

A trial of topical therapy is indicated as the first line of treatment in patients with less than 5% body surface area affected unless they have previously failed topical therapy or are debilitated because of their symptoms or site of involvement. For more severe disease, involving greater than 5% of the body surface, second-line options include phototherapy, oral retinoids, cyclosporine, and methotrexate. Third-line therapies, for recalcitrant disease, include a variety of systemic agents, biologics, and targeted immunotherapy [7] (Table 1).

Because of the toxicity associated with psoriasis treatments, rotation, combination, and sequential use of therapeutic modalities may be helpful in controlling the disease while minimizing side effects [7]. Rotational therapy, for example, can involve treating psoriasis with a systemic medication, such as methotrexate or cyclosporine, followed by switching to light therapy [3]. Combination therapy involves mixing two or more treatments. Often, topical therapies are used in conjunction with phototherapy and/or systemic agents. Alternatively, low dose methotrexate can be used with low dose cyclosporine to minimize the nephrotoxicity of cyclosporine and the hepatotoxicity of methotrexate. Finally, sequential therapy refers to the concept of treatment in which potent medications are used to clear the disease and safer, but less effective agents to maintain remission. The strategy utilized ultimately depends on patient response [7] (Table 1).

Optimal therapies

Mild-to-moderate psoriasis

Anthralin

Anthralin, or dithranol, slows cellular proliferation, decreases inflammation and increases cellular differentiation in psoriasis [8]. With the wide array of alternative treatment options currently available, use of anthralin has declined due to its associated staining and irritation which are lifestyle issues [9].

Current usage patterns of anthralin include short contact regimens and novel, more acceptable formulations used for extended (e.g., 8 h) periods of time. Short contact regimens, in which high concentrations of anthralin are applied for a shorter time period, are more efficacious, cause less staining and are more convenient for patients than longer applications of lower concentrations [10]. Micanol is a 1% anthralin formulation in a temperature-sensitive vehicle so that active medication is only released

at skin surface temperature. While staining of skin can still occur, it is more acceptable to patients as staining of household fabrics and furniture is minimized. In a 6-week, randomized, open, parallel group study of 49 patients with psoriasis, Micanol® (GP Pharma) was shown to be effective in both long and short contact regimens, improving psoriasis by 73% in the short contact group and by 78% in the long contact group [11]. Application of triethanolamine after removal of anthralin has been shown to prevent irritation and skin staining [12].

Topical corticosteroids

Topical corticosteroids remain the mainstay of psoriasis therapy in the USA as they are fast acting, cosmetically acceptable to patients, and cost effective [9]. In a survey of US dermatologists, 85% of responders indicated topical steroids as their first choice for the treatment of mild-to-moderate psoriasis [13].

The mechanism of action of corticosteroids is attributed to their anti-inflammatory, antiproliferative, immunosuppressive and vasoconstrictive properties. Clinical efficacy is directly related to potency and varies depending on vehicle of delivery and concomitant utilization of occlusive agents [14].

Steroid potencies range from Class 7 steroids, such as over-the-counter 1% hydrocortisone, to superpotent Class 1 corticosteroids such as clobetasol propionate (Dermovate®, Glaxo-SmithKline), halobetasol propionate (Ultravate®, Bristol-Myers Squibb) betamethasone dipropionate in optimized base, and diflorasone diacetate in augmented base [9]. A Class 1 steroid is 1000 to 1500 times stronger than a Class 7 steroid. The dosage of superpotent corticosteroids should be limited to 50 g per week or less for a maximum period of 2 weeks. After the initial response is achieved, the strength and frequency of application should be tapered, or the agent should be rotated with steroids of lesser potency [15]. Rapid withdrawal of high potency corticosteroids can rarely produce flares [5].

Treatment with both of the potent corticosteroids, betamethasone dipropionate optimized vehicle (OV) (ointment) and clobetasol-17-propionate, has been shown to improve moderate to severe psoriasis vulgaris by at least 75% in 75% of patients [16]. Although effective, corticosteroids may result in local skin atrophy, tachyphylaxis, fast relapse, and contact dermatitis [15]. These side effects are problematic in long-term treatment of susceptible sites such as the face and intertriginous

Table 1. Summary of treatment options for psoriasis.

First-line therapies	Anthralin	Topical corticosteroids	Vitamin D analogs	Tazarotene	Sun exposure			
Second-line therapies	UVB	Narrowband UVB	PUVA	Acitretin	Methotrexate	Cyclosporine		
Biologic therapies	Infliximab	Alefacept	Etanercept	Efalizumab	Adalimumab			
Seldomly used treatment (will not be discussed herein)	Topical 5-fluorouracil	Sulfasalazine	Mycophenolate Mofetil	Hydroxyurea	Azithioprine	6-Thioguanine	Antibiotics	Tar and UVB

UVB: Ultraviolet B.

areas [9]. In extensive cases of psoriasis requiring large amounts of corticosteroids, systemic absorption can lead to suppression of the hypothalamic–pituitary–adrenal axis [17]. Because of their increased skin surface:body mass ratio, infants and small children may be especially susceptible to this side effect [9].

