis, (ii) chronic psoriatic involvement of the palms and soles with hyperkeratotic, plaquelike lesions and fissuring, and (iii) psoriatic involvement of the scalp.
In eczematous psoriasis, topical treatment for 2-5 days with hydrocortisone 1% in cream or ointment is useful to reduce irritation, but this should be followed by some other conventional antipsoriatic regimen. The use of fluorinated corticosteroids is recommended in chronic, hyperkeratotic psoriasis palmpoplantar as a pretreatment for using PUVA photochemotherapy. In these cases fluorinated corticosteroids, e.g. betamethason, may be used for 3-5 days. In moderate to severe psoriasis of the scalp corticosteroids are used in combination with keratolytic ointments and tar-containing shampoos over a period of 2 - 4 weeks (16, 17).

Vitamin D derivatives
In 1985 patients with psoriasis were reported to respond beneficially to oral or topical administration of 1α,25-dihydroxyvitamin D₃ (calcitriol) (18). Because treatment of patients with orally administered calcitriol has a narrow safety range, topical application has been preferred (19). It was possible to manipulate the structure of calcitriol to enhance antipsoriatic characteristics and limit calcemic side effects. Most of these alterations are done by modifying side chains of calcitriol, and together with calcitriol two analogues, calcipotriol and tacalcitol, are now marketed for treating psoriasis (20-22). In different studies it has been demonstrated that the two Vitamin D analogues were better than topical corticosteroid treatment, although more side effects were noted as compared to ointments containing corticosteroids in terms of local and perilesional irritations. The application mode is 1-2 times daily over a period of 6 weeks. Because of several reports of hypercalcemia resulting from excessive use of calcipotriol ointment, the amount of calcipotriol ointment should be limited to a maximum of 100 g per week. However, both serum and urine calcium levels returned to normal after treatment is discontinued (23). Overall, calcitriol, calcipotriol and tacalcitol appear to be safe and effective for treating moderate plaque psoriasis by local means.

Phototherapy
Broad-band UVB irradiation
Eruptive types of psoriasis respond more rapidly to broad-band UVB (290 – 320 nm) irradiation as compared to chronic plaque-type psoriasis. For choosing the initial UVB dose the patient’s minimal erythema dose (MED) has to be determined. This dose is dependent on the skin type. MED is defined as the lowest UVB dose that causes uniform erythema with distinct
long-wave UV (UV). In the presence of UV A psoralens crosslink the cellular DNA, and generate reactive oxygen species inducing cell damage. Different psoralens are used: 8-methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP), and 4.5',8-trimethylpsoralen (TMP). The administration of psoralens can be performed topically (bath-PUVA, shower-PUVA, cream-PUVA) or systematically (31-33). Topical application of TMP or 8-MOP helps to avoid gastrointestinal and ocular side effects, since there is no systemic photosensitization; only 8-MOP and 5-MOP are available for oral use. If a psoriatic patient appears suitable for receiving PUVA, contraindications such as e.g. pregnancy, breastfeeding, photosensitivity disorders, history of multiple skin cancers etc. have to be excluded and together with the MED, the patient’s minimal phototoxic dose (MPD) has to be determined. As a rule, PUVA therapy is applied in two phases: first, a clearing phase and second, the maintenance characterized by tapering the UV-dose and the number of sessions given per week. In most protocols the initial UVA-dose amounts 40 % of MPD measured. European protocols are characterized by reduced time period required for clearing and lower cumulative UVA dose as compared to the US protocol (34, 35). The risk of patients treated with PUVA to develop non-melanoma skin cancer has been calculated to be 12 fold for squamous cell carcinoma and 4 fold for basal cell carcinoma after more than 260 PUVA treatments (36).

Balneophototherapy
Balneophototherapy with various quantities of diluted salts combines bath water delivery with some anti-inflammatory action or with watersoluble photosensitizers with subsequent UVB or UVA irradiation (see PUVA). The efficacy of salt water baths containing 15% synthetic Dead Sea salt in combination with UV phototherapy was reported in patients with various skin diseases including psoriasis and in atopic dermatitis (37), however, the value of salt water baths has been discussed controversially in psoriasis.

