REVIEW ARTICLE

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Psoriasis: Treatment with Calcipotriol

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Psoriasis is an inflammatory papulosquamous skin disease associated with rapid epidermal proliferation, essentially a disorder of the immune system. Genes and immune events play a key role in the pathogenesis of psoriasis. Levels of arachidonic acid and of its metabolites, polyamines, plasminogen activator, calcium binding protein calmodulin, certain interleukins (IL-1, IL-2, IL-6 and IL-8) and growth factors (TNF-α and TGF α) are elevated. Plaque pattern, guttate pattern, local pustular psoriasis, scalp, nails, flexures, palms, napkin psoriasis, erythrodermic psoriasis are the common presentations. Various therapeutic strategies are available for the treatment of this disease. The disadvantages associated with these treatments have made them unsuitable for use. Research is being carried out to study the effectiveness of review vitamin D_3 analogue i.e. calcipotriol in the management of psoriasis. This analogue has potent immunological properties and it acts by directly regulating keratinocyte proliferation and differentiation.

Psoriasis is a very old disease dating back as far as the Biblical times and is a significant challenge for the practicing physician. Special considerations for the elderly include drug-induced or drug-aggravated psoriasis, especially for patients receiving polypharmacy or with recent worsening or poor response to conventional therapy[1]. The biblical term 'lepra' was actually applied to various cutaneous disorders including psoriasis, vitiligo, eczema, boils and *alopecia areata*. The Roman sage Aurelius Cornelius Celsus is credited with the first clinical description of psoriasis. Galen was the first to use the term psoriasis and Robert Willan (1808) specifically distinguished and described psoriasis as a recognizable entity. *Lepra vulgaris* described by Willan was a variety of psoriasis. In 1841, Hebra definitively distinguished the clinical picture of psoriasis from that of leprosy. Psoriasis is a chronic non-infectious, inflammatory disease of the skin, characterized by well-defined erythematous plaques bearing large, adherent, silvery scales[2].

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CAUSE AND PATHOGENESIS

There is considerable epidemiologic evidence that genes play a key role in the pathogenesis of psoriasis. Important interactions with the environment are also implicated in its development. A number of genetic loci have been identified by genome wide linkage scans and two loci have been replicated: PSORS1 on chromosome 6, within the major histocompatibility complex, and PSORS2 on chromosome 17q[3]. Psoriasis is genetically heterogeneous. A child with one affected parent has a 16% chance of developing the disease and this rises to 50% if both parents are affected. Genomic imprinting may explain why psoriatic fathers are more likely to pass on the disease to their children than are psoriatic mothers. If non-psoriatic parents have a child with psoriasis, the risk for subsequent children is about 10%. The disorder is concordant in 70% of monozygotic twins but only in 20% of dizygotic ones[4]. Much importance has been given in recent years to the major human leukocyte histocompatibility antigens (HLA), which are located on chromosome 6[5]. HLA studies have shown an increased frequency of HLA-B13, HLA-B17 and HLA-Bw16 in patients with psoriasis. Patients with HLA-B17 have an