There have been several recent advances in topical corticosteroid therapy. Data have been presented to suggest that fluticasone propionate, mometasone furoate, prednicarbate (Dermatop[®], Dermik Laboratories) and tipredane are associated with an improved benefit-to-risk profile despite their potency [9]. Recently, the US Food and Drug Administration (FDA) approved foam formulations for the delivery of betamethasone valerate (0.12%, Luxiq[®], Connetics Corporation) and clobetasol propionate (0.05%, Olux[®], Connetics Corporation). Betamethasone valerate foam has been found to be superior in efficacy and patient acceptance for the treatment of scalp psoriasis [101]. Clobetasol propionate foam was originally indicated for the treatment of scalp psoriasis, however, its label has been recently expanded to include the short-term topical treatment of mild-to-moderate plaque-type psoriasis of non-scalp regions excluding the face and intertriginous areas [18]. The hope is that continued development will lead to increases in the benefit:risk ratio and provide safer treatment options for patients that require continuous therapy as well as for those with involvement of steroid sensitive areas.

Vitamin D analogs

Calcipotriene (Dovonex[®], Bristol–Myers Squibb Dermatology) is a derivative of vitamin D topically applied for the treatment of mild-to-moderate plaque psoriasis (an oral version exists but is not used for the treatment of psoriasis in the USA). Its mechanism of action is associated with

antiproliferative activity against keratinocytes, inhibition of cell proliferation and enhancement of differentiation [15]. Overall, reports indicate that approximately 70% of patients treated with calcipotriene for 4 weeks experienced a marked improvement or clearing of lesions [19–22].

Efficacy of topical calcipotriene is comparable or slightly higher than mid-to-high potency corticosteroids [23,24]. Though class I corticosteroids are more efficacious in the short term, combination regimen consisting of both agents are superior to corticosteroids used alone. In a double-blind study, a regimen of calcipotriene ointment in the morning and halobetasol ointment in the evening resulted in significantly more improvement than either agent alone used twice daily [25]. In another study, long-term maintenance using halobetasol ointment twice daily on weekends and calcipotriene twice daily on weekdays was superior to ‘weekend therapy’ with halobetasol and placebo during the week [26].

The most common side-effect of calcipotriene therapy is the development of an irritant contact dermatitis at the site of application [24,26]. There are isolated reports of hypercalcemia in patients who applied excessive quantities of calcipotriene over large surface areas. However, several studies have not revealed clinically significant changes in calcium metabolism in patients who apply less than 100 g per week [9].

Tazarotene

Tazarotene (Tazorac[®], Allergan) is a retinoid that elicits a normalization of abnormal keratinocyte differentiation, a reduction in keratinocyte proliferation, and a reduction in inflammation. It selectively binds retinoid receptor subtypes β and γ , and is therefore associated with fewer side effects than other retinoids [8]. In the USA, tazarotene is used in topical formulations (0.05% cream and

gel and 0.1% gel and cream) to treat psoriasis. An oral version of tazarotene to be used to treat psoriasis was recently rejected by the FDA for approval for use in the USA.

In a clinical trial, tazarotene 0.1 or 0.05% gels were superior to placebo when applied once daily for 12 weeks and had sustained efficacy for an additional 12 weeks after cessation of treatment. The lesional clearance success rate was 70% among patients in the tazarotene 0.1% group and 59% among patients in the 0.05% group. After 12 weeks, 41% of the 0.1% group and 52% of the 0.05% group continued to demonstrate a sustained response [27]. In another trial, tazarotene gel applied once daily was as effective as the corticosteroid fluocinonide 0.05% cream applied twice daily [28]. Tazarotene is also available now as a 0.1 and 0.05% cream. Phase III studies have shown that both concentrations were effective in the treatment of plaque psoriasis (50–60% had a moderate response or better) and exhibited maintenance of therapeutic effect after withdrawal [29].

The major side effect of tazarotene is local skin irritation including pruritis, burning and erythema occurring in a dose-related manner in up to 25% of patients. Concomitant use of mometasone furoate 0.1% cream (Class 4) or fluocinonide 0.05% cream (Class 2) with tazarotene 0.1% gel applied once daily enhance improvement and diminish local cutaneous irritation [30]. Moreover, tazarotene has been shown to significantly counteract the atrophogenic tendencies of corticosteroids [31].

Moderate-to-severe psoriasis

Ultraviolet B

The therapeutic effects of ultraviolet B (UVB) (290–320 nm) are attributed to the induction of pyrimidine dimers, inhibition of DNA synthesis and the depletion of intra-epidermal T-cells in psoriatic skin [5]. Most current regimens involve a combination of UVB treatment three times per week along with topical application of mineral oil or petrolatum [7].

Narrowband UVB (NB UVB) encompasses the sunburn spectrum wavelength of 311 ± 2 nm and has been shown to offer a significant therapeutic advantage over broadband UVB (BBUVB) (290–320 nm). After 6 weeks of treatment, greater than 80% disease resolution is attained with NB UVB [32,33] compared with 24–73% with UVB [32]. The light bulbs used for NB UVB cost considerably more than standard BB UVB light bulbs. However,

because the erythema response to NB UVB was significantly more intense and persistent, treatment should be coupled with obligate minimum erythema dose testing and close clinical observation during dose increases [32].

Both calcipotriene [34] and tazarotene [35] similarly enhance the efficacy of NB and BB UVB. Salicylic acid, on the other hand, acts as a sun block and inhibits the therapeutic effectiveness of UV light [9] while corticosteroids may shorten the duration of remission induced by UVB [15].

