Eur J Med Res (2005) 10: 373-376

Dobesilate in the Treatment of Plaque Psoriasis

Pedro Cuevas[1] and José María Arrazola[2]

[1]Departamentos de Investigación1 y [2]Dermatología,
Hospital Ramón y Cajal, Universidad de Alcalá de Henares, Madrid, Spain

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 pharmaceutical 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 appropiate 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 (Merck) (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.

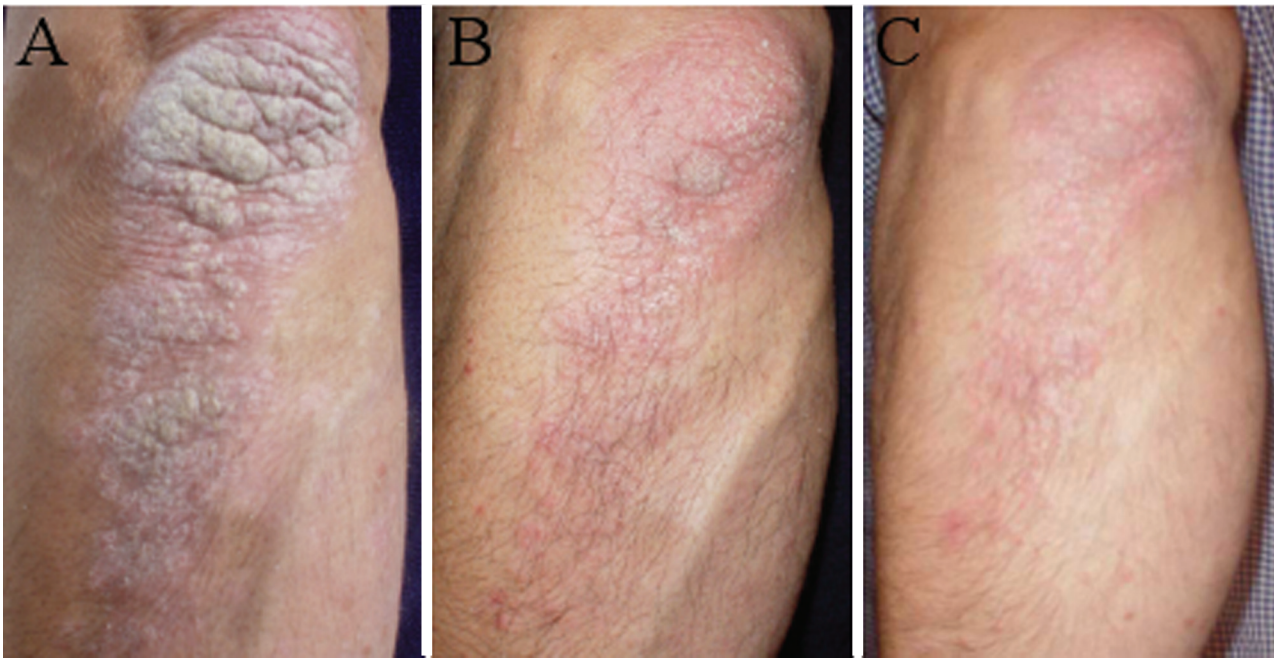

Fig. 1. Psoriasis of the left elbow treated with dobesilate cream 5%. A: disease at baseline. B: disease at day 7; C: disease at day 14.