earlier onset of disease than those with HLA-Bw16. HLA-Bw38 shows a strong association with distal psoriatic arthritis and HLA-B27 with generalized pustular psoriasis and psoriatic sacroiilitis[6]. HLA typing in Indian psoriatics identified HLA-BW17 to be significantly associated with this disease. Thus these HLA antigens could be used as genetic markers for identifying the individuals at high risk for developing the disease. It has been suggested that HLA-B13 and HLA-Bw17 reduce the threshold for clinical expression in subjects predisposed to psoriasis[7-8]. In psoriasis there is increased epidermal proliferation due both to an excessive number of germinative cells entering the cell cycle, and perhaps to a decrease in cell cycle time. The epidermal turnover time is greatly shortened to 10 days as compared with 60 days in normal skin. Hyperproliferation accounts for many of the metabolic abnormalities associated with psoriasis[9-10]. During normal keratinization the profile of keratin types changes as a cell moves from the basal layer (K5 and K14) towards the surface (K1 and K10). In psoriasis K6 and K16 are produced but their presence is secondary and non-specific, merely a result of increased epidermal proliferation[11]. Arachidonic acid is bound to cell membranes and released from them by the activity of phospholipase A_2[12]. Levels of arachidonic acid and of its metabolites prostaglandin E_2 (PGE_2), leukotriene B_4 (LTB_4), 12-hydroxy-eicosatetraenoic acid (12-HETE), and 15-HETE are elevated in the lesional skin of psoriasis[13]. There is evidence that cyclic guanosine monophosphate (cGMP) levels are increased in the lesions of psoriasis and therefore ratio between cGMP and cAMP is increased[14-15]. The biosynthesis of the polyamines i.e. putrescine, spermidine and spermine is intimately associated with cellular proliferation. Levels of the enzyme ornithine decarboxylase, catalyzing the reaction ornithine to putrescine, are raised in the lesions of psoriasis, and the levels of the above polyamines are therefore elevated in lesional skin[16]. Proteinases (e.g. plasminogen activator, cathepsins and certain complement components), and some proteinase inhibitors (e.g. α_1-antitrypsin and β_2-macroglobulin), regulate cell proliferation. Plasminogen activator is greatly increased in the lesions of psoriasis and parallels the mitotic rate; this increase may be due to deficiency of an inhibitor[17]. The level of the specific calcium binding protein, calmodulin, is raised in lesions of psoriasis and falls with successful treatment. The calcium-calmodulin complex may regulate epidermal cell proliferation by influencing phospholipase A_2 and cAMP phosphodiesterase (catalyses cAMP conversion to AMP)[18]. In psoriasis the activity of epidermal phospholipase C increases. This catalyses the conversion of phosphatidyl inositol in the cell membrane to inositol triphosphate (IP_3) and diacylglycerol (DG), both of which are involved in signal transduction. IP_3 induces intracellular calcium release, which in turn, activates calmodulin, DG activates protein kinase C leading to increased cell proliferation[19]. Inflammation is a part of an immunological response to antigens. Certain interleukins (IL) and growth regulators are elevated. Keratinocytes are stimulated by various insults (e.g. trauma, infections, drugs, ultraviolet radiation) to release IL-1 and IL-8. IL-1 upregulates the expression of intercellular adhesion molecule-1 (ICAM-1) and E selectin on vascular endothelium in the dermal papillae and ICAM-1 on keratinocytes. T helper lymphocytes accumulate in these papillary vessels because their lymphocytes accumulate in these papillary vessels because their lymphocyte function associated antigen (LFA-1) sticks to adhesion molecules that are expressed on the vascular endothelium. IL-8 from keratinocytes attracts T lymphocytes and neutrophils to migrate from papillary vessels into the epidermis where the T cells are held by adhesion of their LFA-1 with ICAM-1. T cells accumulated in the epidermis are activated as a result of their interactions with langerhans cells and keratinocytes. Activated T cells release interferon-γ (IFN-γ), tumor necrosis factor alpha (TNF-α) and IL-2. IFN-γ and TNF-α induce keratinocytes to express HLA-DR, to upregulate their ICAM-1 expression and to produce further IL-6, IL-8 and TGF-a. IL-2 ensures proliferation of the local T cells. TGF-α acts as an autocrine mediator and attaches to epidermal growth factor (EGF) receptors inducing keratinocytes proliferation. IL-6 and TNF-α also have mitogenic properties. IL-10 is a pluripotent cytokine with effects on numerous cell populations, in particular circulating and resident immune cells as well as epithelial cells. Its low level expression found in psoriasis may have pathophysiological relevance for this immune disease. Remarkably, induction of IL-10 expression was found by conventional antipsoriatic therapies, supporting the hypothesis that IL-10 may be a key cytokine in psoriasis and that application of this cytokine itself may have therapeutic effects[20-22]. Immune events may play a primary role in the pathogenesis of the disease[23]. Abnormalities associated with immune system are as follows:

Depressed cell-mediated immunity:

Immune and inflammatory mechanisms in patients with psoriasis are different from normal. Intradermal injections of various antigens, e.g., trichophytin, candidin streptokinase/streptodornase (SK/SD) and purified tuberculin protein derivative (PPD), can be used to assess mononuclear cell function. People with psoriasis have delayed hyper-

sensitivity reactions to these antigens, as do those without psoriasis; however, those with the disorder respond to SK/SD with a smaller area of erythema, suggesting decreased ability for amplification of the cell-mediated immune responses to at least some intradermally injected antigens. Psoriatic patients have decreased intradermal skin test reaction and decreased number of T-cells in blood[24]. Psoriatic lymphocytes demonstrate decreased blastogenesis to mitogens, decreased response to mixed leukocyte culture and decreased production of lymphokines[25].

Exogenous factors may also play a role. The genome of human papilloma virus 5 was found in psoriatic keratinocytes. Streptococcus species can evoke a psoriatic response, possibly behaving as an antigen that triggers an immune cascade and leads to lesion formation. A variety of medications can trigger the onset of psoriasis, including beta-blockers, lithium, nonsteroidal anti-inflammatory agents, and progesterone-containing oral contraceptives.

Augmented monocyte activity:

One of the earliest changes, which can be detected in patients with psoriasis, is the appearance of macrophages around blood vessels in the superficial dermis. Whereas peripheral blood T-lymphocytes show decreased immune responsiveness and peripheral blood monocytes show increased responsiveness or activation, monocytes from patients with psoriasis show more chemotactic responsiveness than normal. This is true for both lymphocyte-derived chemotactic factor and for complement-derived chemotactic factors. Chemiluminescence, phagocytic and bacterial responses of monocytes also increase in psoriatic patients as compared to normal persons[26-27].

Serum factors:

Serum from patients with psoriasis generates decreased amounts of chemotactic factor, normalizes chemotaxis and nitroblue tetrazolium reduction by psoriatic leukocytes, inhibits lymphocycle blastogenesis, decreases proliferation inhibitory factor activity for HeLa cells, elevated serum IgA levels, decreased serum IgM levels and presence of circulating antibodies to IgG[23].

Immunologic events in the stratum corneum:

An early event in formation of a psoriatic skin lesion is the deposition of IgG and complement in the region of the stratum corneum. People without psoriasis may have very high titers of antistratum-corneum antibody[28].

Extracts of psoriatic scales contain factors, which are chemotactic for polymorphonuclear leukocytes and monocytes. Furthermore, these extracts are chemokinetic for polymorphonuclear leukocytes i.e. substances in the scales increase the speed of migration in addition to causing directed migration. Such factors in the psoriatic scales may explain the accumulation of neutrophils in the subcorneal pustules and Munro's microabscesses that characterize psoriasis. Some studies suggest that the most important chemotactic factor in the scales is C5a[29].

The dermis is abnormal in psoriasis. The dermal capillary loops in psoriatic plaques are abnormally dilated and tortuous, and these changes come before epidermal hyperplasia in the development of a new plaque. Fibroblasts from psoriatics replicate more rapidly *in vitro* and produce more glycosaminoglycans than do those from non-psoriatics[30].