Systemic therapy

**Methotrexate**

In 1951, Guber and co-workers noted the rapid clearing of psoriasis after systemic therapy with aminopterin, but this drug was later replaced by a more stable derivative, methotrexate. Methotrexate (4-amino-10-methylpteroylglutamic acid, MTX) belongs to the group of antimetabolites competing with natural substances for specific enzymes usually showing greater affinity to the target. As a folic acid antagonist, methotrexate inhibit DNA synthesis and to a lesser extent RNA synthesis. It targets, therefore, cells especially in the S-phase of the cycle. Kinetic studies in psoriasis indicated that more keratinocytes are in the S-phase than in normal skin and since this process can be reversibly by methotrexate epidermal proliferation is normalized in psoriasis. Methotrexate is indicated in recalcitrant disease not responsive to other regimens such as systemic administration of retinoids or PUVA, especially in patients with associated arthropathy. Contraindications are significant abnormalities of the liver or renal function, severe anemia, leukopenia, or thrombocytopenia, female or male fertility, gastritis, active infectious diseases and excessive alcohol consumption (38). Methotrexate can be used by oral medication (single dose 25-35 mg per week or 5-7.5 mg at 12h intervals for three doses per week) or as intramuscular injection (25-35 mg per week). In respect to the cumulative total MTX dose several studies indicated that the incidence of cirrhosis is low if the total dose of MTX does not exceed 1.5 – 2.0 g. Major causes for acute methotrexate toxicity are impaired renal function and concomitant intake of trimethoprim-sulfamethoxazole. A potent antidote in such cases is leucovorin calcium to be given early orally or parenterally (10 mg/m²). In treating patients with psoriasis with MTX the goal is not to achieve complete clearing, but to adequately control the disease and return to other therapeutic modalities (39), if possible to topical treatments alone.

**Etretinate/acitretin**

Oral retinoids are potent antipsoriatic drugs, particularly in severe pustular
and erythrodermic types. The mode of antipsoriatic action of retinoids is not fully understood, but it seems that etretinate/acitretin promote terminal differentiation, normalize keratinocytic proliferation and modulate leukocyte functions. The dosage required for therapy is 0.5 to 1.0 mg/kg bw/day etretinate or 0.3–0.5 mg/kg bw/day acitretin, administered in one or two daily doses with the meals over a period of 6 to 12 weeks. Etretinate/acitretin are administered alone or in combination with other additional topical modalities (e.g. tar, dithranol, vitamin D analogues) and/or with phototherapies (UVB, SUP or PUVA). In combined schedules the dose levels may be reduced to 0.3 to 0.5 mg/kg/day resp. 0.2–0.3/kg bw/day over a period of 6 weeks in order to minimize the adverse effects. The combination of systemic oral retinoids and PUVA therapy (RePUVA) is considered as a most effective treatment modality for recalcitrant severe psoriasis and the response can be maintained by low-dose retinoid therapy. In erythrodermic psoriasis a low initial dosage should be used, increasing the dose over 3 months up to 0.5 – 0.6 mg/kg/day and then maintained for 6 months. In contrast, in psoriasis a high initial dosage is necessary followed by a slow decrease up to 0.5– 0.6 mg/kg/day over a period of 3 to 6 months. Maintenance is then required for 6 to 12 months. The profile of adverse effects of systemic retinoids is closely associated to hypervitaminosis A (mucocutaneous symptoms, alopecia, elevation of serum lipids, hyperostosis and teratogenicity). Therefore, several contraindications for retinoid therapy should be considered and the patients should be carefully monitored. Medication of oral retinoids together with tetracyclines and high doses of acetylsalicylic acid should be avoided (40–42).

**Cyclosporine A**

Cyclosporine A is a lipophilic peptide of fungal origin with profound immunosuppressive effects. It was first used in kidney, heart, and liver transplantations. Its therapeutic effect in psoriasis was shown early as in 1979 (43). Since then numerous clinical studies have demonstrated the efficacy of cyclosporine A in psoriasis. Cyclosporine A decreases interleukin-2 production of T-lymphocytes by inhibiting calcineurin-mediated signaling pathways. Beside this inhibition, cyclosporine A exerts various effects on other cells of the immune system, it disrupts the self-perpetuating process between immune cells and keratinocytes involved in psoriasis. The rapid therapeutic action and weak myelotoxicity are seen as key advantages for the use of cyclosporine A; nevertheless, nephrotoxicity and high rates of relapse after treatment cessation limit its use to patients refractory to other therapies. Several multicenter studies have demonstrated a dose-dependent response of psoriasis and on the basis of these findings, initial dosages of 2.5 to 5 mg/kg/day have been suggested (44).