The xenon chloride gas excimer laser provides local monochromatic 308 nm UV phototherapy of skin and has considerable advantages over current phototherapy treatments. It delivers localized, high-intensity UVB energy at a wavelength similar to NB UVB to the plaques of psoriasis without affecting neighboring normal skin [36]. Because psoriatic lesions can tolerate much higher UV exposures, this specific delivery of UVB energy allows higher doses to be used on the plaques of psoriasis and results in faster clearing with fewer exposures [37]. Treatments are generally well tolerated. Common side effects included erythema, blisters, hyperpigmentation, and erosions [38]. The excimer laser is more expensive for treatment sessions than NB UVB therapy; its relative cost effectiveness has yet to be established.

Ultraviolet A

The second form of UV therapy to become available after BB UVB combines the photosensitizing drug methoxypsoralen (psoralen) with UVA in the range of 320 to 400 nm (PUVA). Psoralen is available to be administered orally, topically and by bath, with oral being discussed herein. Methoxypsoralen is given in an oral dose of 0.6 mg/kg of body weight 2 hours prior to UVA exposure. When photoactivated by UVA, psoralens form crosslinks between pyrimidine bases that interfere with DNA synthesis and block cell proliferation. In addition, PUVA inhibits cytokine release and depletes epidermal and dermal T-cells thereby suppressing cell-mediated immune responses in involved skin [5].

PUVA therapy is highly acceptable to patients because of its efficacy, which can be evident in just a short series of treatment, and the absence of need for topical medications between treatments. The therapeutic schedule typically consists of two (and occasionally three), outpatient treatments per week for 10 weeks followed by a maintenance regimen that can be as little as once every 2 to 4 weeks with tapering eventually.

Short term side effects include nausea, burning and pruritis in 10 to 20% of patients [3].

While PUVA therapy has the potential to induce long term remission in just a single course, the implementation of a maintenance regimen, consisting of one treatment every 1–3 weeks, further improves remission rates significantly [39,40]. In one report of 1308 patients with extensive psoriasis, treatment two or three times a week with PUVA resulted in a clearing rate of 88%. Once remission was induced, there was no difference in maintenance when patients were treated once a week, once every other week, or once every third week and each of these schedules was superior to no maintenance treatment [39].

The major long term concern is the risk of photocarcinogenicity which is dependant on the cumulative dose of UVA received. It has been shown that patients who receive more than 160 treatments have an 11-fold increase in squamous cell carcinomas [41]. In addition, there is a single report of an increased risk of melanoma among patients who received more than 250 sessions [42].

Combining PUVA with therapeutic agents that reduce the UVA dose required for clearance of psoriasis may be of benefit in reducing the long-term risk of cutaneous malignancy. A comparison study in 13 psoriasis patients, for example, found that concomitant use of calcipotriene enhances the response of psoriasis to PUVA [43]. Another study in 31 patients found that tacalcitol ointment and tazarotene gel were both comparably effective in accelerating treatment response to PUVA [44]. Data regarding the combination of PUVA and corticosteroids has yielded conflicting results, with some claiming that it results in faster clearing without shortening the duration of remission, while others claim that the addition of topical corticosteroids to a regimen of PUVA results in shorter remissions. Of note, both methotrexate [45] and cyclosporine [46] have been shown to contribute to the risk of non-melanoma skin cancer in patients receiving phototherapy [9].

Acitretin

Acitretin (Soriatine[®], Connetics Corp.), the active metabolite of etretinate, is an oral retinoid for the treatment of moderate-to-severe forms of psoriasis. Etretinate was withdrawn from the US market because its long half-life and persistence in tissues posed a long term risk of teratogenicity in women of childbearing potential [102]. Etretinate was replaced by acitretin in March, 1998.

Systemic retinoids possess anti-inflammatory, antiproliferative and keratinolytic activity [15].

Used alone, their efficacy in chronic plaque psoriasis is modest in comparison to agents such as UVB, PUVA or methotrexate. In two clinical trials, responder rates after 12 weeks of acitretin treatment were approximately 75% for patients showing a psoriasis area and severity index (PASI) of 50 and 50% demonstrating a PASI of 75 [47].

Oral retinoids work synergistically with phototherapy both in terms of efficacy and reducing another's side effects [9]. Addition of acitretin in doses of 10–25 mg to a regimen of PUVA or UVB dramatically decreases the number of treatments required for clearing, reduces the total amount of exposure to UV light, and minimizes the side effects associated with retinoid use [48,49]. Because of its efficacy in suppression of nonmelanoma cutaneous malignancies, acitretin should be considered as a maintenance therapy for psoriasis patients developing squamous cell carcinomas as a result of PUVA therapy [50].

Increased doses of acitretin provide greater efficacy, however side effects tend to be dose dependent. Mucocutaneous side effects, such as cheilitis, conjunctivitis, hair loss, nail plate abnormalities and dry skin, are associated with acitretin use. Periungual pyogenic granulomas can develop but usually resolve with dose reduction. Systemic side effects may include osteoporosis, calcification of ligaments and skeletal hyperostosis. In addition, patients should be monitored for laboratory abnormalities, such as elevations of serum lipids (particularly triglycerides) and liver function tests [102]. Bone thinning effects are much more severe for isotretinoin than for acitretin.

Although acitretin has a shorter half-life than etretinate, it is still highly teratogenic and contraindicated in pregnant women. In the presence of ethanol, acitretin is esterified to etretinate creating great concern that birth defects might result if acitretin-treated women inadvertently ingest alcohol, a frequent ingredient in a variety of foods and over-the-counter medications. It is therefore not recommended for women of childbearing potential who may become pregnant within 3 years [3,15]. If acitretin is used in women of child bearing age, it should be used with oral contraceptive pills and a β -human chorionic gonadotrophin (HCG) checked monthly. Isotretinoin, is cleared from the body in 1 month, after which time women may safely attempt getting pregnant [51].

