Acta Dermatovenerol Croat 2006;14(3):188-196 REVIEW

Topical Management of Psoriasis - Corticosteroids and Sparing Corticosteroid Therapy

Biljana Gorgievska Sukarovska, Jasna Lipozenčić

University Department of Dermatology and Venereology, Zagreb University Hospital Center, Zagreb, Croatia

Corresponding author:
Biljana Gorgievska Sukarovska, MD
University Department of Dermatology and Venereology
Zagreb University Hospital Center
Šalata 4
HR-10000 Zagreb
Croatia
jasna.lipozencic@zg.htnet.hr

Received: June 30, 2006
Accepted: August 17, 2006

SUMMARY Psoriasis is a complex disease that requires safe, long-term treatment. Topical steroid therapy, topical non-steroid therapy only, and a combination of various topical therapies in the treatment of mild to moderate forms of psoriasis are presented. Topical therapy includes corticosteroids, vitamin D3 analogs, retinoids, tars, anthralin, keratolytics, and topical immunomodulators. While most medications are approved for use as a single agent in the treatment of psoriasis, some of these drugs are most effective when used in combination with topical corticosteroids. Topical therapy is generally administered for mild and localized forms of psoriasis, whereas phototherapy and systemic therapy are reserved for extensive lesions and more severe forms of the disease. Individual approach is absolutely necessary in each patient with psoriasis.

KEY WORDS: topical glucocorticosteroids; adverse effects of topical corticosteroids; psoriasis

INTRODUCTION

Psoriasis is considered to be a genetically caused, chronic relapsing and inflammatory disease that involves the skin, the scalp and the joints. Psoriasis is now considered to be an immune-mediated, organ-specific inflammatory disease in which intralesional T lymphocytes trigger primed basal stem keratinocytes to proliferate and perpetuate the disease. It may occur in a number of different clinical forms and is usually induced by some extrinsic factors (e.g., infection, medications, physical or emotional stress). Immune mechanisms are implicated in the pathogenesis of psoriasis, stimulating the proliferation of epidermal keratinocytes, the absence of keratinocyte differentiation, and vascular proliferation by the activation of T lymphocytes and release of TH1 cytokines (IL-2, INF-γ, TNF-α, IL-6) and cellular growth factors (EGF and TGF-α2). In psoriasis, the epidermis is 4-6 times thicker than the normal epidermal volume, manifesting as acanthosis. Mitotic activity of the basal layer cells in psoriatic epidermis is 8-fold that in normal cells. Due to the reduced keratinocyte cell cycle (from an average of 28 days to 3-4 days), keratinocytes with preserved nuclei are seen in the epidermis (parakeratosis) (1).

The disease is organ-specific, involving the skin, the scalp and the nails, with joint involvement in 5%-40% of cases (2). Clinically, psoriasis may present in the form of droplike (guttate psoriasis), coin-shaped (nummular psoriasis), plaque form, or as generalized skin lesions in erythrodermic psoriasis. Skin lesions can involve intertriginous regions, while pustular psoriasis and psoriasis arthropathica are considered severe and specific forms of the disease.

Clinically, psoriatic lesions may vary from mild and moderate through severe clinical manifestations that may considerably interfere with the

Acta Dermatovenerol Croat
2006;14(3):188-196

patient's quality of life. There are a number of approaches in defining the disease severity. According to one approach, the severity of psoriasis is determined according to skin involvement in percentage. For example, if more than 10% of the skin surface is involved, it is considered a case of severe psoriasis. According to an alternative approach, in addition to skin involvement in percentage, the quality of life impairment and lesion localization (e.g., lesions on the skin of the face and hands) are also considered in each individual patient.

THE TREATMENT OF PSORIASIS

The goals of successful treatment of psoriasis include the earliest possible control of the disease process, reduction of lesion area in the shortest time possible, and increase of the time in remission with minimal side effects. Topical therapy is generally administered for mild and localized forms of psoriasis, whereas phototherapy and systemic therapy are reserved for extensive lesions and more severe forms of the disease. However, phototherapy and systemic therapy (and their combinations with topical agents) may also be used in mild cases when topical therapy has failed.

Topical therapy includes corticosteroids, vitamin D3 analogs, retinoids, tars, anthralin, and keratolytics, while methotrexate, acitretin, cyclosporine and biological agents are used in systemic therapy (3).