PRESENTATION

Plaque pattern is the most common pattern of psoriasis. Lesions are well demarcated and range from a few millimeters to several centimeters in diameter. The lesions are pink or red with large, dry silvery-white scales (like candle grease). The elbows, knees, lower back, and scalp are sites of predilection[30,31]. Guttate pattern is usually seen in children and adolescents and may be the first sign of the disease, often triggered by tonsilitis. Numerous small round red macules come up suddenly on the trunk and soon become scaly[32]. The scalp is often involved. Areas of scaling are interspersed with normal skin; their lumpiness is more easily felt than seen. Frequently there is an overflow just beyond the scalp margin[33]. Involvement of the nails is common, with 'thimble pitting', onycholysis (separation of the nail from the nail bed)[33,34]. Psoriasis of the submammary, axillary and anogenital folds is not scaly though the glistening sharply demarcated red plaques, often with fissuring in the depth of the fold, are still readily recognizable. Flexural psoriasis is commonest in women and in the elderly. Palmar psoriasis may be hard to recognize as its lesions are often poorly demarcated and barely erythematous[33,35]. A psoriasiform spread outside the napkin (nappy/diaper) area may give the first clue to a psoriatic tendency in an infant. Usually it cleans quickly but there is an increased risk of ordinary psoriasis developing in later life[36]. Localized pustular psoriasis affects the palms and soles, which become studded with numerous sterile pustules, 3-10 mm in diameter, lying on an erythematous base. The pustules change to brown macules or scales[37]. In erythrodermic psoriasis the skin becomes universally and uniformly red with variable scaling. Malaise is accompa-

nied by shivering and the skin feels hot and uncomfortable[38].

TREATMENT OF PSORIASIS

Faced with an array of topical and systemic drug therapy options, it is of paramount importance that the physician remains focused on the holistic management of the patient, in order to achieve optimal compliance and benefit. This can be achieved through careful attention to quality-of-life issues, especially since many elderly patients may have other medical, social and economic comorbidities that can further negatively affect their overall quality of life. It is also essential that the severity of psoriasis be assessed on a more balanced, holistic scale that incorporates both physical and psychological parameters, such as the Salford Psoriasis Index. The patient and caregiver education should be multi-faceted, regularly conducted and practically orientated. Treatment goals should be kept simple and individualized for each patient, based on concomitant comorbidities, potential adverse effects, existing quality of life, self-care capability, drug history, caregiver situation, financial needs, feasibility for follow-up and patient's preferences. Topically applied medications, such as topical corticosteroids, salicylic acid, tar and dithranol preparations, calcipotriol and tazarotene, are the favoured first-line therapeutic options in the elderly. Narrowband ultraviolet B phototherapy is also well established as a standard therapy for psoriasis. Systemic therapy with agents such as methotrexate, acitretin and cyclosporin should be judiciously reserved for severe, extensive cases in view of their lower therapeutic index in the elderly. The ambulatory psoriasis treatment centre is an integral part of the overall cost-effective management of patients with psoriasis that can function as a 'one-stop' treatment and resource centre for the elderly patient[1] (Table 1). In case of infants treatment is very conservative. Vaseline Petroleum jelly and moisturizers can be a good first step.

TABLE 1: TREATMENT OF PSORIASIS

Type of psoriasis	Treatment of choice	Alternative treatments
Stable plaque	Short contact dithranol[39] or Calcipotriol (a vitamin D analog, approved for the topical treatment of psoriasis in 1994)[40]	Tar Topical Steroids[41]
Extensive stable plaque, (>30% surface area) recalcitrant to local therapy	UVB PUVA*+eretinate, isotretinoin (I) and+tretinoin (T)[40,42]	Methotrexate, cyclosporin A
Widespread Small plaque	UVB	Tar
Guttate	Emollients while erupting; then UVB	Weak tar preparations, Mild local steroids [hydrocortisone (0.1-1.0%) alclomethasone, fluocinolone (0.0025%), methylprednisolone]
Facial	Mild local steroids	
Flexural	Mild to moderately potent local steroids + antifungal	
Pustular psoriasis of hands and feet	Moderately potent or potent local steroids[43]	Acitretin/ etretinate (as available)
Acute erythrodermic, unstable generalized pustular	Inpatient treatment with ichthammol paste, local steroids may be used initially with or without wet compresses[44]	Acitretin/ etretinate (as available) Methotrexate, Cyclosporin – A

*PUVA is psoralen plus UVA. Psoralen (obtained from citrus fruits and other plants), e.g. methoxsalen is used to induce photochemical reactions in the skin. UVA-ultraviolet solar radiation which consists of UVA- (320-400 nm): causes skin ageing (damage to collagen), and probably skin cancer.

