Psoriasis: Current Therapeutical Strategies

Abstract
Psoriasis is a chronic, genetically determined skin disease. A variety of biochemical and molecular biological alterations have been identified, but the pathogenesis of psoriasis is still not clear. For patients with mild to moderate psoriasis, topical therapies are generally used. However, approximately one-third of the patients have a moderate to severe psoriasis and need a systemic therapy. Beside well known therapeutical approaches, e.g. PUVA, retinoids, ciclosporine A, methotrexate or fumaric acid derivatives, innovative therapeutical strategies have been developed recently. Fusion proteins (e.g. alefacept, denileukin diftitox, etanercept), monoclonal antibodies (e.g. adalimumab, efalizumab, infliximab) or enzyme inhibitors (e.g. mycophenolate mofetil) have been successfully used in the treatment of patients with severe psoriasis and/or psoriatic arthritis. (Iran J Dermatol 2008;11: 159-167)

Keywords: psoriasis, treatment, topical therapy, systemic therapy, phototherapy

Introduction
Psoriasis is a common, chronic, genetically determined skin disease affecting approximately 1-3% of adults, although the gobal and racial prevalence varies widely. Women and men are equally affected. The mean age of onset of psoriasis skin lesions is 28 years, but initial lesions may appear in 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 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 often after upper respiratory infections, (ii) psoriasis pustulosa, which may develop in patients with or without preexisting 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, \(\beta\)-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. Psoriasis arthropathica affects approximately 5-7% of psoriatic patients. The most common type is a nonsymmetrical, monoarticular arthritis. HLA-B27 histocompatibility antigen is strongly associated with psoriatic arthritis, Reiter’s disease, and ankylosing spondylitis. Very recently, several possible genetic factors have been identified by genotyping of patients with psoriatic arthritis.\(^3\)

A variety of 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. During recent years, new pathogenic concepts have focussed on T-lymphocytes.\(^4-6\) Therapeutic regimen may clear the skin lesions but relapses occur regularly and most of the patients need once a year sufficient therapy for more than several weeks. Without therapy, spontaneous remission rate in psoriasis is approximately 30%, whereas the therapeutic strategies available can induce remission in 90-100% of the patients. 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 possible side effects.

Before the initiation of any type of treatment, factors that may provoke psoriasis such as alcohol intakes, infections, drugs or local mechanical irritations (Koebner’s phenomenon) 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 toxicity (Figure 1). To minimize organ damage, combination and/or rotational therapy may be considered for the management of psoriasis. Recent therapeutical developments have focussed on the T-cell function in the pathogenesis of psoriasis. Over the last decades, a broad spectrum of immunosuppressive drugs has been introduced in psoriasis therapy (Figure 2).

**Topical Therapies**

**Tars**

Tars are mainly used in combination with UV phototherapy. In 1925, W. Goeckerman introduced this therapy schedule consisting of daily application of crude coal tar followed by UVB irradiation in patients with generalized psoriasis. 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).

**Dithranol (Anthralin, Cignolin)**

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**Figure 1: Therapeutic standard concepts in psoriasis**
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 araroba. The active compound of this natural product is chrysarobin and its synthetic derivative 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. 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 lesions 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. In order to reduce side effects and to increase the efficacy, many dithranol-containing combination therapies have been proposed. For example, 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.

**Topical Corticosteroids**

Topical treatment of psoriasis with corticosteroids shows fast remission of the psoriatic plaques and leads to cosmetically acceptable results. This advantage, however, does not overweight 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 intervall. Also, the potential for topical fluorinated glucocorticosteroids to cause significant systemic effects has been reported. Nevertheless, topical corticosteroids are still useful in psoriasis in three particular indications: (i) eczematous psoriasis, (ii) chronic psoriatic involvement of the palms and soles...
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with hyperkeratotic, plaquelike lesions and fissuring, and (iii) psoriatic involvement of the scalp.12,13

Vitamin D Derivatives

In 1985, patients with psoriasis were reported to respond beneficially to oral or topical administration of 1α,25-dihydroxyvitamin D3 (calcitriol).14 Because treatment of patients with orally administered calcitriol has a narrow safety range, topical application has been preferred.15 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 is now marketed for treating psoriasis together with its two analogues, calcipotriol and tacalcitol.16-18 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 lesional and perilesional irritations. Because of cases 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. Overall, calcitriol, calcipotriol and tacalcitol appear to be safe and effective for treating moderate plaque psoriasis by local means.

Topical retinoids

Tazarotene belongs to the new group of receptor-selective retinoids binding to the retinoic acid receptor (RAR) family members.19-20 A good response of stationary, plaque-type psoriasis by topical tazarotene (0.05-0.1% gel) has been reported.21 In order to reduce irritation, a combination with topical corticosteroids is useful.