Topical corticosteroids

Although the mechanism of topical agents used in the treatment of psoriasis is different, involvement in the activation of genes for the cytokines that regulate inflammation and immune response is common to all. Appropriate use of these drugs enables their synergistic efficacy, lower requirements of one or both drugs, and reduction of their side effects. If appropriately applied, corticosteroids are useful in all phases of anti-inflammatory therapy in psoriasis, especially as maintenance therapy. Efficacious management of psoriasis includes different drugs, alone or in combination, in sequential or rotational course. These drugs are available in a variety of formulations, i.e. as cream, ointment, lotion, gel and foam. The medium is chosen according to the skin regions involved. The medium may influence the clinical effect, drug action, and patient compliance. Topical corticosteroid preparations were introduced in dermatologic therapy in 1952, when hydrocortisone acetate was synthesized. Fluorohydrocortisone became available on the market in 1955, to be followed by triamcinolone acetonide (1958) and fluorometholone (1959) (4). Topical corticosteroids have since remained the most widely used topical agents in the management of inflammatory dermatoses, including psoriasis and atopic dermatitis. These agents have proved efficacious, simple for use, acceptable for patients, relatively inexpensive, and safe when appropriately applied. When used for the treatment of psoriasis, they frequently lead to rapid improvement or regression of skin lesions (4).

Corticosteroids have anti-inflammatory, antiproliferative, immunosuppressive and vasoconstrictive action. The mechanism of action varies. In cellular cytoplasm, corticosteroids bind to the corticosteroid receptor to form the steroid-receptor complex which translocates into the cell nucleus, where it binds as a homodimer to the glucocorticoid-responsive factor in target genes for corticosteroids, which either stimulates or inhibits the transcription of protein synthesis (5,6).

Corticosteroids may also exert an indirect effect on the target gene transcription by blocking the effect of other transcription factors. Corticosteroids stimulate the level of nuclear inhibitory factor-$\kappa B\alpha$ ($I\kappa B\alpha$) through $I\kappa B\alpha$ gene expression (5). $I\kappa B\alpha$ protein acts by binding to nuclear factor-κB (NF-κB), another transcription regulator, thus blocking its migration to the nucleus. Corticosteroids can influence transcription of the genes that do not contain a receptor responsible for corticosteroids. Corticosteroids can inhibit transcription of various genes for proinflammatory cytokines including interleukin 1 (IL-1), IL-2, IL-6, interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α). They also appear to be implicated in the stimulation of lymphocyte expression of the genes for the production of anti-inflammatory cytokines such as transforming growth factor (TGF) and IL-10 (7).

In the process of regulation of cytokine production, corticosteroids are probably involved in the control of type 1 helper T cell, and TH1 and TH2 lymphocyte presence in the skin. The anti-inflammatory effect of corticosteroids also includes inhibition of capillary dilation and dermal edema as well as suppression of endothelial cells and lymphocyte function (6). They diminish vascular permeability and thus lymphocyte transfer to skin lesions. The antiproliferative effect of corticosteroids has not yet been fully elucidated; however, they seem to be implicated in the blockade of cytokine effect expression (5).

According to the intensity of action, corticosteroid preparations are divided into 4 groups

Acta Dermatovenerol Croat
2006;14(3):188-196

(Europe) and into 7 groups (USA), from group 1 of high-potency through group 7 of low-potency corticosteroids (4, 8, 9) (Table 1). This classification is based on the vasoconstrictive effect of topical corticosteroids on the skin of healthy volunteers. Vasoconstriction test (blanching effect), first used in 1962, is most widely employed to roughly evaluate the efficacy of topical corticosteroids (9). The medium containing active (corticosteroid) component can greatly modify clinical efficacy and potency of

Table 1. Potency ranking of selected topical corticosteroid preparations (9)