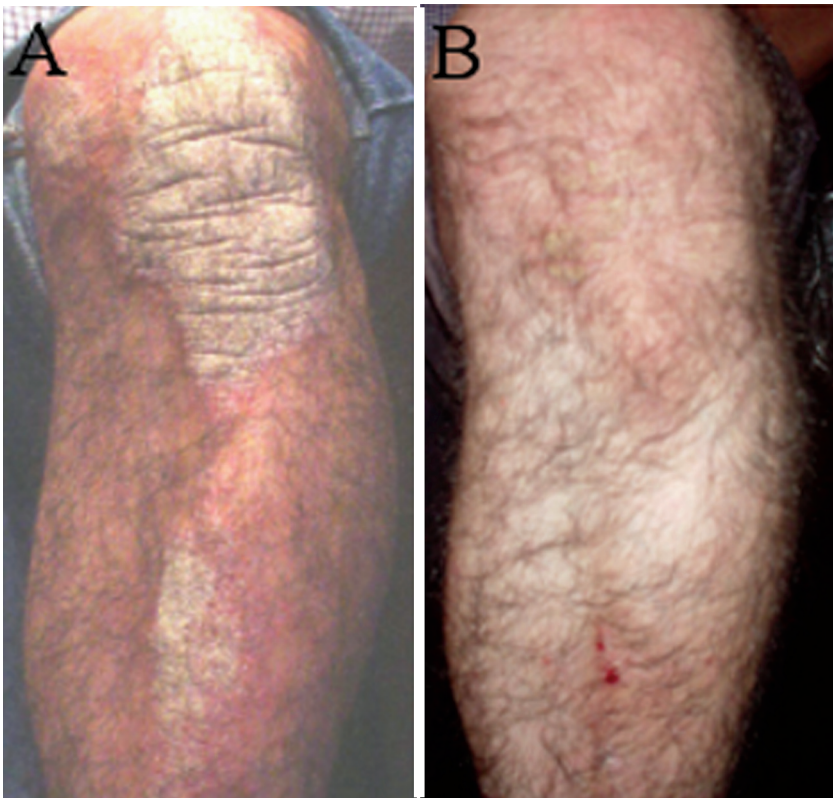

Fig. 2. Psoriasis of the right knee. A: at baseline plaque psoriasis is evident. B: process is cleared at day 14 of treatment.

Dicussion

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 tachyphylaxis, 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

1. Christophers E (2001) Psoriasis-epidemiology and clinical spectrum. Clin Exp Dermatol 26: 314-320
2. National Psoriasis Foundation. Facts About Psoriasis: htp/www.psoriasis.org. Accessed 11/21/04
3. Fortune DG, Mian CJ, O'Sullivan TM, Griffiths CEM (1997) Quality of life in patients with psoriasis: the contribution of clinical variables and psoriasis-specific stress. Br J Dermatol 137: 255-260
4. Barker JNWN (1991) Pathophysiology of psoriasis. Lancet 338: 227-230
5. Nickoloff BJ (1991) The cytokine network in psoriasis. Arch Dermatol 127: 871-884
6. Wrone-Smith T, Mitra RS, Thompson CB, Jasty R, Castle VP, Nickoloff BJ. (1997) Keratinocytes derived from psoriatic plaques are resistant to apoptosis compared with normal skin. Am J Pathol 151: 11321-11329
7. Folkman J (1995) Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med 1: 27-31
8. Wang F, McKeehan WL (2003) Handbook of Cell Signaling. Vol. 1 (Bradshaw R and Denis E, eds) pp. 265-270, Academic/Elsevier Press, New York
9. Tan Y, Low KG, Boccia C, Grossman J, Comb MJ (1994) Fibroblast growth factor and cyclic AMP (cAMP) synergistically activate gene expression at a cAMP response element. Mol Cell Biol 17: 7546-7556
10. Bushdid PB, Brantley DM, Yull FE, Blaeuer GL, Hoffman LH, Niswander L, Kerr LD (1998) Inhibition of NF-kB activity results in disruption of the apical ectodermal ridge and aberrant limb morphogenesis. Nature 392: 615-618
11. Geller SF, Lewis GP, Fisher SK (2001) FGFR1, signaling, and AP-1 expression after retinal detachment: reactive Muller and RPE cells. Invest Ophthalmol Vis Sci 42: 1363-1369
12. Byrd VM, Ballard DW, Miller GG, Thomas JW (1999) Fibroblast growth factor-1 (FGF-1) enhances IL-2 production and nuclear translocation of NF-kB in FGF receptor-bearing Jurkat T cells. J Inmunol 162: 5853-5859
13. Reilly JF, Maher PA (2001) Importinb-mediated nuclear import fibroblast growth factor receptor: role in cell proliferation. J Cell Biol 152: 1307-1312
14. Schlessinger J (2004) Common and distinct elements in cellular signaling via EGF and FGF receptors. Science 306: 1506-1507
15. Robert C, Kupper TS (1999) Inflammatory skin diseases, T cells and inmune surveillance. New Engl J Med 341: 1817-1828
16. Kaufman CK, Fuchs E (2000) It's got you covered: NF-kB in the epidermis. J Cell Biol 29: 999-1004
17. Miracco C, Pellegrino M, Flori M, Vatti R, Materno M, Andreassi L (2000) Cyclin D1, B and A expression and cell turnover in psoriatic skin lesions before and after cyclosporin treatment. Br J Dermatol 143: 950-956
18. Haase I, Hobbs RM, Romero R, Broat S, Watt FM (2001) A role for mitogen-activated protein kinase activation by integrins in the pathogenesis of psoriasis. J Clin Invest 108: 527-536
19. Sano S, Chan KS, Carbajal S, Clifford J, Peavey M, Kiguchi K,Itami S, Nickoloff BJ, Digiovanni J (2005) Stat 3 links activated keratinocytes and inmunocytes required for development of psoriasis in a novel transgenic mouse model. Nat Med 11: 43-49
20. Carmena-Ramón R, Cuevas-Sánchez B, Fernández-Ayerdi A, Barriandrés-Rodriguez O, Gárate-Ayastay MT, Arrazola-Mayona JM, García-Gómez I, Cuevas P. (2002) Niveles séricos del factor de crecimiento para fibroblastos básico (bFGF) en la psoriasis. Actas Dermatosifilog 93 (S2): 53
21. Berthet Ph, Farine JC, Borras JP (1999) Calcium dobesilate (Doxium"). Pharmacological profile related to its use in diabetic retinopathy. Int J Clin Pract 53: 631-636
22. Parés-Herbute N, Fliche E, Monnier L (1999) Involvement of nitric oxide in the inhibition of aortic smooth muscle cell proliferation by calcium dobesilate. Int J Angiol 8: 5-10
23. Cuevas P, Díaz-González D, Dujovny M (2005) Dihidroxy-2,5 benzenesulfonate (dobesilate) elicits growth arrest and apoptosis in glioma cells. Neurol Res (in press).
24. Ashcroft DM, Li Wan PA, Griffiths CE (2000) Therapeutic strategies for psoriasis. J Clin Pharm Ther 25: 1-10
25. Van de Kerkoff P (2003) Papulosquamous and eczematous dermatoses: psoriasis. In: Bologna JL, Jorizzo JL, Rapini RP, Editors. Dermatology St. Louis: Mosby p 125-149
26. Mills CM, Marks R (1993) Side effects of topical glucocorticoids. Curr Probl Dermatol 21: 122-131
27. Kragballe K (1992) Treatment of psoriasis with calcipotriol and another vitamin D analogues. J Am Acad. Dermatol 27: 1001-1008
28. Piller NB (1990) Assessment of the anti-inflammatory action of calcium dobesilate. Effect on macrophage attaching to subcutaneously implanted coverslip in guinea pigs. Arzneimitelforschung 40: 698-700