Phototherapies

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. Combination of broad-band UVB and etretinate/acitretin (0.3 - 0.5 mg/kg daily) is useful in order to reduce the doses required for clearing, both for retinoid and UVB. After 20 to 30 irradiations, etretinate/acitretin should be administered for additional three months in order to increase the remission-free interval.22

Narrow-band UVB therapy

Narrow-band (311-313 nm) UV phototherapy has been shown to be superior to conventional broad-band UVB with respect to clearing and remission times.22 Furthermore, the severity of UV-induced erythema is reduced. Narrow-band UVB has been successfully used in several combination regimens, such as with dithranol, vitamin D derivatives or tazarotene.24-26 Combination with systemic retinoids (etretinate / acitretin) increases the efficacy particularly in patients with hyperkeratotic plaque-type psoriasis.

Selective UV phototherapy (SUP)

The spectrum emitted by SUP lamps ranges from 285 to 350 nm with maxima in the UVB spectrum (310-315 nm). In our clinic, selective UVA/UVB irradiation in combination with liquor carbonis detergens (10% in petrolatum) and low-dose dithranol in petrolatum has been shown to be very successful. SUP can also be combined with oral retinoids reaching the same high levels of efficacy as systemic PUVA.27

PUVA photopherotherapy

PUVA is the combination of psoralens with subsequent irradiation with long-wave UV (UVA). In the presence of UVA, 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 systemically.28-30 Topical application of TMP or 8-MOP helps avoid gastrointestinal and ocular side effects, since there is no systemic photosensitization; only 8-MOP and 5-MOP are available for oral use. 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. 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.31

Balneophototherapy

Balneophototherapy with various quantities of diluted salts combines bath water delivery with some anti-inflammatory action or with water soluble photosensitizes 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, however, the value of salt water baths has been discussed controversially in psoriasis.

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.32, 33

**Systemic Therapies**

**Methotrexate**

In 1951, Guber and coworkers noted the rapid clearing of psoriasis after systemic therapy with aminopterin. This drug was replaced by a more stable derivative, methotrexate. Methotrexate (4-amino-10-methylpteroylglutamic acid, MTX) belongs to the group of antimetabolites. As a folic acid antagonist, methotrexate inhibits DNA synthesis and to a lesser extent RNA synthesis. It targets, therefore, cells especially in the S-phase of the cell cycle. Kinetic studies in psoriasis have indicated that more keratinocytes are in the S-phase than in normal skin and since this process can be reversed by methotrexate epidermal proliferation is normalized in psoriasis. Methotrexate is indicated in recalcitrant diseases 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.34 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). Regarding the cumulative total MTX dose, several studies have indicated that the incidence of cirrhosis is low if the total dose of MTX does not exceed 1.5 – 2.0 g. A potent antidote of acute toxic MTX effects is leucovorin calcium to be given 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, if possible to topical treatments alone.

**Retinoids**

Oral retinoids, like etretinate or acitretin, 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 T-lymphocyte 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 meals over a period of 6 to 12 weeks. Eretinate/acitretin is 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. In erythrodermic psoriasis, a low initial dosage should be used with increasing the dose over 3 months up to 0.5 – 0.6 mg/kg/day and then it should be maintained for 6 months. In contrast, in pustular 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. 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.36-38

Very recently, a new retinoid has been introduced into the market. Aliretinoin binds at RXT as well as at the RAR-receptors and has successfully been used as a systemic therapy for chronic hand eczema.39 However, it may also be useful for the treatment of palmoplantar psoriasis.

**Cyclosporine A**

Cyclosporine A is a lipophilic, immunosuppressive peptide of fungal origin. It was first used in kidney, heart, and liver transplantations. Its therapeutic effect in psoriasis was shown as early as in 1979.40 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. Besides 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.\textsuperscript{41}

**Fumaric acid derivatives**

The beneficial effect of fumaric acid derivatives in psoriasis was first reported by the chemist Schweckendiek in Germany. In a recent multicentre study, an overall efficacy of 80\% was shown after four months of treatment with fumaric acid esters; however, adverse events (e.g. gastrointestinal complaints, flush, lymphocytopenia) were reported in 69\% of the patients.\textsuperscript{42} 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, and blood cell count including white cell differential count.\textsuperscript{43} Fumaric acid esters should not be combined with UV phototherapy, other immunosuppressives or potential nephrotoxic drugs.