Emollients help to hydrate, soften, and loosen psoriatic plaques. Water-based moisturizers are less greasy than oil-based preparations but need to be applied more frequently. Heavier emollients, such as petrolatum or aquaphor ointment, are more effective but cosmetically less acceptable to patients. An aveeno oatmeal bath and benedryl cream can help relieve the itching, but a physician must be consulted before starting any treatment with an infant. For mild psoriasis in children, sunlight may be helpful. For moderated cases, regular UVB or narrow band UVB therapy can help clear the lesions. Most treatments in use for adults also help children. Methotrexate, acitretin and PUVA are not given to children.

For relatively mild disease, the standard topical treatments include coal tar based preparations, dithranol and topical steroids. Crude coal tar and its distillation products have been used to treat psoriasis for many years. Their main mode of action is probably by inhibiting DNA synthesis. Dithranol inhibits DNA synthesis[2]. However these treatments have certain disadvantages. Tar preparations are messy, malodorous; stain clothes and time consuming to apply. Dithranol may burn normal skin. High potency topical steroids can only be used for short periods because of their potential to induce skin atrophy and tachyphylaxis.

Salicylic acid ointment has been traditionally used for its keratolytic effect. Either alone or in combination with coal tar or topical corticosteroids, salicylic acid (2% to 10%) helps to soften and remove psoriatic scale. It also enhances the efficacy of topical corticosteroids or coal tar by increasing their absorption. Salicylic acid should not be applied near the eyes because of its irritant effect. In more severe psoriasis, there are number of second-line therapies available, but again they have significant drawbacks. Long-term maintenance psoralen-ultraviolet A (PUVA) therapy increases the risk of non-melanoma skin cancers. Methotrexate, etretinate and cyclosporin A are all potentially toxic and require careful supervision and monitoring. Chromosomes involved in psoriasis have already been mapped, and more genes involved in the expression of psoriasis are being identified. Gene therapy promises to be one of the most important areas of treatment of psoriasis for the new millennium. T-cell receptor vaccines have been developed and

TABLE 2: COMPARISON OF DIFFERENT TREATMENTS OF PSORIASIS

Treatment	Advantage	Disadvantages
Dithranol	Less expensive	Burn normal skin and difficult to apply
Topical Steroids	Rapid acting and useful when there are a limited number of lesions	Skin atrophy and tachyphylaxis
Methotrexate	Used for patients whose psoriasis does not respond to other forms of therapy	Liver damage and impaired immunity
Cyclosporin A	Effective in severe psoriasis	May cause high blood pressure and damage the kidneys
Phototherapy, PUVA	Can help clear up psoriasis for several months at a time, when large areas of skin are involved	Pain and reddening similar to sunburn, increases the long-term risk of skin cancer
Tar preparations (crude coal tar, coal tar solution, oil of cade)	Relatively inexpensive	Messy, ill-smelling, stain clothes, time consuming to apply and photo sensitivity
Etretinate, Isotretinoin and Tretinoin	Rapid onset of action	Raises fat (lipid) levels in the blood, dry skin, chelitis, nose bleeds, conjunctivitis, hair loss, hepatitis, teratogenicity
Calcipotriol	Easy to apply, cosmetically acceptable and overcomes the limitations of other treatments	Hypercalcaemia, expensive

are undergoing trials in patients with psoriasis[45]. There is, therefore clearly a need for newer therapies that are effective, easy to apply, cosmetically acceptable and without unacceptable side effects in long-term treatment (Table 2). Vitamin D_3 has been recognized as beneficial in psoriasis[46].