29. Bos JD, De Rie MA (1999) The pathogenesis of psoriasis: Inmunological facts and speculations. Immunol Today 20: 40-46
30. Blotnick S, Peoples GE, Freeman MR, Eberlein TJ, Klagsbrun M (1994) T Lymphocytes synthesize and export heparin-binding epidermal growth factor-like growth factor and basic fibroblast growth factor: mitogens for vascular cells and fibroblasts: differential production and release CD4+ and CD8+ cells. Proc. Natl Acad Sci USA 91: 2890-2894
31. Zhao X-M, Byrd VM, McKeehnan WL, Reich MB, Miller GG; Thomas JM (1995) Costimulation of human CD4+ T cells by fibroblast growth factor-1 (acidic fibroblast growth factor). J Immunol 155: 3904-3911
32. Byrd V, Zhao X-M, McKeehnan WL, Miller GG, Thomas JW (1996) Expression and functional expansion of fibroblast growth factor receptor T cells in rheumatoid synovium and peripheral blood patients wtih rheumatoid arthritis. Arthritis Rheum 39: 914-922

Received: January 14, 2005/ Accepted: June 2, 20005

Address for correspondance:
Prof. Dr. Pedro Cuevas
Servicio de Histología
Departamento de Investigación
Hospital Ramón y Cajal
Ctra. de Colmenar, km. 9.100
E-28034-Madrid - Spain
Tel.: +3491-336 82 90
Fax: +3491-336 82 90
e–mail: pedro.cuevas@hrc.es