Systemic Absorption of Topical Tacrolimus in Pyoderma Gangrenosum

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Accepted April 29, 2004.

Sir,

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis characterized by painful ulcerations with purple edges. It is frequently associated with other diseases such as intestinal inflammatory diseases, rheumatoid arthritis, monoclonal gammopathies and other haematological diseases. Treatment includes topical and systemic steroids, cyclosporine and other immunosuppressants. Several cases of PG treated with topical tacrolimus have been published recently. We present here a case of extensive PG treated successfully with tacrolimus, with significant systemic absorption of the drug.

CASE REPORT

A 54-year-old man, previously diagnosed as having Crohn's disease, presented with painful, extensive ulcers with purple edges on the face, trunk and extremities that affected approximately 3% of body surface area. Biopsy of a lesion showed an ulceration with a dense inflammatory infiltrate with abundant neutrophils. The diagnosis of PG was made, based on clinical and histopathological findings. Intravenous methylprednisolone was administered at a dose of 1.5 mg/kg/day in combination with topical clobetasol propionate (0.05% ointment). As lesions did not improve, treatment with infliximab (Remicade®, Centocor Inc., Malvern, USA) at a dose of 5 mg/kg, and tacrolimus 0.1% ointment (Protopic®, Fujisawa Pharmaceuticals Co. Ltd, Osaka, Japan) was started. Tacrolimus ointment was applied once daily for 4 weeks, with a daily amount of 15 g. Serum tacrolimus concentration was 13.0 ng/ml (therapeutic range as immunosuppressant, 5–15 ng/ml) 12 days after starting tacrolimus. There were no increases in arterial pressure or serum creatinine during topical application of tacrolimus. No local reactions were observed. After 1 week ulcers started healing, with completely healed lesions after 5 weeks.

DISCUSSION

Tacrolimus is an immunomodulator that suppresses cytokine production, mainly interleukin (IL)-2, and thereby inhibits activation and proliferation of T lymphocytes (1). Local adverse effects include itching and burning, systemic adverse effects include nephrotoxicity and hypertension. When there is no alteration of the skin barrier, percutaneous absorption of tacrolimus is minimal. In atopic dermatitis, drug levels can be detected during the first days of application in a few patients, but systemic absorption decreases as the skin barrier recovers (2). Systemic absorption increases when tacrolimus is applied to extensive surfaces, on certain locations (i.e. the face), on damaged skin or cutaneous diseases with impaired skin barrier. Significant systemic absorption has been described in erosive mucosal lichen planus, Netherton syndrome, lamellar ichthyosis, PG, generalized leukaemic erythroderma and exceptionally atopic dermatitis (2–8). Although serum levels were in the therapeutic range for patients undergoing solid organ transplantation, no secondary effects were described in the vast majority of these patients.

We believe that in our case increased systemic absorption of tacrolimus is secondary to the use on extensive and ulcerated areas of skin, where the skin barrier is completely suppressed. We are unaware if concomitant treatment with infliximab modified the pharmacokinetics of tacrolimus and may have contributed to increased serum levels. Oral tacrolimus, alone or in combination with topical tacrolimus, has been shown to be effective in PG in other patients (9). Possibly, increased serum levels in our patient, equivalent to oral tacrolimus, had contributed in an important way to the healing of the lesions. No secondary effects attributable to tacrolimus or infliximab were observed, so in this case the combination of both drugs was shown to be sure and effective in extensive PG refractory to other therapies. We suggest that all patients who receive topical tacrolimus on large skin areas or with impaired skin barrier should have their serum concentrations monitored.

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 ISSN 0001-5555
DOI: 10.1080/00015550510040923

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