**Fumaric acid derivatives**

The beneficial effect of fumaric acid derivatives in psoriasis has been first reported by the chemist Schweken-diek in Germany. In a recent multicentre study an overall efficacy of 80% was shown after four months treatment with fumaric acid esters, however, adverse events (e.g. gastrointestinal complaints, flush, lymphocytopenia) were reported in 69% of the patients (45). Immunohistological studies pointed out that systemically administered fumaric acid esters reduce infiltrating T-lymphocytes in the skin, followed by a reduction of acanthosis and parakeratosis. The recommended dosage of fumaric acid esters follows an established, increasing schedule (maximum dose 1.2g per day) whereby the dose levels should be individually adjusted after clinical response. The following laboratory parameters should be monitored monthly in the first 6 months: serum creatinine, blood urea nitrogen, liver enzymes, blood cell count including white cell differential count (46). Fumaric acid esters should not be combined with UV phototherapy, other immunosuppressives or potential nephrotoxic drugs. A randomized, double-blind, placebo-controlled short-term study also revealed the efficacy and safety of fumarates also in psoriatic arthritis (47).

**New developments and innovative therapies**

**Tazarotene**

Tazarotene belongs to the new group of receptor-selective retinoids binding to the retinoic acid receptor (RAR) family members (48,49). A beneficial response of stationary, plaque-type psoriasis by topical tazarotene (0.05-0.1% gel) has been reported recently (50). However, topical retinoids are more potent in combination with phototherapy or with mild topical corticosteroids in order to avoid retinoid-induced irritation (51).

**Mycophenolate mofetil**

Several case reports have shown that the new immunosuppressive drug mycophenolate mofetil has a good therapeutc effect in patients with psoriasis (52,53). Mycophenolic acid (MPA), the active metabolite of mycophenolate mofetil, reversibly blocks the de novo biosynthesis of guanine nucleotides required for DNA and RNA synthesis. Therefore, all cell types that rely predominantly on this pathway, such as T- and B-lymphocytes, are most significantly affected. Mycophenolate mofetil is a morpholinoester of mycophenolic acid found to be effective in patients with severe psoriasis in the 1970s (54). Mycophenolate mofetil has better bioavailability and thus an improved therapeutic window and it has been initially applied to prevent acute rejection after renal and cardiac transplantation. Also, oral MMF (dosage: 2g daily) has been shown to be safe and effective for treating severe psoriasis (55). This new immunosuppressant may be especially useful in patients with contraindications for other systemic antipsoriatic drugs or in patients not responding to established antipsoriatic therapy. In two recent clinical trials, the topical effect of mycophenolic acid and mycophenolate mofetil was investigated showing that mycophenolate mofetil may exert an antipsoriatic effect when applied topically, whereas mycophenolic acid was not effective (56, 57).

**Tacrolimus (FK506)**

Tacrolimus belongs to the group of macrolides like ascomycine and rapamy-cine. This immunosuppressive drug is
unrelated chemically to cyclosporine A but also inhibits helper T-lymphocyte activation and the synthesis and secretion of cytokines. Furthermore, it has a similar toxicity profile, therefore, patients with nephrotoxicity from cyclosporine are probably not suitable candidates for tacrolimus because it also causes hypertension and renal insufficiency. Systemic (0.1 mg tacrolimus per kg daily) as well as topical (0.1% tacrolimus ointment) administration of tacrolimus have been reported to be sufficient to improve psoriasis. However, in contrast to atopic dermatitis topical tacrolimus showed a limited efficacy in psoriasis (58, 59).

**Alefacept (B-9273)**

Alefacept is an LFA-3-Ig fusion protein that binds to CD2 receptor on T-lymphocytes, inhibiting their activation into CD3+Ro+ memory T-cells. On the background that psoriasis plaques are characterized by an infiltration of memory effector T-lymphocytes, the effect of alefacept on psoriasis was studied in a multicenter, randomized, placebo-controlled, double-blind study. 229 Patients with chronic psoriasis received 0.025, 0.075 or 0.150 mg alefacept/kg body weight or placebo intravenously weekly over a period of 12 weeks, with follow-up for additional 12 weeks. The study revealed considerable improvement in the alefacept groups (38%, 53%, and 53% respectively), greater than in the placebo group (21%) (60). Overall, a ≥75% PASI score reduction occurs in 25 – 30% of the treated patients, indicating that alefacept is less effective in psoriasis than methotrexate or cyclosporine.

**Infliximab**

A growing body of data supports the role of the proinflammatory cytokine tumor necrosis factor (TNF) alpha in the pathophysiology of psoriasis and psoriatic arthritis since elevated TNF alpha levels are detectable in psoriatic skin lesions as well as in the joints of patients with psoriatic arthritis. In order to target the TNF alpha system, a chimeric monoclonal anti-TNF alpha antibody (infliximab) has been developed. In first trials, this antibody was used in order to treat rheumatoid arthritis and Crohn’s disease. The efficacy of infliximab in patients with psoriasis has been reported and a double-blind, randomised trial has been published recently. Of 33 patients enrolled, three dropped out, 9/11 (82%) patients receiving 5 mg infliximab/kg at weeks 0, 2 and 6 responded, and 10/11 (91%) patients receiving 10 mg/kg at weeks 0, 2, and 6 responded. In both groups the median time to response was four weeks. A successful therapy of severe recalcitrant psoriasis has also been reported with a combination of infliximab and methotrexate (61-63). However, severe side effects has been reported such as reactivation of tuberculosis (64, 45).

