DOBESILATE IN THE TREATMENT OF PLAQUE PSORIASIS

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Abstract: Fibroblast growth factor (FGF)-mediated pathways participate in many of the cellular events implicated in the pathogenesis of psoriasis. Thus, targeting FGF signals may be potentially therapeutic in the treatment of psoriasis. We report for the first time on a 43-year-old man with chronic-type plaque psoriasis with a daily topical treatment of dobesilate, a new FGF inhibitor. As early as at day 14, the patient had cleared or achieved excellent improvement of psoriatic skin lesions. Topical dobesilate offers the potential for treatment of plaque psoriasis without atrophy or other local side effects associated with the use of topical corticosteroids.

Key words: Plaque psoriasis; Topical therapy; Dobesilate

INTRODUCTION

Psoriasis is one of the most common dermatologic diseases afflicting 4% of the world's population, including approximately 5 million people in Europe, 2.5 million in Japan, and more than 7 million in the US [1]. The disease has substantial economic impact. The National Psoriasis Foundation estimates that in the US, 56 million hours of work are lost each year by patients with psoriasis, and between 1.6 and 3.2 billion US dollars are spent annually on treatment [2]. In addition, patients with psoriasis have a variety of psychosocial problems and stress concomitant to their physically disfiguring illness [3]. There is at present no cure for psoriasis, only suppressive therapy. The most common form for which most types of treatment are tested is plaque-type psoriasis, characterized by well-demarcated, erythematous, scaling plaques. It appears that several cell signaling events regulate the four major signs of this disease: keratinocyte hyperproliferation, low rate of keratinocyte apoptosis, angiogenesis and infiltration of inflammatory cells [4-7]. Targeting such signaling and transcriptional events with pharmacological intervention may help to reduce downstream cellular effects in psoriasis. The fibroblast growth factor (FGF) family is an ubiquitously expressed transmembrane signaling family that elicits receptor-mediated regulatory effects on cell growth, function, differentiation and survival. The FGF ligands are single polypeptides consisting of 22 genetically distinct homologues, and the FGF receptors (FGFRs) are transmembrane tyrosine kinases encoded by four homologous gene products, which form a complex with pericellular matrix heparan sulfates independent of the FGF ligand [8]. Binding of FGF ligands to FGFR-heparan sulfate complexes activates the kinase activity and transmits regulatory signals to downstream signaling mediators or targets. FGF stimulates a repertoire of canonical intracellular signaling pathways controlling many of the cellular events implicated in the pathogenesis of psoriasis [9-19]. We have shown previously that elevated plasma levels of FGF in psoriatic patients may be a useful predictor of clinical outcome and affect management [20]. Calcium dobesilate (Doxium®) has been widely used for the treatment of diabetic retinopathy [21]. Furthermore, it has been reported that this agent inhibits proliferation of vascular smooth muscle cell growth in serum containing, among other things, FGF [22]. Recently, we have shown that dobesilate inhibits cell proliferation and promotes apoptosis in glioma cell cultures acting as an FGF inhibitor [23]. Based on the hypotheses about the activities of dobesilate, we assessed the effect of topical dobesilate in chronic plaque psoriasis.

CASE REPORT

A 43-year-old man with stable chronic-type plaque psoriasis involving the elbows and knees for at least 6 months was treated with dobesilate. After an appropriate wash-out period of other medications, the patient provided written informed consent before entering the study. Lesions were treated with potassium dobesilate (hydroquinone monosulfonic acid potassium salt (Merek) (5 percent in a cream formulation, applied twice daily by the patient himself)) for a maximal period of 2 weeks. Clinic visits during the treatment phase were at day 0 (baseline), day 7 and day 14. Assessments of efficacy and adverse events were made at each visit. Efficacy was evaluated based on the disease signs and symptoms in lesions. Disease signs include erythema, induration, desquamation and overall severity. Photographs of the lesions were taken at baseline and each visit until study completion. Compliance was judged to be good because of the patient’s high motivation. As Figure 1 shows, a progressive clearance of plaque psoriasis is observed during the treatment. After 2 weeks of treatment, the patient had almost completed clinical resolution of the lesions (Fig. 2). With no recurrence after two months of treatment withdrawal. No adverse events were observed.
DISCUSSION

Psoriasis varies widely in its clinical expression, from a single fingernail pit to widespread disfiguring skin lesions and disabling arthritis. The primary goal of therapy is to maintain control of the illness so as to avoid disruption of the patient’s quality of life, as cure is seldom achieved. Treatment options include systemic agents, topical therapies, and phototherapies. Many of the currently available systemic treatments and phototherapies are associated with unacceptable toxicity or side effects [24]. The most common treatment for
plaque psoriasis is topical corticosteroids. Topical corticosteroids may induce skin atrophy, irreversible striae, telangectasia, perioral dermatitis, glaucoma and acne [25, 26]. These adverse reactions are more common with use in facial and intertriginous areas. Facial and intertriginous skin is more susceptible to corticosteroid-induced atrophy because of higher percutaneous absorption in these areas. In addition, continued corticosteroid therapy is thought to result in tachyphyaxis, a condition in which stronger formulations of the medication are required to maintain the therapeutic benefit. There may also be a recurrence of the disease if corticosteroid therapy is abruptly withdrawn. A derivate of vitamin D, calcipotriene, another topical therapeutic option for psoriasis, is associated with local skin irritation, particularly in intertriginous areas, often requiring adaptation of the therapeutic regime such as dilution [27]. Thus, from a clinical perspective, a nonatrophogenic, nonirritating topical treatment would address a significant patient need. Potassium dobesilate cream 5% is effective for the treatment of chronic-type plaque psoriasis. Substantial and rapid clinical improvement was demonstrated in the assessment of lesions, resulting in improvements in erythema, desquamation, induration and overall severity. Although the mechanism of action of dobesilate in psoriatic skin lesions is not yet known, this case report suggests that dobesilate suppressing FGF signal pathways may act as an antiproliferative, proapoptotic and antiinflammatory agent [28] in psoriasis. Recognition of psoriasis as a T-cell mediated immune disease has led to the development of various therapeutic approaches directed against T cell and T-cell processes such as activation, trafficking and cytokine release [29]. T cells synthesize FGF and have FGF receptors [30-32], suggesting that this growth factor may also be involved in T cell activation within psoriasis sites. Thus, in addition to its antiproliferative and proapoptotic functions, dobesilate may also be effective by abolishing T cell activities in psoriasis. Large-scale studies with long-term follow-up are necessary before dobesilate may be available for treating psoriasis.

References


Received: January 14, 2005/ Accepted: June 2, 2005

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