Class 1 (superpotent)	Betamethasone dipropionate ointment, cream, 0.05% (Diprolene, Diprosone)
	Clobetasol propionate ointment, cream, 0.05% (Temovate, Dermoxin)
	Diflorasone diacetate ointment, 0.05% (Fluorone, Psorcon)
	Halobetasol propionate ointment, cream, 0.05% (Ultravate)
Class 2 (potent)	Amcinonide ointment, 0.1% (Cyclocort)
	Desoximetasone ointment, cream, 0.25%; gel, 0.05% (Topicort, Ibaril)
	Diflorasone diacetate ointment, 0.05% (Florone, Maxiflor)
	Fluocinonide ointment, cream, gel, 0.05% (Lidex)
	Halcinonide cream, 0.1% (Halog)
	Mometasone furoate ointment, 0.1% (Elocon, Ecural)
	Triamcinolone acetonide ointment, 0.5% (Kenalog)
Class 3 (potent)	Amcinonide cream, lotion 0.1% (Cyclocort)
	Betamethasone valerate ointment, 0.01% (Valisone)
	Diflorasone diacetate cream, 0.05% (Florone, Maxiflor)
	Fluticasone propionate ointment, 0.005% (Cutivate)
	Fluocortolone cream, 0.25% (Ultralan)
	Fluocinonide cream, 0.05% (Lidex E cream, Topsyn)
	Halcinonide ointment, 0.1% (Halog)
	Triamcinolone acetonide ointment, 0.1% (Aristocort A)
	Triamcinolone acetonide, cream 0.5% (Aristocort-HP)
Class 4 (midstrength)	Betamethasone valerate lotion, 0.01% (Valisone, Luxiq)
	Desoximetasone cream, gel 0.05% (Topicort-LP)
	Fluocinolone acetonide cream, 0.2% (Synalar-HP)
	Fluocinolone acetonide ointment, 0.025% (Synalar)
	Flurandrenolide ointment, 0.05% (Cordran)
	Halcinonide cream, 0.025% (Halog)
	Hydrocortisone valerate ointment, 0.2% (Westcort)
	Mometasone furoate cream, 0.1% (Elocon, Ecural)
	Triamcinolone acetonide ointment 0.1% (Kenalog)
Class 5 (midstrength)	Betamethasone dipropionate lotion, 0.05% (Diprosone)
	Betamethasone valerate cream, 0.01% (Valisone)
	Fluocinolone acetonide cream, 0.025% (Synalar)
	Fluocinolone acetonide oil, 0.01% (Dermasmoothe/FS)
	Flurandrenolide cream, 0.05% (Cordran)
	Fluticasone propionate cream, 0.05% (Cutivate)
	Hydrocortisone butyrate cream, 0.1% (Locoid)
	Hydrocortisone valerate cream, 0.2% (Westcort)
	Triamcinolone acetonide lotion, 0.1% (Kenalog)
Class 6 (mild)	Alclometasone dipropionate ointment, cream, 0.05% (Aclovate)
	Betamethasone valerate lotion, 0.05% (Valisone)
	Desonide cream, 0.05% (Desowen, Tridesilon)
	Fluocinolone acetonide cream, solution 0.01% (Synalar)
	Prednicarbate 0.1% cream (Dermatop)
	Triamcinolone acetonide cream, 0.1% (Aristocort)
Class 7 (least potent)	Dexamethasone cream, 0.1% (Decadron phosphate)
	Hydrocortisone, 0.5%, 1%, 2.5% (Hytone, and others)
	Methylprednisolone, 1% (Medrol)
	Topical preparations with flumethasone, prednisolone

From: Hengge UR, Ruzicka T, Schwartz RA, Cork MJ. Adverse effects of topical glucocorticosteroids. J Am Acad Dermatol 2006;54(1):1-25 (9).

Acta Dermatovenerol Croat
2006;14(3):188-196

the active substance. Particular pharmaceutical forms are more appropriate for use on some skin regions (e.g., ointment is more suitable for use on the palms, feet and other dry skin areas, whereas lotion and foam are cosmetically more suitable for use on the scalp) (4,9).

Patient age, type and extension of lesion, and the site of lesion should be considered on deciding on the choice and formulation of corticosteroid. So, low-potency corticosteroids are reserved for the face, inguinal and axillary regions, and for use in children. The anatomic site of lesion is of substantial importance because of different absorption of topical agents on various skin regions. The rate of absorption is 4% on the scalp through 35% in the scrotum region. The rate of drug penetration on eyelids is about 300-fold that on the feet, probably entailing a higher probability of unwanted effects. On other skin regions, initial therapy in adults usually includes the use of medium-potency corticosteroids, whereas high-potency agents are employed for thick chronic lichenified plaques on the feet and hands (4,9). Therefore, the protocol on the use of topical corticosteroids according to potency of action should be strictly followed: low- and high-potency agents for acute inflammatory lesions on the face and in intertriginous regions, and high-potency agents for chronic, hyperkeratotic and lichenified lesions on the hands and feet. It is recommended to apply them once or twice a day. The use on every other day or on weekends is efficient in the management of various chronic states. Low-potency corticosteroids are used in children and elderly patients (9). For many patients the intermittent use of topical corticosteroids is highly effective.

Topical preparations produce best therapeutic results when inflammatory lesions involve less than 20% of the skin surface. In the treatment of psoriasis, these have been successfully used in combination with acitretin, cyclosporine, methotrexate, PUVA, UVB, tazarotene, tar, and dithranol. The optimal use of topical corticosteroids implies initial therapy with a potent compound to achieve disease control; continuation with a less potent preparation after an adequate response has been achieved; reduction of the frequency of application (alternate-day therapy; weekend use); continuation of daily application of the least potent preparation; tapering off treatment upon complete healing and care in treating children, the elderly and treatment at certain locations (e.g., around eyes, face, scrotum, flexures) (9).