**Etanercept**

An other TNF alpha neutralising agent is a TNF alpha receptor fusion protein (etanercept). The antiinflammatory action of etanercept has been first reported in rheumatoid arthritis and Crohn’s disease. In a randomised, double-blind, placebo-controlled clinical trial the efficacy and safety of etanercept in psoriasis patients was investigated. Thirty patients were treated with etanercept (25 mg subcutaneously twice weekly) over a period of 12 weeks and compared with 30 placebo-treated patients. An improvement of psoriasis was achieved in 26/30 (87%) of etanercept-treated patients compared to 7/30 (13%) of the controls. Further reports on a positive effect of etanercept in psoriasis and psoriatic arthritis were published recently (66-68). Safety issues are a concern because of the ubiquitous role of TNF alpha. At the moment infections occurred at the same rate and with the same frequency as in the placebo population. There should be caution in using anti-TNF agents. In general they should not be administered to patients with serious or recurrent infections or in patients with untreated or latent tuberculosis.

**Leflunomide**

Leflunomide is a novel immunomodulatory compound which has been proved for the therapy of active rheumatoid arthritis in several countries. The active metabolite inhibits proliferation of activated T- and B-lymphocytes predominantly through inhibition of the de novo biosynthesis of pyrimidine nucleotides (69). Very recently, the successful treatment of a patient with severe psoriasis and psoriatic arthritis with leflunomide (10 mg daily) in combination with prednisolone (10 mg daily) and topical Vitamin D3 analogues was reported (70).

**Pimecrolimus (SDZ ASM 981)**

The ascomycin macrolactam derivative pimecrolimus is a cell-selective inhibitor of pro-inflammatory cytokines and has been found to be effective in T-lymphocyte-driven skin diseases. In a first study, 15 patients were treated topically with pimecrolimus, a potent halogenated corticosteroid or vehicle. All patients treated with pimecrolimus or the corticosteroid showed a significant improvement of psoriatic lesions. This was confirmed by a further study comparing topical pimecrolimus (0.3% and 1.0%) and clobetasol-17-propionate ointment (0.05%) (70, 71).

**DAB$_{389}$IL-2 (denileukin diftitox)**

The fusion protein DAB$_{389}$IL-2 is composed by human interleukin-2 and fragments of diphtheria toxin. It blocks selectively the proliferation of activated lymphocytes by binding to the IL-2 receptor (CD 25). The mechanism of action is the specific toxic effect after internalization of the receptor/fusion protein complex. In a phase II multicenter trial, psoriatic patients received 5, 10, or 15 µg DAB$_{389}$IL-2/kg or placebo daily intravenously for three consecutive days each week for four consecutive weeks. The degree of improvement for treated patients was significantly greater than for placebo-treated patients. However, DAB$_{389}$IL-2 was not well tolerated at this dosing regimen (73, 74).

**Interleukin 10**

The anti-inflammatory and immuno-suppressive cytokine interleukin-10 (IL-10) has been investigated in patients with moderate to severe psoriasis in one pilot trial and two phase II studies and its administration was welltolerated. IL-10 was injected subcuta-
neously over 3-7 weeks and a clinical efficacy was reported in the majority of patients. This possible novel therapeutic approach has to be further investigated in larger, controlled clinical trials (75).

Lasers

Different approaches of treatment of chronic plaque-type psoriasis by lasers have been published. Whereas CO2 laser resurfacing of psoriatic plaques was ineffective, the 308-nm excimer laser has been shown recently to be effective. In a pilot dose-response study investigating 13 patients with stable plaque-type psoriasis clearing of the lesions was reported. Laser therapy may become an alternative for limited psoriasis only, however, further controlled trials are required (76, 77).

Conclusion

In conclusion, the various regimen for psoriasis all have their relative advantages and disadvantages, whereby combinations resp. rotation of therapeutic means may be chosen in an attempt to improve their long lasting efficacy, safety, and tolerability. According to the type and severity of psoriasis and the patient’s individual needs, therapies are to be carefully selected by the physician. A broad spectrum of established antipsoriatic agents are now available and an increasing number of new drugs is being developed. Their clinical benefit will be determined in the near future.

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