Methotrexate

Methotrexate is a folic acid antagonist which inhibits dihydrofolate reductase, an enzyme necessary for nucleotide and amino acid synthesis. As

a result, it decreases DNA synthesis, inhibits mitosis, and inhibits the proliferation of rapidly dividing cells, including psoriatic keratinocytes. Methotrexate is a powerful alternative for patients with moderate-to-severe psoriasis who fail topical or phototherapy [7]. It is particularly useful for treatment of patients with psoriatic arthritis, psoriatic erythroderma and pustular psoriasis.

The potent efficacy of methotrexate in psoriasis is tempered by its potential side effects. According to one report of 113 severe psoriasis patients treated with low-dose methotrexate (maximum weekly dose of 15 mg; mean cumulative dose of 4803 mg) for an average of approximately 9 years, 81% achieved prolonged, complete or near complete clearance and 73% had side-effects, most frequently abnormal liver function tests, nausea, and gastric complaints. A total of 71 patients discontinued therapy, 33 because of associated side effects. In addition, of the 55 who had one or more liver biopsies, 13% had fibrosis and 4% had cirrhosis [52].

Methotrexate is immunosuppressive, hepatotoxic and teratogenic. Patients must have normal hematologic status, renal, and liver function before the initiation of therapy and the drug must be avoided in alcoholics as well as in pregnant women. Bone marrow toxicity is the most serious short-term side effect and can result from concomitant use of the antibiotic trimethoprim-sulfamethoxazole or medications that reduce renal clearance of methotrexate. Other side effects include mucosal ulceration or stomatitis, nausea, macrocytic anemia, photosensitivity, and pulmonary toxicity [102].

A hypersensitivity syndrome to methotrexate exists. The most concerning and common long-term problem is hepatotoxicity. Retrospective studies have indicated that cirrhosis develops in 3% of psoriasis patients who have received a cumulative dose of methotrexate of 4 g [3]. The American Academy of Dermatology guidelines recommends a liver biopsy under the proper circumstances at the onset of therapy and at 1.5 g intervals of cumulative dose for the duration of treatment [53]. In addition, it is suggested that males taking the drug discontinue treatment several months before attempting to impregnate a woman [102].

Cyclosporine

Cyclosporine is an immunosuppressive agent that works by suppressing proliferation of activated T-cells and inhibiting synthesis of proliferative cytokines. It is indicated for the treatment

of recalcitrant plaque psoriasis, in patients who have failed to respond to other systemic therapies or for whom other therapies are contraindicated or intolerable [15]. This agent is not teratogenic and may be a useful alternative to methotrexate or acitretin in women planning pregnancy [102].

Cyclosporine can work very rapidly to clear psoriasis. In a 181 patient study, cyclosporine, 5.0 mg/kg per day, the median time to achieve a 70% reduction in body surface area affected was 8 weeks. Thereafter, cyclosporine 3.0 mg/kg per day, adequately and safely maintained 58% of patients with psoriasis for a 6-month period after clearing of their psoriasis [54]. Data from a randomized trial of 88 patients with moderate-to-severe psoriasis, however, indicate no significant differences in efficacy between methotrexate and cyclosporine after 16 weeks of treatment [55].

Side effects include headaches, paresthesias, hypertrichosis, gastrointestinal disturbances, gingival hyperplasia, hypertension, hyperlipidemia, nephrotoxicity, and electrolyte disturbances. With long term therapy, nephrotoxicity is the major concern. Out of 122 patients treated with cyclosporine for an average of 22 months, 28% discontinued its use due to renal failure and 19% due to hypertension. The risk of toxicity increases with age, duration of therapy, preexisting hypertension, or elevated serum creatinine [56].

Biologic Agents

The need for safe and effective therapies together with an improved understanding of the pathogenesis of psoriasis has led to the development of targeted biologic therapies. The mechanistic design of each of the biologics is based on one of four general strategies:

- Reduction of the pathogenic T-cells
- Inhibition of T-cell activation
- Cytokine mediated immune deviation from a T-helper (Th) type 1 to a Th2 response
- Blocking the activity of inflammatory cytokines (Table 2) [57]

Alefacept

Alefacept is recombinant protein (human leukocyte functional antigen [LFA]-3-immunoglobulin[Ig]G1 fusion protein) that binds to CD2 on memory effector T-lymphocytes, inhibiting their activation and modifying the inflammatory process [57].

In a Phase II trial, patients given intravenous (i.v) alefacept once weekly for 12 weeks showed significant improvement in disease severity relative to

Table 2. Routes of administration of psoriasis biologic agents.

Drug	Subcutaneous	Intravenous	Bolus Infusion	Intramuscular
Infliximab			X	
Alefacept		X		X
Efalizumab	X			
Etanercept	X			
Adalimumab	X			

placebo treated patients at 2 and 12 weeks after the initiation of therapy [57]. In a Phase III trial, more than two thirds of patients who received two 12-week courses of intravenous alefacept achieved greater than 50% improvement. Although most of the improvement came from the first course of therapy, a further increase in efficacy was observed after the second [58]. Another Phase III trial showed that intramuscular administration of alefacept at 15 mg/wk was a convenient, well-tolerated and effective alternative to intravenous dosing [59]. In addition, data from an international double-blind study indicate that response to alefacept correlates with decreases in circulating blood lymphocyte counts [FDA. Alefacept product insert. Vol. 2004, (2003)].