Adverse effects of topical corticosteroids

Although corticosteroids are drugs intended for topical application and make the basis of topical therapy for psoriasis and inflammatory dermatoses, their prolonged and excessive use is accompanied by numerous undesired side effects. Children are especially susceptible to side effects because of the great skin surface relative to their body mass.

The prevalence of local side effects is by far greater upon topical application of corticosteroids than with their systemic use. The use of topical corticosteroids can be associated with numerous local and systemic side effects.

Atrophic changes can occur with a prolonged use of any topical corticosteroid. The skin turns shiny, transparent, with the possible occurrence of striae. The factors that determine the grade of skin atrophy include age, lesion localization, potency of the corticosteroid applied, and use of occlusion. Atrophic process begins with microscopic degenerative changes in the epidermis with a decrease in the cell volume and number of cell layers. It is observed in 3-14 days of therapy initiation.

Histological changes can also be perceived in the dermis. Corticosteroids exert an antiproliferative effect on fibroblasts, leading to reduction in the synthesis of collagen and mucopolysaccharides. Elastic fiber becomes significantly thinned and fragmented, and the skin is sensitive to mechanical force, thus favoring the occurrence of striae. While the initial atrophic changes of the skin are still reversible alterations, the occurrence of striae indicates their transformation to an irreversible process (4,9).

Telangiectasias are abnormally dilated capillaries and arterioles, which occur due to the action of microvascular endothelial cells stimulated by corticosteroids. On the skin affected with telangiectasias even a minor trauma may lead to purpura, because of damage to local vasculature.

The application of potent corticosteroids on facial skin will nearly always result in exacerbation of previous or newly induced dermatoses such as rosacea, contact dermatitis, perioral dermatitis, and fungal infections (4,9,10). Fungal infections frequently occur in association with persisting psoriatic lesions. Exacerbation of pustular psoriasis is very common upon discontinuation of topical corticosteroid therapy, and when it has been used over a large skin surface for a prolonged period of time. Acneiform eruption has also been reported with the use of corticosteroid preparations on facial skin.

Acta Dermatovenerol Croat
2006;14(3):188-196

Inappropriate use of corticosteroids may mask the diagnosis of the existing fungal dermatoses (9). Tinea incognita is a term that refers to various clinical manifestations of mycotic infection, which should always be taken in consideration in the presence of persisting and relapsing lesions (11).

Although rarely reported in association with topical corticosteroids, hypertrichosis of a variable grade is rather common with the use of systemic corticosteroids. Contact sensitization due to topical corticosteroids is recorded in 0.2%-6% of cases, mostly manifesting in the form of chronic dermatitis unresponsive to the therapy applied, or as acute eczema, contact urticaria, acute local edema or id-like reaction (10). It should be noted that sensitization to active (corticosteroid) component and to other ingredients of a topical preparation has to be distinguished. Cross sensitivity among various topical corticosteroids has also been demonstrated. Thus, there are 4 groups of corticosteroids that help determine contact sensitivity to corticosteroids: group A, hydrocortisone; group B, triamcinolone; group C, betamethasone; and group D, hydrocortisone butyrate (9). Corticosteroid dependence develops when potent corticosteroids are continuously used on the skin of the face for fear from the eruption of acne, rosacea, perioral dermatitis or telangiectasias upon therapy discontinuation.

Tachyphylaxis may also occur after topical corticosteroid therapy, and is described as the need of substituting low-potency corticosteroids by high-potency agents because the desired effect cannot be achieved with the former anymore (4).

Besides local side effects, topical use of corticosteroids may also result in systemic side effects. Systemic side effects generally occur upon the application of high-potency corticosteroids over a large skin area and for a prolonged period of time, however, they have also been described with inappropriate use of medium-potency topical agents. The changes may be endocrine (Cushing's disease, centripetal obesity, striae), metabolic (glucose intolerance, osteopathy, aseptic femoral necrosis, adrenocortical suppression, growth retardation), electrolyte disbalance (edema, hypocalcemia, hypertension), or ocular (cataract, glaucoma) (9).