**Mycophenolate mofetil**

Several case reports have shown that the new immunosuppressive drug mycophenolate mofetil has a good therapeutic effect in patients with psoriasis.\textsuperscript{45, 45} 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.\textsuperscript{46} Mycophenolate mofetil has a better bioavailability and thus an improved therapeutic window. It was initially applied to prevent acute rejections after renal and cardiac transplantation. Also, oral MMF (dosage: 2g daily) has been shown to be safe and effective for treating severe psoriasis.\textsuperscript{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.\textsuperscript{47, 48}

**Biologicals**

**Efalizumab**

Efalizumab is a humanized monoclonal antibody directed against the CD11a subunit of LFA-1 (lymphocyte function associated antigen 1) which is involved in T-cell function. The efficacy and safety of efalizumab in the treatment of psoriasis has been established in several studies during the last years. A recent multicenter study over 3 years indicated that Efalizumab is appropriate for long-term therapy of psoriatic patients. After receiving 2mg /kg Efalizumab weekly for more than 3 months, 41.3\% of patients achieved a \( \geq 75\% \) improvement of PASI and 13\% achieved a \( \geq 90\% \) improvement in PASI. The clinical benefit was maintained during continuous therapy for the observation period. Efalizumab is an effective and well-tolerated treatment option for severe cases of psoriasis. However, immunosuppressive agents may confer risks of enhanced susceptibility to infections.\textsuperscript{49,50}

**Alefacept (B-9273)**

Alefacept is an LFA-3-Ig fusion protein that binds to CD 2 receptor on T-lymphocytes, inhibiting their activation into CD45Ro + 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 /kg body weight Alefacept or placebo intravenously weekly over a period of 12 weeks, with follow-up for an additional 12 weeks. The study revealed a considerable improvement in the Alefacept groups (38\%, 53\%, and 53\% respectively), greater than that in the placebo group (21\%).\textsuperscript{51} Overall, a \( \geq 75 \% \) PASI score reduction occurs in 25 – 30 \% of the treated patients, indicating that Alefacept is less effective than methotrexate or cyclosporin in psoriasis.

**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 different double-blind, randomised trials have been published. A successful therapy of severe recalcitrant psoriasis has also been reported with a combination of Infliximab and methotrexate.\(^{52-54}\) However, severe side effects have been reported such as reactivation of tuberculosis.\(^{55}\)

**Etanercept**

Another 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 were 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 studies on the positive effect of Etanercept in psoriasis and psoriatic arthritis have been published recently.\(^{56-58}\) Safety issues are a concern because of the ubiquitous role of TNF alpha. At the moment, infections occur at the same rate and with the same frequency as in the placebo population. However, there should be caution with using Etanercept in patients with serious infections or recurrent infections or in patients with untreated or latent tuberculosis.

**Adalimumab**

Adalimumab is a full human monoclonal antibody that binds to the proinflammatory cytokine tumour necrosis factor alpha (TNF alpha). A phase III trial including 1212 patients was able to show that 40 mg Adalimumab every other week for 16 weeks achieved a 75% reduction in PASI score in 71% of treated patients.\(^{59}\) The CHAMPION study compared Adalimumab with methotrexate. The investigators showed that Adalimumab had a significantly superior efficacy and induced more rapid improvement in psoriasis compared to methotrexate.\(^{60}\) However, in this study, the initial methotrexate dosage was 7,5mg/week, which is quite low.

**Ustekinumab / ABT-874**

Interleukin 12 (IL-12) and its related cytokine interleukin 23 (IL-23) are central mediators of the adaptive immune system. They contribute to the development of the type 1 T-helper cell immune response in psoriasis as shown in animal models.\(^{61}\) Very recent results of a phase II study showed that an IL-12/IL-23 monoclonal antibody (ABT-874) is highly effective and well tolerated in psoriasis patients. Using 100mg every other week for 12 weeks, 93% (28 of 30 patients) achieve a 75% PASI reduction.\(^{62}\) A long-term trial of over 76 weeks using Ustekinumab underlined the effectiveness of IL-12/IL-23 monoclonal antibodies in psoriasis.\(^{63}\)

**Conclusion**

Over the past decade, our armamentarium of antipsoriatic therapeutics has grown tremendously. Most of these new agents are biologics. Currently, four FDA approved biologics are available for the treatment of psoriasis: Alefacept, Efalizumab, Etanercept and Infliximab. In addition, Adalimumab is approved for psoriatic arthritis although it has been shown to be active in plaque psoriasis and promising results have been published for Ustekinumab. On the background that biologics like monoclonal antibodies or fusion proteins are very expensive, first studies on the cost/effectiveness have been published. Very recently, a study investigated the cost/effectiveness of five biologic treatments (Adalimumab, Alefacept, Efalizumab, Etanercept, Infliximab) used over a 12-week treatment period. This study pointed out that Infliximab and Adalimumab appear to be the best cost-effective biologics in psoriasis therapy.\(^{64}\) However, in terms of cost-effectiveness, biologics have no chance if compared to common systemic therapies like methotrexate or PUVA.

In conclusion, all various therapeutical regimens for psoriasis have their relative advantages and disadvantages, therefore, combinations or rotations of therapeutic strategies 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 is now available and an increasing number of new drugs are being developed. Their clinical benefit will be determined in the near future.

**References**

Current Therapeutical Strategies