Despite the reduction of CD45RO⁺ T-lymphocytes in patients treated with alefacept, no clinically significant signs of immunosuppression, opportunistic infections or increase in malignancy have been observed. Adverse events may include serious infections, malignancies, lymphopenia, and hypersensitivity reactions. Since alefacept is an immunosuppressant, it should not be initiated in patients with reduced CD4⁺ lymphocyte counts [Amevive. Full prescribing information. Vol. Amevive, 2003 (2004)]. Patients receiving alefacept should undergo weekly monitoring of T-cell counts and discontinue therapy if counts fall below 250 cells/ μ L. Alefacept was approved by the FDA for treatment of psoriasis in January, 2003. Alefacept is available as either a 15 mg intramuscular injection or a 7.5 mg intravenous injection [60]. (The intravenous injections have recently been withdrawn from the market due to a lack of doctor and patient interest in such dosing).

Efalizumab

CD11a and CD18 comprise subunits of leukocyte function associated antigen (LFA-1), a T-cell surface molecule important in T-cell activation, T-cell emigration into skin, and cytotoxic T-cell function. Efalizumab (Raptiva[®], Genetech Inc.) is a humanized monoclonal antibody (mAb) against CD11a. In an early open label study, single doses higher than 1.0 mg/kg

blocked CD11a expression completely for at least 14 days in both blood and psoriatic plaques. This pharmacodynamic response was accompanied by decreased numbers of epidermal and dermal CD3⁽⁺⁾ T-cells, decreased keratinocyte and blood vessel expression of the intracellular cell adhesion molecule (ICAM)-1, epidermal thinning and statistically significant drops in PASI compared with baseline [61,62].

In a double blind, placebo-controlled Phase II trial of 145 patients, anti-CD11a antibody in 8 weekly doses of 0.3 mg/kg i.v was well tolerated and induced significantly greater clinical improvement than placebo [63]. In Phase III trials, significantly more patients who received efalizumab subcutaneously reached 50–75% improvement than patients who received placebo after 12 weeks of treatment [64, Raptiva. Prescribing information. Vol. Jan, (2004)]. Continuation of therapy for an additional 12 weeks provided continued clinical benefit while discontinuation of therapy resulted in regression toward baseline [64].

The most common adverse event reported was a flu-like syndrome consisting of headache, chills, fever, nausea and myalgias within 2 days of treatment [61,62, Raptiva. Prescribing information. Vol. Jan, (2004)]. Therefore, a conditioning dose of 0.7 mg/kg is recommended to reduce the incidence and severity of reactions associated with initial dosing [65]. Administration of efalizumab did not result in a decrease in the number of circulating lymphocytes. Rather, it was associated with a transient increase that persisted for the duration of treatment [61–64]. There is no evidence of increased risk of end-organ toxicity, malignancy or infection with efalizumab treatment to date [57].

However, since efalizumab is an immunosuppressive drug, it should not be given to patients with infections, malignancy or history of malignancy. Furthermore, vaccines should not be administered during efalizumab therapy. In a small clinical study with i.v administered efalizumab, a single dose of 0.3 mg/kg given before primary immunization with a neoantigen decreased the

secondary immune response, and a dose of 1 mg/kg almost completely ablated it. A dose of 0.3 mg/kg IV has comparable pharmacodynamic effects to the recommended dose of 1 mg/kg subcutaneously (s.c). In chimpanzees exposed to efalizumab at greater than or equal to ten times the clinical exposure level (based on mean peak plasma levels) antibody responses were decreased following immunization with tetanus toxoid compared with untreated control animals. Efalizumab gained FDA approval in October, 2003 and is available in the form of a 125 mg s.c injection [65]. It was approved for use in the EU in June, 2004. Low platelet counts (thrombocytopenia) have been frequently observed (in 0.3% of clinical trial patients) during treatment with efalizumab, and thus the complete blood count should be monitored.

Etanercept

Recognition that the pro-inflammatory cytokine tumor necrosis factor (TNF)- α is overproduced in patients with various inflammatory disorders including psoriasis has led to the development of a soluble recombinant human TNF- α -receptor fusion protein that antagonizes the effects of endogenous TNF- α by competitively inhibiting its interaction with cell surface receptors. Based on the success of anti-TNF- α treatment in rheumatoid arthritis (RA), a 12-week, randomized, double-blind, placebo-controlled study assessed the efficacy of etanercept in 60 patients with psoriatic arthritis and psoriasis skin lesions. Administration of etanercept in 25 mg twice-weekly subcutaneous injections proved to be significantly more effective than placebo in all measures of disease activity [66].

Subsequently, a multicenter, randomized, double-blind, placebo-controlled, phase II study in 148 patients demonstrated that etanercept was superior to placebo and that etanercept-treated patients continued to improve through week 24 of treatment [67].

A phase III, multicenter, placebo-controlled, double blind, parallel group trial evaluated the efficacy of etanercept administered at low dose (25 mg once weekly), medium dose (25 mg twice weekly) or high dose (50 mg twice weekly) for 12 weeks. At week 12, there was a 75% improvement in PASI score in 4% of placebo patients, as compared with 14% of those in the low dose etanercept group, 34 in the medium dose group, and 49% in the high dose group. All three dosing schedules were significantly superior to placebo and improvement continued with longer treatment [103].