In children, all corticosteroids irrespective of their potency can provoke systemic side effects, due to the greater skin surface to body mass ratio. Suppression of the hypothalamic-pituitary-adrenal (HPA) axis has been reported even after the use of low- and medium-potency corticosteroids for 3-4 weeks (4). Children with atopic dermatitis are at a high risk of HPA axis suppression because of the increased corticosteroid penetration through the dermatitis changed skin (9). Growth retardation has also been recorded, however, usually of no clinical significance, showing complete normalization upon therapy discontinuation (4). Therefore, great caution is warranted on using corticosteroid preparations in children. In England, there is the British National Formulary defining the use of these drugs in children. Alclometasone dipropionate is used in children older than 1 year, mometasone furoate in children older than 2 years, fluocinolone acetonide oil in children older than 6 years, and betamethasone and clobetasone in children older than 12 years (9).

The development of glaucoma due to the use of topical corticosteroids is a rare but serious problem. Vision impairment associated with glaucoma has also been described with a prolonged use of topical corticosteroids on the skin of the face.

The risk of HPA axis suppression is increased with the use of high-potency topical corticosteroids, especially in combination with occlusion. The use of low corticosteroid doses (2 g *per* day of 0.05% clobetasol propionate cream) for several days can decrease the level of cortisol. Prolonged topical application of high-potency corticosteroids results in the manifestation of iatrogenic Cushing's syndrome. In rare cases, addisonian crisis associated with the use of topical corticosteroids can lead to lethal outcome (9).

In diabetic patients, glycemia is elevated by percutaneous absorption of topical corticosteroids. It should be noted that the manifestation of latent diabetes is also possible. Great caution should be exercised when topical corticosteroids are used in patients with diabetes, hypertension, impaired liver function, glaucoma, or positive tuberculin test (4).

The rate of corticosteroid side effects can be reduced and the therapeutic effect of corticosteroids in psoriasis patients improved by using a combination of various drugs to produce a synergistic effect (1). Rotational treatment from monotherapy through a combination of drugs reduces the cumulative toxicity of drugs; however, topical corticosteroids are not used (4). Sequential treatment (two drugs) is used in various stages of the disease, with step-wise exclusion of the first drug while retaining the second drug during the period of maintenance therapy (9). Specific drugs used in continuation to corticosteroid therapy include vitamin

Acta Dermatovenerol Croat
2006;14(3):188-196

D3 analogs, retinoids, and topical immunomodulators. The action of the commonly used agents discussed herein, i.e. corticosteroids, topical immunomodulators, retinoids and vitamin D analogs, occurs through varying and divergent pathways. However, common to all of them is that they all interface with the transcriptional activation of cytokine genes that control inflammation and immune response (5).

Vitamin D3 analogs in topical therapy

Vitamin D3 analogs regulate proliferation and differentiation of epidermal keratinocytes. These drugs were introduced in therapy with the use of calcipotriene at the beginning of the 1990s. Calcipotriene is the only drug from this group that is currently available in the USA, whereas in Europe calcitriol and tacalcitol are also available (4,5).

Calcipotriene inhibits proliferation and stimulates terminal differentiation of keratinocytes in psoriatic lesions. It binds to vitamin D-selective receptor in keratinocyte nuclei. Receptors of this type are also found in fibroblasts, T and B lymphocytes, monocytes and macrophages. The activation of these receptors is also likely to play a role in the antipsoriatic action of calcipotriene. Similar to corticosteroids, it antagonizes the action of other factors of transcription such as nuclear factor of T lymphocyte activation (NF-AT), thus indirectly reducing cytokine expression (IL-2, IL-6, IL-8, IFN-γ and GM-CSF) (5).

Calcipotriene has been found to be less efficient than class I corticosteroids in topical therapy. An initial period is needed for its effect to become observable (i.e. its action is relatively slow), and is associated with a high incidence of irritative skin reactions when applied as topical therapy. When used in combination with topical corticosteroid agents, their synergistic action has proved efficient in the management of psoriasis with better clinical results by reducing particular agent toxicity. Also, local skin irritation is considerably reduced when calcipotriene is used in combination with topical corticosteroids. In 1996, 84% of patients were treated with calcipotriene (4). It should be noted that calcipotriene is relatively unstable in acidic medium; therefore its use in combination with 6% salicylic preparations, 12% ammonium lactate lotion and 0.2% hydrocortisone-17-valerate ointment is discouraged (4).

Combinations of topical vitamin D3 with acitretin, cyclosporine, methotrexate, PUVA and UVB, topical corticosteroids, tars, and dithranol have proved successful (12). Topical vitamin D3 analogs such as tacalcitol, calcipotriol, maxacalcitol and paricalcitol have found wide usage as a successful treatment modality for squamous psoriasis (12-15).

