

METHODS AND COMPOSITION FOR TREATING SKIN PROLIFERATIVE DISEASES

INTRODUCTION

1. Technical Field

This invention relates to a method of treating non-malignant proliferative diseases of the skin. This invention is exemplified by the use of a composition comprising aminoguanidine to treat psoriasis.

2. Background

Proliferative skin diseases are widespread throughout the world and afflict millions of humans and their domesticated animals. Proliferative skin diseases are characterized by keratinocyte cell proliferation, or division, and may also be associated with incomplete epidermal differentiation. Keratinocyte hyperproliferation has been seen in the absence of inflammatory infiltrate in an experimental model of psoriasis, but inflammation is not seen without keratinocyte hyperproliferation and abnormal differentiation (Carroll et al *Cell* 83:957 (1995)).

Psoriasis is the most serious of the proliferative skin diseases with which this invention is concerned. The incidence of psoriasis in the United States is about 2% of the population.

About 3% of whites and 1% of blacks are affected. Occurrence is extremely low in Native Americans. Psoriasis affects both sexes equally. It occurs in about 2.5% of HIV-infected patients. Abortive forms of psoriasis share many features with seborrheic dermatitis, a disease affecting at least 2 to 5 percent of the population; clinically and histologically the lesions of chronic seborrheic dermatitis are often difficult to distinguish from those of psoriasis.

Psoriasis is a genetically determined disease of the skin characterized by two biological hallmarks. First, there is a profound epidermal hyperproliferation related to accelerated and incomplete differentiation. Second, there is a marked inflammation of both epidermis and dermis with an increased recruitment of T lymphocytes, and in some cases, formation of neutrophil microabscesses. Many pathologic features of psoriasis can be attributed to alterations in the growth and maturation of epidermal keratinocytes, with increased proliferation of epidermal cells, occurring within 0.2 mm of the skin's surface. Traditional investigations into the pathogenesis of psoriasis have focused on the increased proliferation and hyperplasia of the epidermis. In normal skin, the time for a cell to move from the basal layer through the granular layer is 4 to 5 weeks. In psoriatic lesions, the time is decreased sevenfold to tenfold because of a shortened cell cycle time, an increase in the absolute number of cells capable of proliferating, and an increased proportion of cells that are actually dividing. The hyperproliferative phenomenon is also expressed, although to a substantially smaller degree, in the clinically uninvolved skin of psoriatic patients.

A common form of psoriasis, psoriasis vulgaris, is characterized by well-demarcated erythematous plaques covered by thick, silvery scales. A characteristic finding is the isomorphic response (Koebner phenomenon), in which new psoriatic lesions arise at sites of cutaneous trauma. Lesions are often localized to the extensor surfaces of the extremities, and the nails and scalp are also commonly involved. Much less common forms include guttate psoriasis, a form of the disease that often erupts following streptococcal pharyngitis, and pustular psoriasis, which is

characterized by numerous sterile pustules, often 2 to 5 mm in diameter, on the palms and soles or distributed over the body.

Therapeutic efforts in psoriasis are aimed at decreasing the proliferative rate of the epidermis, either by direct action on cell division or indirectly by reducing the immunological response with agents that reduce the inflammatory response or vascular permeability (Guzzo, *C. Derm. Clinics* 15:59 (1997)). For patients with localized, limited psoriasis, administration of topical corticosteroids is the most convenient outpatient therapy. Rapid improvement may be seen with this approach, but the beneficial short-term efficacy is limited and chronic topical corticosteroid treatment is not advisable. Side effects from chronic topical corticosteroid therapy can include atrophy of the skin, development of tolerance to the agent used (tachyphylaxis), and serious exacerbation of the disease after discontinuation. Pituitary-adrenal suppression is a potential and serious complication of potent topical corticosteroid therapy, particularly when the agent covers a large portion of the body surface and is used under occlusive dressings. Despite these potential drawbacks, topical corticosteroid therapy, in combination with emollients or used alone, remains the most commonly prescribed treatment for psoriasis.

Other treatments used for localized disease include topical application of calcipotriene, coal tar preparations, or tazarotene. Calcipotriene is a vitamin D3 derivative that may be applied topically twice daily to improve plaque-type psoriasis. At recommended dosages, calcium metabolism appears to be minimally affected, although hypercalcemia has been seen in patients using excessive amounts of the topical ointment. The safety and efficacy of this treatment have not been established beyond 8 weeks of therapy. Topical coal tar preparations have been effective when used alone to clear psoriatic plaques by inhibiting mitotic activity in the epidermis; however, the unpleasant odor of the preparations and the propensity to stain fabrics reduce the acceptance of these preparations by patients. Hospitalization may be required for patients with more extensive disease, who are treated with topical coal tar preparations followed by irradiation with B-spectrum ultraviolet light (290 to 320 nm). This regimen, known as Goeckerman's regimen, can be modified to include the use of topical steroids. Intensive tar and ultraviolet B exposure can lead to development of skin cancer, especially in people with fair skin. It has been reported that in 50% to 70% of patients with mild to moderate psoriasis treated with either 0.05% or 0.1% concentration of tazarotene (a retinoid), produced an improvement or a complete clearing of lesions. However, irritation, burning, stinging, pruritus and erythema can occur at the site of application, especially with the 0.1% gel. After four months of use, some patients reported aggravation of the disease and an increased erythema response to sunlight (G D Weinstein *J Am Acad Dermatol* 37:S33 (1997)).

For patients with extensive disease, systemic antimitotic agents such as methotrexate are used. Methotrexate usually is administered on an intermittent basis and should not be given more frequently than once weekly. Patients receiving it should be monitored for hematologic and liver toxicity; because methotrexate-induced cirrhosis is a risk, especially after a cumulative dose of 1.5 g has been reached, liver biopsy may be indicated.

Extensive psoriasis can also be treated with photochemotherapy. In this regimen, oral 8-methoxypsoralen produces photosensitization, which is followed by exposure to ultraviolet A (PUVA, 320 nm). Like Goeckerman's regimen (supra), this therapy inhibits mitotic activity in the