Currently, a two step dosing schedule is recommended for etanercept administration:

- Step 1: Etanercept 50mg (2 \times 25 mg injections) s.c twice weekly for 3 months.
- Step 2: Etanercept 50mg (2 \times 25 mg injections) s.c weekly for maintenance

Adverse effects observed in the aforementioned clinical trials were unremarkable, and were similar in patients receiving either etanercept or placebo [66,67,102]. Etanercept has been FDA approved for the treatment of RA since 1998 and for psoriatic arthritis since 2002. Although data regarding long-term safety in patients with psoriasis are not available, clinical studies in more than 2000 patients with RA who received etanercept for up to 5 years have demonstrated continued efficacy and a favorable risk-benefit profile suggesting that long-term treatment with etanercept may be a viable option for patients with psoriasis, an important consideration for management of this chronic disease [67,102]. Nevertheless, risks associated with etanercept include serious infections, nervous system disorders, lymphomas (uncertain, evidence does not show a definite increase), and injection site reactions [68].

Infliximab

In contrast to etanercept which antagonizes TNF- α via competitive inhibition, infliximab (Remicade[®], Schering-Plough) is a humanized, chimeric, monoclonal antibody that recognizes, binds to and neutralizes TNF- α . The efficacy of infliximab was demonstrated in a double-blind, 10 week phase II trial in which 33 patients with moderate-to-severe plaque psoriasis involving at least 5% of the body surface area were randomly assigned to receive placebo or a three-dose induction regimen of infliximab 5 or 10 mg/kg at weeks 0, 2 and 6. Significantly more patients in both infliximab dosing arms improved than patients in the placebo group, however the difference between the infliximab 5 and 10 mg/kg doses was not clinically important [69].

Immunohistochemical analysis of lesional and nonlesional biopsies conducted by the investigators on the same subset of patients showed rapid and marked decreases in epidermal T-cell infiltration and adhesion molecule expression, along with normalization of keratinocyte differentiation in psoriatic plaques after treatment with infliximab. These changes occurred in large part at least 8 weeks before observing the maximal clinical response and were correlated with improvement [104].

Overall, studies suggest that infliximab, administered in a three-dose induction regimen of either 5 or 10 mg/kg at weeks 0, 2 and 6, produces a rapid, effective, and sustainable (through week 26) effect that is associated with decreases in epidermal inflammation and normalization of keratinocyte differentiation in patients with moderate-to-severe psoriasis [69,104].

Infliximab is not yet FDA approved for the treatment of psoriasis. Though it has been generally well tolerated in studies, it has been associated with infusion reactions and infections, including rare serious infections, and reactivation tuberculosis among patients who received this therapy for approved indications [57].

Adalimumab

Adalimumab (Humira[®], Abbot Laboratories) is a monoclonal antibody that targets the TNF- α receptor. A double-blind, Phase II study measured the effectiveness and tolerability of adalimumab after 12 weeks and then continued through 24 weeks. Patients received either 40 mg every other week, 40 mg weekly, or placebo. Those who continued for 24 weeks continued the same dosing. Beginning at week 12, patients in the placebo arm received an initial dose of 80 mg of adalimumab followed by 40 mg every other week [105].

The results of this study showed that patients achieved significant and continued improvement in disease activity and quality of life over 24 weeks of treatment, with nearly half of patients experiencing a 90% improvement in disease activity. The percentages of patients on adalimumab therapy with a PASI 75 response were statistically significantly greater than those for patients on placebo as early as 4 weeks. Additionally, patients taking adalimumab experienced a statistically significantly greater mean percentage change in PASI score relative to baseline compared to placebo as early as one week after the initial dose (every other week = -14%, weekly = -15% vs. placebo = -1%). In total, 64% of patients in the adalimumab 40mg every other week group and 72% of patients in the weekly adalimumab 40 mg group achieved at least a 75% improvement in disease extent and severity after 24 weeks. Of the patients who switched from placebo to the 40 mg every other week regimen, 55% achieved PASI 75.

The rates of adverse events were comparable between adalimumab and placebo. There were no new safety issues in the psoriasis population compared with those observed in the RA

population. Serious side effect concerns for patients receiving adalimumab include infection, specifically tuberculosis and histoplasmosis, demyelinating disease, malignancy, hypersensitivity, and cytopenia [70].

Expert opinion

The current gold standard for limited psoriasis is calcipotriene and an ultrapotent topical corticosteroid. Phototherapy with NB UVB is probably the most effective treatment with least side-effects of any of the systemic treatments but is inconvenient. Methotrexate is both cost effective and effective in psoriasis but can have side effects if used long term. Biologic therapy is effective but expensive and generally very safe, however, the long term side effect of the biologics is still being defined. As more knowledge is gained, we will better understand the cost benefit analysis of using of such expensive treatments. It is exciting that so many treatments are available; it improves the lives of patients and provides options that can be mixed and matched by their caregivers to optimize care.

Outlook

Over the next 5 years, a variety of novel therapeutic options for psoriasis will emerge. The use of topical tacrolimus (Protopic[®], Fujisawa) and pimecrolimus (Elidel[®], Novartis Pharma), calcineurin inhibitors used for the treatment of atopic dermatitis, will likely increase as additional investigations determine the ideal formulations for particular body sites in the treatment of psoriasis [71]. Oral tazarotene has shown promising results for moderate to severe psoriasis in Phase III trials [72] and is awaiting approval for the treatment of psoriasis by the FDA. On July 12, 2004, two FDA advisory committees voted against the oral retinoid recommendation. The FDA rejected the application for approval of oral Tazrotene in 2004, but the company is considering amending its application.

