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Influence of FK 506 on T Lymphocytes, Langerhans' Cells and the Expression of Cytokine Receptors and Adhesion Molecules in Psoriatic Skin Lesions: A Preliminary Study

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PSORIASIS is a chronic dermatosis of presumed autoimmune etiology[1] that is characterized by epidermal hyperproliferation and by infiltration of the dermis, epidermis, and stratum corneum by lymphocytes and other inflammatory cells. Activated $CD4^+$ T cells and secreted cytokines, including IFN- (which is elevated in psoriatic lesions) and interleukin-2 (IL-2), have been implicated in disease pathogenesis. Thus, T cells are found in close association with MHC class II^+ ($HLA\text{-}DR^+$) epidermal Langerhans' cells (candidate antigen presenting cells).[2] Moreover, IFN- has been shown to induce the expression of HLA-DR and adhesion molecules (including intracellular adhesion molecule 1; ICAM-1) on vascular endothelium and epidermal keratinocytes.[3] Increased expression of adhesion molecules on these cells promotes the binding of lymphocytes[4,5] and may predispose both to the recruitment of T cells into lesional tissue and to their activation.[6]

Cyclosporine A (CyA), an immunomodulatory drug used commonly to prevent graft rejection, inhibits $CD4^+$ T-cell activation, cytokine gene expression, and cytokine production. It is highly effective in the treatment of psoriasis.[7] We have shown previously that CyA markedly reduces the T-cell infiltrate within lesional skin, including numbers of IL-2 $receptor^+$ ($IL\text{-}2R^+$) cells. This effect is evident within 4 weeks of the start of therapy.[8] However, we also observed the persistence of adhesion molecule expression on lesional vascular endothelium despite resolution of the psoriatic plaques.[9] FK 506 is a new immunosuppressive agent with a similar mode of action to CyA.[10] It has been shown to be highly effective in the prevention and treatment of organ transplant rejection and has been reported to exhibit fewer side effects than CyA in transplant patients.[11,12] Its efficacy in psoriasis has been demonstrated recently in a preliminary study.[13]

In this study we examined immunohistochemical changes within lesional skin of patients with severe recalcitrant psoriasis before and following the instigation of systemic FK 506 therapy. In view of our aforementioned observations concerning CyA, we were interested especially in the influence of FK 506 on T lymphocytes, epidermal Langerhans' cells, IL-2R-bearing lymphocytes, and the expression of adhesion molecules within lesional skin.

MATERIALS AND METHODS

Patients and Biopsies

Elliptical or 3-mm punch biopsies were obtained under local xylocaine anesthesia from lesional skin of four female patients with severe chronic plaque psoriasis. Tissue was obtained immediately before and 4 weeks after start of treatment with 0.15 mg/kg/d FK 506 (Fujisawa Pharmaceutical Co. Ltd., Osaka, Japan) administered in oral gelatin capsules. Biopsies were mounted in OTC mounting medium (Fisher Scientific), snap-frozen in arcton/liquid nitrogen, and then stored at −70°C before sectioning.

Immunohistochemistry

The method described by Horrocks et al[9] was used. Six-micron cryostat sections were fixed in acetone for 20 minutes, air-dried, then incubated for 1 hour at room temperature with the appropriate, primary, mouse anti-human monoclonal antibody. These included CD1 (Langerhans' cells), CD3 (mature T cells), CD4 (T helper cells; Langerhans' cells), and CD8 (T suppressor/cytotoxic cells), CD25 (α chain IL-2R; activated T cells), CDw60 (disease-associated T cells),[14] HLA-DR and the adhesion molecules CD11a–c/18 (β_2 integrin family), CD54 (ICAM-1), ELAM (endothelial leukocyte adhesion molecule), and VCAM (vascular cell adhesion molecule). Sections were incubated for 30 minutes with biotinylated polyclonal rabbit anti-mouse immunoglobulins (Dako). The color was developed using diaminobenzidine in buffered saline containing H_2O_2.

RESULTS

Clinical

All patients showed marked improvement in their PASI (Psoriasis Area and Severity Index) score within 4 weeks of the start of FK 506 therapy, and histological examination of lesional skin revealed a rapid decrease in inflammatory cells and progressive loss of elongated rete pegs with the return of a normal stratum corneum.

Immunophenotypic Analysis

Examination of biopsies obtained during disease remission showed that, in comparison to pretreatment lesions, there were reductions in epidermal and dermal $CD4^+$, $CD8^+$, $CD25^+$, and $CDw60^+$ mononuclear cells (Fig 1). In contrast, there was a striking rise in $CD1^+$ epidermal Langerhans' cells. With respect to adhesion molecules, expression of CD54 (ICAM-1) on residual lymphocytes and vascular endothelium persisted during FK 506-induced

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Fig 1. Few residual IL-2R* (CD25$^+$) mononuclear cells in the basal epidermis of lesional skin from a patient with severe psoriasis showing marked reduction in disease activity 4 weeks after the start of systemic FK 506 therapy. (×100)

disease remission, although staining became more restricted to the upper dermis. Staining for ELAM, which was observed in blood vessels throughout the dermis in active disease, was similar or reduced in intensity in response to FK 506 treatment although there was disappearance of positive cells in the deeper dermis (Fig 2). Blood vessel staining for VCAM was focal and only faintly positive in active disease specimens, and there was evidence of persistent expression during disease remission.

DISCUSSION

The findings of this preliminary immunohistochemical analysis of lesional skin from psoriasis patients treated with FK 506 are similar to those reported previously by several groups investigating the effects of systemic CyA.

Fig 2. Persistence of expression of the adhesion molecule ELAM on vascular endothelium within the dermis despite remission of psoriasis 4 weeks after the start of systemic FK 506 therapy. (×100)

The reductions in overall T-cell numbers and in activated (IL-2R$^+$) cells are consistent with the mode of action of FK 506. The significance of the increase in epidermal Langerhans' cells, which accompanied the diminution both in T-cell numbers and disease remission, remains to be elucidated. This early increase in Langerhans' cells upon instigation of therapy is not restricted to CyA and FK 506, as treatment of psoriasis with retinoids, PUVA, or anthralin has also been shown to elevate CD1$^+$ cell numbers.[15] Possible explanations have been discussed elsewhere.[16] In vitro studies of the influence of these Langerhans' cells on lesional (CDw60$^+$) T-cell function would prove informative. The persistence of CD54 and other adhesion molecule expression during FK 506-induced disease remission suggests the likelihood of facilitated T-cell extravasation and disease recurrence following drug curtailment or withdrawal, as has been reported with CyA and in two out of seven severe psoriasis patients treated thus far at the University of Pittsburgh Medical Center. Further in vitro studies are clearly required to further elucidate the in vivo action of FK 506 in psoriasis.

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