VITAMIN D IN PSORIASIS

Vitamin D receptors were initially discovered in the intestinal epithelium, bone and kidney. Receptors for 1,25 dihydroxy vitamin D_3 (1,25 dihydroxy cholecalciferol; $1,25(OH)_2 D_3$; Calcitriol, fig. 1a)[55] were also found in many other cells and tissues including epidermal keratinocytes, dermal fibroblasts and T-lymphocytes in the normal skin[47,48].

The rationale for the use of vitamin D_3 analogues in psoriasis is based on the role played by the active form of vitamin D_3 in regulating epidermal proliferation and differentiation in the normal epidermis, and in modulating the immune response[49,50]. The presence of the vitamin D receptors in skin, the effects of $1,25(OH)_2D_3$ on keratinocyte proliferation and differentiation, and the known beneficial effects of vitamin D in psoriasis, all are tempting to hypothesise that some abnormality of vitamin D metabolism is a pathogenetic mechanism in psoriasis[51].

Development of calcipotriol:

In fact, the beneficial effects of vitamin D on psoriasis were first noticed in the 1940s, but it was a chance finding in the mid-1980s that reawakened interest in the potential benefits of $1,25(OH)_2D_3$ and related compounds in this disease. In 1985, the prodrug of $1,25(OH)_2D_3$ i.e.1α - hydroxyvitamin D, was being tested in the treatment of patients with bone disorders. A Japanese patient being treated for osteoporosis with oral 1α-hydroxy vitamin D showed remarkable clearing of previously resistant psoriasis[51]. This chance finding was confirmed by further studies using oral 1α-hydroxy vitamin D or topical or oral $1,25(OH)_2D_3$[52-54]. One of the most promising of the new $1,25(OH)_2D_3$ analogue was calcipotriol (fig.1b)[52], first synthesized in 1985[54]. In the light of the previous evidence of the efficacy of $1,25(OH)_2D_3$ in psoriasis, these findings meant that calcipotriol was an obvious candidate for the treatment of psoriasis, and clinical trials were started in 1987.

Efficacy:

In *in vitro* studies, calcipotriol has shown effects on cell proliferation and differentiation similar to those of $1,25(OH)_2D_3$ Calcipotriol inhibits U937 cell proliferation in