The development of directed therapy is perhaps the most significant advancement in the management of psoriasis. Rather than general suppression of the immune system through drugs such as methotrexate or cyclosporine, biologic agents target the specific alterations responsible for the pathogenesis of psoriatic lesions. Over the next 5 years, it is likely that additional directed therapeutics will emerge and that the use of biologics will increase. The market for these medications will grow as more people discover their potential for efficacy and as confidence increases

Highlights

- Psoriasis is a chronic disease for which there is no cure
- Topical therapies can be combined to increase efficacy
- Anthralin is a useful topical agent that can be used in a variety of combination regimens
- Phototherapy, specifically NB UVB, is a good second line treatment option
- Methotrexate is safe for short term use (<1-2 years)
- Cyclosporine is the agent of choice if rapid clearance of psoriasis is required
- The biologic agents target the molecular alterations in psoriasis specifically
- Biologics are generally very safe and well tolerated.

with regard to their side effect profiles. However, because of the high cost, there will be a push and pull in regard to the use of biologics: older Americans will have access to the medications because the government will pay most of their cost, while

younger Americans will have less access as insurers refuse to pay for them, a right they have under *AETNA v. DAVILA* 542 US (2004), which states that patients can not sue a Health Maintenance Organization (HMO) in state court if the HMO refuses to pay for a medication or requires that other medication be used first.

Information resources

The National Psoriasis Foundation (www.psoriasis.org/home/) is among the best of its kind. It has important information on new treatment or how to get a HMO to pay for a new treatment. It also provides information on psoriasis experts in a certain area and where to obtain phototherapy.

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introduced into the therapeutic armamentarium for the treatment of hypertension. The drug, 2-n-butyl-4-chloro-5-hydroxymethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole potassium salt is a potent, orally active, specific, competitive Ang II receptor antagonist both *in vitro* and *in vivo*. Losartan possesses significant antihypertensive activity in all species studied and also prevents all known cardiovascular effects of Ang II both in animals and humans [30,31]. The efficacy of the compound is associated with a high degree of tolerability, as the side effect of this new class of antihypertensive agents is not really discernible from that of placebo [32–34]. Both the parent compound and the de-esterified moiety, EXP-3174, act as an antagonist for the angiotensin type (AT)₁ Ang II receptor [35]. The terminal half-life for the metabolite is 6–9 h, whereas for the parent compound it is 2 h. Both losartan and its active metabolite, EXP-3174, are highly bound to plasma protein. The volume of distribution of the parent compound is 34 l and that of the metabolite about 12 l. With renal insufficiency, plasma clearance is not altered until creatinine clearance reaches levels below 30 ml/min. At lower renal function the area under the curve may increase by 50%. Although plasma aldosterone concentrations may be reduced with losartan, minimal effects on serum potassium occur [36,37]. The antihypertensive characteristics of losartan were tested and dosages ranging from 10 to 150 mg per day resulting in the two approved once-daily doses of 50 and 100 mg [38,39]. Low-dose hydrochlorothiazide (HCTZ) therapy (12.5–25 mg/day) markedly improves antihypertensive effects particularly in salt-sensitive individuals such as African-Americans and the elderly [40–42]. The significant side effect characteristics of ACE inhibitors, angioneurotic edema and cough, are very rarely encountered with losartan therapy. The adverse effect of suppression of RAS in the second and third trimester of pregnancy is similarly associated with AIIA therapy. Therefore, their use in pregnancy is contraindicated.

Within a particular class of drugs, molecular differences may render additional pharmacological properties which can translate into either positive or negative effects. Although as a class of antihypertensive agents, losartan therapeutic actions are comparable with those of the other six AIIA currently marketed in the USA, losartan has additional mechanisms of action entailing competitive blockade of the thromboxane A₂ receptor [43–45] and increase in the excretion of

uric acid [46–51]. Building on the demonstration that losartan inhibited platelet aggregation in pharmacological studies in animals and isolated blood vessels, Levy and colleagues first demonstrated that losartan reduced platelet aggregation in hypertensive subjects within 4 weeks after initiation of therapy at a dose of 50 mg/day. More recently, Kramer and colleagues reported the presence of an intermediate metabolite of losartan (EXP3179) which not only possessed potent antithrombotic effects but also inhibited cyclooxygenase (COX)2 expression [52]. Both the unique antithrombotic and uricosuric effects of losartan may favor increased cardiorenal protective actions which are independent of blood pressure control, as these pharmacological actions may act to reverse the components of the metabolic syndrome entailing vascular endothelial injury and the hypercoagulability stage of hypertensive vascular disease. Germane to these possibilities is the observation that the principal benefit of losartan therapy compared with the atenolol-based regimen in the Losartan Intervention For End point study (LIFE trial) was a 25% reduction in the risk of strokes and left ventricular hypertrophy [30,48,53–56].

Effects of angiotensin receptor antagonists on progression of diabetes nephropathy

The positive renal function characteristics of the AIIA class gave further impetus to explore its capability of being renal protective [57]. The rationale for this investigation was based on the availability of multiple short term studies which in both animals and humans indicated that blockade of AT₁ receptors could be as potent as ACE inhibition in reversing the intraglomerular hemodynamic and structural changes that lead to increased excretion of protein [28,30,58–72].