Topical retinoids

Retinoids are vitamin A derivatives that regulate cellular growth and differentiation. The only retinoid used in topical therapy of psoriasis is tazarotene, a third-generation retinoid, available in the form of cream and ointment. Tazarotene leads to normalization of keratinocyte differentiation, and reduces keratinocyte proliferation as well as inflammation. It binds selectively to retinoid receptors (RARs). Tazarotene shows high affinity for RAR-β and RAR-γ, and low affinity for RAR-α, regulating gene transcription directly and indirectly, similar to the action of corticosteroids and calcipotriene (5).

Tazarotene is a retinoid with selective action upon β and γ retinoid receptors, and is useful in the management of squamous psoriasis. In combination with corticosteroids (alternatively), it also efficiently prevents relapses of psoriasis (4). Tazarotene has proved efficacious and safe in the treatment of psoriasis. Remissions of at least 12 weeks after therapy discontinuation have been recorded. When used as monotherapy, many patients develop skin irritation at the site of application, known as retinoid dermatitis. Tazarotene is compatible with many corticosteroids for topical use. Combinations of tazarotene and topical corticosteroids have proved more efficient and tolerable than either monotherapy. A combination of tazarotene-clobetasol applied on Mondays, Wednesdays and Fridays with a corticosteroid on Tuesdays and Thursdays resulted in side effect reduction as compared with monotherapy (4). The use of tazarotene is contraindicated in pregnancy because of retinoid teratogenicity.

Tars, anthralin and keratolytics

Besides emollients, first-line topical agents for mild and moderate forms of psoriasis include tars, dithranol and vitamin D3 analogs (4,12,13). Topical therapy with phototherapy and/or systemic therapy is used in severe and refractory forms of psoriasis (4,12).

Coal tars are topical preparations of lower efficacy than topical corticosteroids or corticosteroids and calcipotriene. They are characterized by strong odor, and leave stains on bedclothes and clothes. Tars (e.g., anthralin cream 1%) are used in combination with UVB rays by the method of Göckerman. Like coal tars, anthralin is less

Acta Dermatovenerol Croat
2006;14(3):188-196

efficient than corticosteroids, also causing folliculitis and photosensitivity, irritating the skin and leaving stains on clothes. Anthralin is used in combination with phototherapy (UVB rays) by the method of Ingram (short contact therapy), frequently employed in the management of plaque psoriasis. Phototherapy as immunosuppressive therapy is one of the oldest approaches to treating psoriasis. Narrowband UVB at 311 nm or less effective broadband UVB is commonly used for disruption of key cells in the pathogenesis of psoriasis.

Salicylic acid at 3%-10% concentration is the most widely used keratolytic. It is used in combination with topical corticosteroids to remove squamae, thus enabling better corticosteroid penetration and anti-inflammatory effect. Salicylic acid is used initially in the treatment of stationary psoriasis. It has also been successfully used in combination with topical immunomodulators and phototherapy (13).

Topical immunomodulators

The first immunomodulators were topical corticosteroids, used for a half a century. New immunomodulators used in the treatment of psoriasis are topical calcineurin inhibitors, tacrolimus and pimecrolimus. Tacrolimus and pimecrolimus are relatively novel agents in the treatment of inflammatory dermatoses. The two agents have a similar mechanism of action. They act by inhibition of calcineurin, an intracellular enzyme that is involved in the regulation of gene transcription in T lymphocytes. Topical immunomodulators bind to macrophillin-12, a cytosol receptor, to form the TI-macrophillin complex that precludes dephosphorylation of the nuclear factor AT2 (NF-AT2) by blocking the production of calcineurin serine phosphatase. Thus, the synthesis of Th1 and Th2 type inflammatory cytokines is blocked. Topical immunomodulators are also involved in the modification of the structure and function of epidermal dendritic antigen-presenting cells, thereby reducing their ability of T lymphocyte stimulation. Their anti-inflammatory action also includes the inhibition of histamine release from mastocytes (5,16).