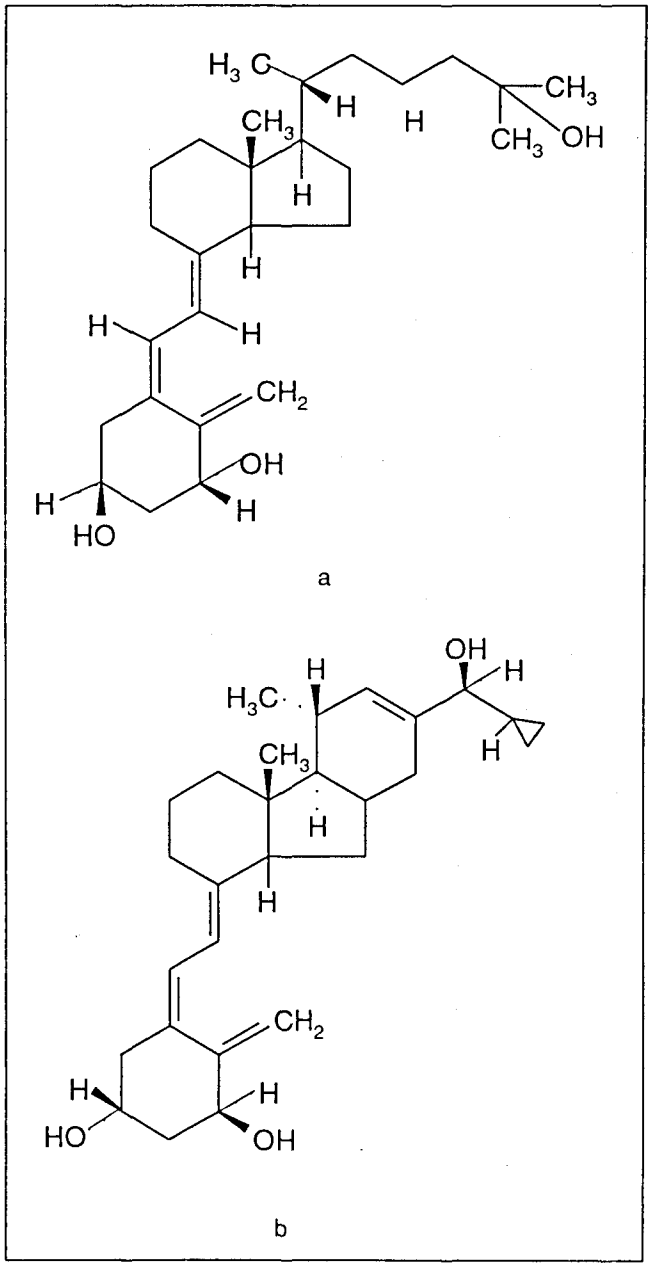

Fig 1: Chemical structures of calcitriol (a) and calcipotriol (b)

concentrations from 10^{-9} M upwards, and is at least as potent as $1,25(OH)_2D_3$ in inducing cell differentiation along the monocyte-macrophage pathway[56].

In cultured human keratinocytes, calcipotriol induces terminal differentiation (as measured by the formation of cornified envelopes) and inhibits cellular DNA synthesis, at similar concentrations to $1,25(OH)_2D_3$. In mouse

keratinocytes, cellular DNA content is inhibited by calcipotriol and cell differentiation enhanced, with a similar potency to that of $1,25(OH)_2D_3$[54].

In cultured mouse thymocytes, calcipotriol inhibits proliferation induced by interleukin-1[58] (a mediator of immunity and inflammation, which is implicated in the pathogenesis of psoriasis). Calcipotriol also reduces immunoglobulin production by interfering with T-helper cell function[59] and inhibits lymphocyte proliferation in mixed cultures of human peripheral blood cells and allogeneic epidermal cells. In addition, calcipotriol inhibits the release of the inflammatory mediator and growth regulator interleukin-6 from activated human peripheral blood mononuclear cells[60].

The effects of calcipotriol on cytokeratins in psoriatic skin have been investigated using skin biopsies or keratome shaving, and suggest that calcipotriol has a direct action on keratinocyte differentiation and proliferation. Resolution of psoriatic lesions was accompanied by a reduction in the concentration of keratins 6, 16 and 18, indicating a decrease in keratinocyte hyperproliferation[61-64].

Furthermore, there was an increase in keratins 1, 2 and 10, indicating an increase in differentiation. Down-regulation of keratin 16 correlated especially well with regression of psoriatic lesions. Keratin 17 is not present in normal human skin but can be found in psoriatic skin with marked keratosis, and was significantly decreased by calcipotriol treatment[62]. It is believed that the effects of calcipotriol on keratinocyte proliferation and differentiation may be mediated by its effects in raising intracellular calcium of cyclic GMP levels, or by binding to nuclear receptors[65]. Its genomic effects i.e. regulation of gene transcription following binding of vitamin D, complexed with its receptor, to a multitude of genes are probably most important[66]. Calcipotriol has also been found to decrease cutaneous inflammation in psoriatic skin. A progressive reduction has been seen in the dermal vascular infiltrate, with a change form predominantly CD4+helper T-lymphocytes to CD8+ suppressor cells[67]. The reduction in T-lymphocytes has been shown to be preceded by a decrease in infiltrating polymorphonuclear cells[62]. However, one study found that though calcipotriol markedly reduced the number of activated T-lymphocytes in patients with psoriasis, this did not appear to be related to the degree of clinical improvement[68]. Interleukin-6 is secreted by keratinocytes, where it is thought to play a role in growth. IL-6 and IL-8 are increased in psoriatic lesions[65]. During treatment with calcipotriol, the amount and distribution of IL-6 in psoriatic and normal skin decreases[69].