Substantiation of the renal protective effects of AIIAs came with the publishing of the losartan Reduction of End points in Noninsulin-dependant diabetes with the AIIA Losartan (RENAAL) study in 2001 [73]. This was a randomized placebo-controlled study of losartan in 1513 Type 2 diabetic patients with diabetic nephropathy. This multinational study included 250 centers in 28 countries throughout the world. The parallel, blinded, randomized design sought a 4.5 year follow-up utilizing the primary composite end point of doubling of serum creatinine, ESRD or death as the primary end points. Losartan at doses of 50 and 100 mg was compared with placebo

with both arms receiving conventional antihypertensive agents (excluding ACE inhibitors and AIIA) to control blood pressure to a target of less than 140 mmHg systolic and 90 mmHg diastolic pressures. After 1 month of medication at a dose of 50 mg of losartan, investigators were instructed to titrate the study drug to 100 mg once daily if the through blood pressure goal of less than 140/90 mmHg was not achieved. Overall, 72% of patients received the 100 mg daily dose of losartan more than 50% of the time they were on the study drug. In this study, nephropathy was defined as a serum creatinine of 1.3 to 3.0 mg/dL in females or males less than or equal to 60 kg and 1.5 to 3.0 mg/dL in males less than 60 kg, while proteinuria was defined as a urinary albumin to creatinine ratio of greater than or equal to 300 mg/g. The baseline characteristics noted a mean serum creatinine of 1.9 mg/dL, a mean urinary protein of 1385 mg/dL, a 12% incidence of cardiovascular heart disease, and an initial blood pressure of 152/82 mmHg prior to randomization. In actuality a mean of 3.4 years of follow-up was obtained. Ages ranged 60 ± 7 years, with 35–38% women and 48–50% nonwhite. In the losartan group, 327 patients reached the primary end point compared with 359 in the placebo group, accounting for a 16% risk reduction ($p = 0.02$) for the losartan arm of the study (Figure 2). Today, rather than using reduction in glomerular filtration rate, the doubling of creatinine and the percent reaching ESRD are the more commonly utilized parameters. At the end of the study, the risk reduction in the primary composite end point of doubling of serum creatinine, ESRD (defined as need for dialysis or renal transplantation) or death averaged 16.1% ($p = 0.022$). Doubling of creatinine was reduced by 25% in the losartan arm ($p = 0.006$) and by 28% for ESRD ($p = 0.002$). The overall death rates were similar in the two groups. Proteinuria did decline in the losartan arm of the study, by a total of 35% ($p < 0.001$), reiterating the significance of proteinuria reduction and the progression of renal disease. As reported in the Heart Outcome Prevention Evaluation (HOPE) trial and the MICRO-HOPE substudy [74–77] the HOPE study, the heart failure risk reduction decreased by 32% ($p = 0.005$) although that was not evident in the death rate. However, in RENAAL, the definition of heart failure was based upon evaluation of stated signs and symptoms, not on hospitalizations.

Cardiovascular end points were similar between the two groups. At the end of the study, the average blood pressures for the losartan and placebo group were 140/74 and 142/74 mmHg, respectively. Notably, although the blood pressures in the two groups were similar, the systolic goal of less than 140 was not truly achieved in either arm of the study. Ancillary hypertensive medications were used in both groups including calcium channel antagonist, predominantly dihydropteridines (78–81%), diuretics (84%), α -blockers (40–65%), β -blockers (34–37%), and central acting agents (18–22%). The distribution of the additional agents was comparable in the two groups. Concomitantly, a second AIIA renal protection study completed and was published in parallel with the RENAAL study. The Irbesartan in Diabetic Nephropathy Trial (IDNT) [78], also involving Type 2 diabetic hypertensive patients, utilized three arms consisting of placebo (standard therapy), the AIIA, irbesartan, and the calcium channel blocker amlodipine. This also was a large, multinational, randomized, parallel design. Standard antihypertensive therapy was compared with the AIIA, irbesartan at doses of 150 and 300 mg, and to amlodipine at doses 5 and 10 mg, all force titrated to maximal dose as tolerated. A total of 1715 patients were involved for a duration of 54 months (mean 31 months) utilizing the same end points of doubling serum creatinine, arrival at ESRD, and in this case, cardiovascular mortality and morbidity. In the IDNT study the blood pressure goal of less than 130/85 mmHg was similarly not achieved with the overall average blood pressure at study end being 140/77 mmHg [78]. Again, a significant decrease in the doubling of creatinine was noted in the AIIA group compared with placebo at 23% ($p < 0.003$); and a 27% ($p < 0.001$) reduction compared with amlodipine. The unadjusted relative risk for the composite end point of doubling serum creatinine and ESRD or death was 0.80 ($p < 0.02$) for irbesartan versus placebo and 0.73 ($p < 0.006$) for irbesartan versus amlodipine. Proteinuria was reduced by 33% in the AIIA arm versus 6% in the patients medicated with amlodipine and 10% in the placebo arm [78].

Taken together, these two long-term, well designed and monitored studies underscored the efficacy and safety of AIIA therapy in Type 2 diabetic patients to lessen the progression of renal disease. Hostetter's editorial in the *N. Engl. J. Med.* positively appraised the position of AIIA in

Highlights

- Angiotensin II antagonists.
- Renal protection.
- Suppression of proteinuria.
- Suppression of cytokines/inflammatory markers.

will then be needed if we are to provide our aging population greater quality of life in their remaining years. Wider dissemination of this knowledge must occur before the end of this first decade of the 21st century to help offset the rising costs of medical care.

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