Immunomodulators were presented in the mid-1990s: tacrolimus as the first one, and pimecrolimus soon thereafter, as efficacious alternatives to topical corticosteroids in the treatment of atopic dermatitis, especially in cases where long-term topical therapy is indicated. Tacrolimus is available as 0.03% and 0.1% ointment, and pimecrolimus as 1% cream which can also be used in children older than 2 years (5,14,17). These agents are ever more widely used in the treatment of psoriasis, as shown by numerous studies. Topical immunomodulators are also useful in the management of intertriginous psoriasis (14). Studies have demonstrated the efficacy of pimecrolimus for psoriasis to improve when used with occlusion. Experimental formulations of this agent showed greater efficacy than the commercially available ones, thus opening new prospects for its use in the management of psoriasis (16,17). Pimecrolimus 1% cream has been reported to be efficient in the treatment of inverse psoriasis, with a rapid onset of action and excellent tolerance (16), whereas tacrolimus 1% cream has been recommended as the drug of choice for facial psoriatic lesions (16,18). A combination of tacrolimus 0.1% ointment and 6% salicylic gel proved efficient in the treatment of psoriasis (19). The use of a combination of topical immunomodulators and topical corticosteroids to reduce the rate of side effects has also been reported (4). In a preclinical trial, topical sirolimus proved efficient in the treatment of psoriasis (20).

Discussion on optimal topical therapy of psoriasis

Psoriasis is a chronic relapsing disease quite frequently necessitating long-term therapy. More than 60% of patients in the USA were on single drug therapy (21). One of the approaches to the treatment of psoriasis includes the use of combined rotational and sequential therapy. There has been increasing emphasis on utilizing combination treatment regimens to address the complicated nature of psoriasis management. In combined therapy, agents with different mechanisms of action are simultaneously used to potentiate their additive or synergistic effects, while reducing side effects by lowering the dosage of particular agents (21). In rotational therapy, different monotherapies or combined therapies are alternatively applied to reduce cumulative toxicity of particular agents (21). Rotational approach may occasionally be necessary due to exacerbation of the clinical picture or local skin irritation. In practice, therapeutic switch to rotational approach is performed after a prolonged use of a particular therapy, mostly months or years (4).

The goal of sequential therapy is to achieve rapid initial improvement of lesions by use of a more potent agent, then switching to a less potent drug as maintenance therapy. The treatment is performed in three phases: first, clearing phase, with potent agents at maximal dosage; second,

Acta Dermatovenerol Croat
2006;14(3):188-196

transition phase, with gradual introduction of the second drug while gradually reducing the first one; and third phase, i.e. continuation of maintenance therapy. In practice, so-called pulsed therapy is also frequently used, where high-potency corticosteroids are usually applied in the initial phase for rapid improvement of lesions, then maintenance therapy is only applied on particular, predetermined days.

The efficacy of the combination of topical corticosteroids and calcipotriene has been clinically confirmed (4). When used in combination, these agents provide synergistic efficacy in the management of psoriasis while reducing the toxicity of particular drugs and local skin irritation (4). The higher efficacy *versus* monotherapy was verified by the application of calcipotriene in the morning with halobetasol in the evening. In another study, the same regimen was used for 2 weeks, followed by pulsed therapy with halobetasol during weekends and with calcipotriene on week days. This regimen yielded higher efficacy than monotherapy (5).

A combination of corticosteroid dermatologic agents and tazarotene also leads to improved efficacy and local tolerability as compared with monotherapies. A combination of tazarotene with the corticosteroids mometasone (medium potency) and fluocinonide (high potency) proved more efficient than the combination with a low-potency corticosteroid (5). In comparison with tazarotene monotherapy, combined therapy with tazarotene-clobetasol propionate on Mondays, Wednesdays and Fridays, and a corticosteroid on Tuesdays and Thursdays led to reduction of psoriasis relapses (4).

Studies have recently focused on the possible combinations of topical corticosteroids with topical calcineurin inhibitors. This treatment modality has been verified in the management of atopic dermatitis. Tacrolimus in combination with the medium-potency chlorocortolone pivalate proved more efficient than monotherapy in various lesions (excoriation, induration, erythema, lichenification, pruritus and burning sensation) (4). *In vitro* studies have demonstrated that a combination of betamethasone valerate in the form of foam with tacrolimus ointment or pimecrolimus cream results in better penetration of calcineurin inhibitors. This is of special relevance for tacrolimus in the light of its rather poor skin penetration (4). Using therapies in rotational or intermittent fashion reduces the toxicity to any organ. The strategy may include so-called “treatment holidays” until relapse of the disease is achieved (intermittent therapy) (22).

CONCLUSION

Psoriasis is a complex disease that requires safe long-term therapy. Clinical management is currently dictated by physical, psychological aspects of the disease, with historic response to therapy and aspects identified as mild to severe. In many patients, intermittent therapy with topical corticosteroids is most efficacious. The use of potent topical corticosteroids is discouraged in resistant cases and on sensitive skin areas. The optimal use of topical corticosteroids consists of initial administration of potent agents to achieve efficient control of the disease, followed by the use of less potent agents. It is reasonable to reduce the frequency of corticosteroid application by skipping it on particular days or by use of weekend therapy. Caution is warranted with the use of corticosteroids in children and elderly patients, especially on sensitive skin regions such as the face, scrotum, intertriginous area, periocular area, etc.