Safety consideration of vitamin D Analogues:

Overdose of vitamin D leads to hypercalcaemia as a result of increased calcium absorption from the gut and resorption of bone[70]. The actions of vitamin D on bone are complex because both compounds also increase osteoblast activity[71]. Symptoms, which may occur, include malaise, headache, drowsiness, constipation, polydypsia, polyuria, muscle weakness, fatigue, irritability, nausea and vomiting. Chronic hypercalcaemia may result in urinary stones, soft tissue calcification in blood vessels, myocardium and cornea, nephrocalcinosis and renal failure[72].

Mode of action:

Vitamin D analogues appear to function in a manner similar to other group of steroids. They combine with highly specific nuclear receptors (a member of gene super family including steroid, thyroid, and retinoid receptor genes) that regulate gene transcription by binding, in the presence of a nuclear accessory factor (NAF) to a specific sequence of DNA, known as the vitamin D response element[73,74]. In addition, non-genomic effects operate through different mechanisms. These include elevation of intracellular calcium and cyclic GMP levels.

Pharmacokinetics:

In human study, less than 1% of calcipotriol was systemically absorbed after a single application of calcipotriol ointment 50μg/g to psoriatic lesions. Only small amounts of radiolabelled (<1%) drug were recovered in the urine and faeces. Animal experiments have shown that calcipotriol has a relatively low systemic bioavailability and this coupled with rapid metabolism and deactivation makes it unsuitable for oral administration. Extensive hepatic metabolism would appear to explain the rapid elimination of calcipotriol, and two main metabolites (MC 1046 and MC 1080), with markedly reduced pharmacological activity relative to calcipotriol, have been identified[75]. Further calcipotriol's rapid deactivation may be partially attributed to its low affinity for serum vitamin D-binding protein. *In vitro*, the affinity of calcipotriol for human vitamin D- binding protein was 30 times less than that of calcitriol[76].

Marketed products:

Dovonex is the tradename of three products, which are manufactured from a derivative of vitamin D. There is a scalp solution, a cream and an ointment for the body (Table 3).

TABLE 3: MARKETED PRODUCTS OF CALCIPOTRIOL ALONG WITH THEIR PACK SIZE AND DOSE

Product name (Manufacturer)	Pack size	Dose
Dovonex cream and ointment (Leo Pharma, UK)	30 g, 60 g, 120 g, 240 g tubes (50 μg calcipotriol per g of the base)	Adults: apply once or twice daily to the affected area. Maximum weekly dose of ointment should not exceed 100 g. Children over 12 years: maximum weekly dose of ointment should not exceed 75 g. Children over 6-12 years: maximum weekly dose of ointment should not exceed 50 g.
Dovonex scalp solution (Leo Pharma, UK)	60 ml bottle (50 μg calcipotriol per ml of solution)	

The makers say it is not suitable for the treatment of the facial area (or other tender areas of the body), as it might have an irritant effect on some people in these areas. It is also not indicated for pustular psoriasis - the type that presents as blisters under the skin, on the palms of the hands and soles of the feet. It is obtainable on prescription only, and cannot be bought over-the- counter[77].

Topical calcipotriol is now well established as a first line treatment for mild to moderate chronic plaque psoriasis. Calcipotriol may allow a reduction in the frequency of the use of other treatments mentioned in the review. Calcipotriol may be useful in other dermatological disorders, such as ichthyoses, pityriasis rubra pilaris. Calcipotriol is the first of vitamin D_3 analogues to find widespread application in dermatology. Many other vitamin D_3 analogues are under investigation. Some exert potent effect on cell differentiation and proliferation, while others appear to act as immunosuppressants[78]. A decade after the synthesis of calcipotriol, the future for the vitamin D_3 analogues in medicine looks bright.

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