

## Combination of Low-dosage Cyclosporine and Topical Pimecrolimus in Severe Atopic Dermatitis with Chronic Hepatitis B

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Sir,

Atopic dermatitis (AD) is associated with genetic and environmental factors, defects in the cutaneous barrier, bacterial and viral skin infections and immunological changes (1). AD influences the quality of life of both the patient and his or her family (2).

Topical steroids are the gold standard treatment for AD, but their use is limited by potential adverse effects, including impairment of the function Langerhans' cells, cutaneous atrophy, telangiectasias and acne. Non-steroidal immunomodulant drugs, such as calcineurin inhibitors, tacrolimus and pimecrolimus, do not have these side-effects.

Pimecrolimus is indicated in both the short- and long-term treatment of AD (3) and can be applied to areas such as the face and neck. Cyclosporin A (CsA) is another calcineurin inhibitor that blocks the activation of T lymphocytes with transcriptional block of the interleukin (IL)-2, IL-4, tumour necrosis factor (TNF)- $\alpha$  and interferon (IFN)- $\gamma$  cytokine genes. CsA is used in adults and in children with severe AD refractory to topical treatments (4).

AD may be associated with hepatitis; in fact, atopic patients have presented an inadequate Th-1 response and impaired function of natural killer (NK) cells, promoting chronic liver infections such as hepatitis B (5). Treatment with CsA has a therapeutic effect both on hepatitis B and hepatitis C as it inhibits viral replication (6).

We report here a patient with severe AD and chronic hepatitis B who was treated successfully with combined treatment of low-dose of CsA (100 mg/daily) and local pimecrolimus.

### CASE REPORT

A 55-year-old woman had had severe AD since the age of 15 years, and had been treated for a long time with topical and systemic steroids. The patient's history revealed she had contracted hepatitis B 10 years before her present examination (HbsAg<sup>+</sup>, Ig anti-Hbe, Ig anti-Hbc and HBV-DNA polymerase – 2382 IU/ml).

Clinically, the patient presented with bilateral blepharitis (Fig. 1A) and erythematous-desquamative cutaneous lesions on both hands (Fig. 1B), achieving a 7.6 Eczema Area Severity Index (EASI). AD adversely affected the patient's relationships and caused a high level of emotional stress that got worse following the viral hepatic infection, causing her to leave her job.



Fig. 1. (A) Blepharitis and eczema on eyelids before treatment. (B) Erythematous-desquamative lesions and diffused lichenification on both hands before treatment.



Fig. 2. (A) Remission of clinical signs on eyelids after treatment. (B) Resolution of cutaneous lesions on both hands after treatment.

In agreement with our patient, we prescribed CsA at a dosage of 100 mg/day (1.5 mg/kg/day) for 6 months, together with topical pimecrolimus cream (1% twice a day for 4 weeks and then once a day for another 4 weeks).

The therapeutic association of low-dose CsA and pimecrolimus for topical use led to complete remittance of the cutaneous clinical picture, with a strong improvement in the patient's visual capability, which allowed her to overcome the personal and social difficulties she experienced due to the disorder (Fig. 2A and B).

## DISCUSSION

Pimecrolimus acts by inhibiting calcineurin, which is an enzyme necessary for the dephosphorylation of the inactive cytosolic form of the Nuclear Factor of Activated T cells (NFAT) (7). Therefore pimecrolimus blocks the transcription and release of Th1- and Th2-dependent cytokines (IFN- $\gamma$ , IL-2, -4, -5, -10). Moreover, pimecrolimus reduces the release of histamine, hexosaminidase and tryptase by mast cells (8). Contrary to corticosteroids, pimecrolimus does not influence the differentiation, maturity and function of keratinocytes, endothelial cells, fibroblasts and dendritic cells in adults and children (3, 9). Its efficacy is demonstrated through 2 daily applications for 3–6 weeks. Moreover, pimecrolimus has shown a diffusion level from topical application lower than that of tacrolimus and steroids (see also ref 10).

The most effective drug for treatment of severe forms of AD that are non-respondent to local treatments is cyclosporine, which greatly reduces the EASI score, the extent of the disorder, itching, insomnia and improves quality of life (4). In these patients, the recommended dose of cyclosporine is 3–5 mg/kg/day for 4–6 months, but occasionally the treatment is suspended due to adverse effects. In our case, we preferred to use a lower dose of cyclosporine from the start, i.e. 1.5 mg/kg/day together with pimecrolimus for local use. We obtained complete remission of clinical symptoms and the haematochemical tests made throughout the treatment were at normal values. Liver functions and hepatitis markers did not change.

There are anecdotes in the literature of patients affected by acute re-exacerbation of chronic hepatitis B, treated successfully with CsA and IFN- $\beta$  at a dosage of 200 mg/day (11). Furthermore, there is a report on a controlled clinical trial on patients with chronic hepatitis C treated with IFN- $\alpha$  and CsA with good results better than dose achieved with IFN- $\alpha$  alone (12).

Xia et al. (6) have recently described the mechanism of action of *in vitro* CsA on cells infected by the hepatitis B virus. The HBx protein is essential for replicating the HBV virus. The protein is activated by the calcium-dependant cytosolic sign mediated by the mitochondria and the pathway of Src kinase. It has been observed that CsA inhibits viral replication by binding the mitochondrial cyclophilin D of Ca<sup>2+</sup>, inhibiting the cytoplasmatic calcium-dependent sign and Src kinase that are essential for the activated HBx protein.

We have reported this clinical case in order to underline the efficacy of a combined treatment of CsA and pimecrolimus in AD. Our treatment gave good results for a low dosage of CsA, thus reducing the risks of adverse effects. Moreover, in the light of the above-mentioned studies, thanks to the antiviral action of CsA, we can achieve a further therapeutic advantage in the treatment of patients affected by both AD and hepatitis.

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