Several novel medications have challenged traditional treatment paradigms and created new issues on decision-making. Some therapeutic regimens can be continuously used for a prolonged period of time; however, intermittent therapy for several months at the most is generally required. Selective glucocorticoid agonists (ligands), currently in the phase of preclinical trials, may prove most efficient. Combinations of drugs administered according to a sequential or rotational protocol and various combinations of topical and systemic medications have proved successful and minimize the rate of adverse effects of any medication. However, individual approach is absolutely necessary in each patient with psoriasis.

References

1. Pašić A. Psorijaza. In: Lipozenčić J, ed. Dermatovenerologija. Zagreb: Medicinska naklada; 2004. p. 197-206.
2. Gordon KB, Ruderman EM. The treatment of psoriasis and psoriatic arthritis: an interdisciplinary approach. J Am Acad Dermatol 2006;54:S85-91.
3. Lebwohl M. A clinician’s paradigm in the treatment of psoriasis. J Am Acad Dermatol 2005;53:S59-69.
4. Del Rosso J, Friedlander SF. Corticosteroids: options in the era of steroid-sparing therapy. J Am Acad Dermatol 2005;53:S50-8.

5. Norris DA. Mechanisms of action of topical therapies and the rationale for combination therapy. J Am Acad Dermatol 2005;53:S17-25.
6. Hughes J, Rustin M. Corticosteroids. Clin Dermatol 1997;15:712-21.
7. Elenkov IJ, Chrousos GP. Stress hormones, proinflammatory and anti-inflammatory cytokines, and autoimmunity. Ann N Y Acad Sci 2002;966:290-3.
8. Steroids. Portland (OR): National Psoriasis Foundation; 1998.
9. Hengge UR, Ruzicka T, Schwartz RA, Cork MJ. Adverse effects of topical glucocorticosteroids. J Am Acad Dermatol 2006;54:1-25.
10. Matura M, Goossens A. A contact allergy to corticosteroids. Allergy 2000;55:698-704.
11. Celić D, Radoš J, Skerlev M, Dobrić I. What do we really know about “tinea incognita”? Acta Dermatovenerol Croat 2005;13:17-21.
12. Van de Kerkhof PCM. Therapeutic strategies: rotational therapy and combinations. Clin Exp Dermatol 2001;26:356-61.
13. Fairhurst DA, Ashcroft DM, Griffiths CE. Optimal management of severe plaque form of psoriasis. Am J Clin Dermatol 2005;6:283-94.
14. Takashi H, Hajime I. Treatment of the keratinizing skin disorder, psoriasis by topical vitamin D3. Clin Calcium 2004;14:129-32.
15. Durakovic C, Ray S, Holick MF. Topical paricalcitol (19-nor-1 alpha,25-dihydroxyvitamin D2) is a novel, safe and effective treatment for plaque psoriasis: a pilot study. Br J Dermatol 2004;151:190-5.
16. Lipozenčić J. Pimecrolimus – safe and effective local immunomodulator in the treatment of inflammatory skin diseases. Acta Dermatovenerol Croat 2005;13:63-9.
17. Gribetz C, Ling M, Lebwohl M, Pariser D, Draelos Z, Gottlieb AB, *et al.* Pimecrolimus cream 1% in the treatment of intertriginous psoriasis: a double-blind, randomized study. J Am Acad Dermatol 2004;51:731-8.
18. Kroft EB, Erceg A, Maimets K, Vissers W, van der Valk PG, van de Kerkhof PC. Tacrolimus ointment for the treatment of severe facial plaque psoriasis. J Eur Acad Dermatol Venereol 2005;19:249-51.
19. Carroll CL, Clarke J, Camacho F, Balkrishman R, Feldman SR. Topical tacrolimus ointment combined with 6% salicylic acid gel for plaque psoriasis treatment. Arch Dermatol 2005;141:43-6.
20. Ormerod AD, Shoh SAA, Copeland P, Omar G, Winfield A. Treatment of psoriasis with topical sirolimus preclinical development and randomized, double-blind trial. Br J Dermatol 2005;152:758-64.
21. Pearce DJ, Stealey KH, Balkrishnan R, Fleischer AB, Feldman SR. Psoriasis treatment in the United States at the end on the 20th century. Int J Dermatol 2006;45:370-4.
22. Sacareno R, Griffiths ChEM. A European perspective on the challenges of managing psoriasis. J Am Acad Dermatol 2006;54:S81-S83.