Lack of Efficacy of Topical Cyclosporin A in Atopic Dermatitis and Allergic Contact Dermatitis

MENNO A. DE RIE, MARCUS M. H. M. MEINARDI and JAN D. BOS

Department of Dermatology, University of Amsterdam, The Netherlands

Since oral cyclosporin A (CsA) has demonstrated its effectiveness in psoriasis and atopic dermatitis, efforts have been made to develop a topical CsA formulation, thus avoiding systemic adverse events. A limited number of publications are available on the use of topical CsA in allergic contact dermatitis and atopic dermatitis. Moreover the response rate of humans to topical CsA is about 50% or less. We now report our results with three new topical CsA formulations on allergic contact dermatitis and atopic dermatitis. No significant improvement was found in 16 atopic dermatitis patients and 7 allergic contact dermatitis (nickel sulphate) patients.

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M. A. de Rie, Department of Dermatology, University of Amsterdam, Academisch Medisch Centrum, Meibergdreef 9, 1105AZ Amsterdam, The Netherlands.

Cyclosporin A (CsA) was orginally introduced as a potent immunosuppressivum to facilitate allogeneic organ transplantation, and was subsequently studied in dermatology for the treatment of T-cell-mediated skin diseases such as psoriasis and atopic dermatitis (see reviews, 1, 2). However, oral use with high (but also low, i.e. < 5 mg CsA/kg/day) dosage CsA may lead to dose- and time-related side effects such as hypertension and nephrotoxicity (3, 4). Therefore serious efforts have been made to develop a topical CsA formulation.

To date, no effective topical CsA formulations have yet been developed for psoriasis (5–8). However, studies on allergic contact dermatitis in animals (9, 10, 11), in humans (12, 13) and studies on alopecia areata patients (14, 15) have been presented indicating that topically administered CsA can inhibit the elicitation of allergic contact dermatitis. Except for one paper (16) on the effect of topical CsA on atopic dermatitis, no other studies have been published.

We now report the effect of three recently developed CsA formulations for allergic contact dermatitis (i.e. pretreatment-, elicitation- and treatment phase) and atopic dermatitis in humans.

PATIENTS AND METHODS

Atopic dermatitis

Patients suffering from three or more basic features of atopic dermatitis (viz. pruritus, typical morphology and distribution, chronic or chronically-relapsing dermatitis, personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)) plus three or more minor features of atopic dermatitis (17), were included. The Atopic Dermatitis Severity Index (ADSI; value of pruritus + erythema + exudation + excoriations + lichenification, ranging from 0 to 15) was used to evaluate these patients. Only patients with at least two comparable lesions (10–25 cm^2/lesion; ADSI > 7) entered the study. In this double-blind randomized study, one lesion was treated twice daily with CsA suspension gel or CsA ointment for 3 weeks, while the other lesion was treated with the control vehicle only. Patients were evaluated weekly for ADSI, blood pressure, hematology, biochemistry and CsA trough blood levels (RadioImmuno Assay (RIA); lower detection level: 10 ng/ml).

Allergic contact dermatitis

Seven patients with an established diagnosis of nickel contact hypersensitivity were tested patch-wise with active agents, including the topical CsA formulations and a topical corticosteroid, and vehicles with and without 4% nickel sulphate in soft paraffin preparations. The study consisted of three items: inhibition by CsA of elicitation; treatment with CsA; and pre-treatment of the patch area with CsA. The duration of the study was 8 days; the patch areas and vital signs were evaluated daily according to standard procedures adopted from the European Contact Dermatitis Research Group. At the end of the study a final evaluation including hematological and biochemical blood tests and CsA trough levels (RIA) were performed.

Inclusion and exclusion criteria

These studies had approval from the local medical ethics committee and signed informed consent was obtained from all patients. Patients undergoing systemic therapy or topical treatment within 2 weeks of entering the study were excluded. Also pregnant or lactating women and patients suffering from hypertension, renal dysfunction or infectious skin diseases were excluded.

Table I. *Review of previous publications on topical CsA in allergic contact dermatitis and atopic dermatitis*

Ref.	Disease	Allergen	Species	[CsA][a]	Vehiculum	Response
10	ACD	DNFB	NH	10, 20	Ethanol + olive oil	Pos.
12, 14	ACD	Ni	H	5	Ung Merck	4/18
11	ACD	DNCB	NH	1.6–25	Olive oil	Pos.
13	ACD	Various[b]	H	5, 10	Several[c]	1/10
16	AD	n.a.	H	100	Oily gel	11/20

ACD: allergic contact dermatitis; AD: atopic dermatitis; DNCB: 2,4-dinitrochlorobenzene; DNFB: dinitrofluorobenzene; H: human; NH: non-human (guinea pigs); n.a.: not applicable; Ung: unguentum.
[a]The CsA concentration [CsA] is given in mg/ml. [b]Fragrance; mercaptomix; mercaptobenzothiazole; quaternium-15; tetramethylthiuram disulphide. [c]Labrafil; Cremophor (plus 20% propylene glycol).

Cyclosporin A (CsA) formulations (Sandoz Ltd., Basle, Switzerland):

1) CsA ointment: CsA microcrystalline 10% in Amerchol CAB, white petrolatum and liquid paraffin;

2) CsA suspension gel: CsA microcrystalline 10% in polyethyleneglycol 300, Labrafil M 2130 CS, carbapol 934 P, sodium hydroxide, methylparaben, propylparaben and purified water.

3) CsA oleogel: CsA microcrystalline 10% in olive oil, ethanol, Labrafil M 1944 CS and aerosil 200.

RESULTS

Atopic dermatitis

Eight patients (5 females, 3 males; age range 3–55 years) suffering from atopic dermatitis were treated with 10% CsA suspension gel, and 8 patients (5 females, 3 males; age range 17–63 years) with 10% CsA ointment. Only 2 patients showed a moderate improvement ($\leq$ 25%) of the lesions treated, without detectable CsA trough levels. Detectable CsA trough levels were only found in 2 irresponsive patients treated with the 10% CsA suspension gel (11 and 18 ng/ml). No adverse events were found. The CsA oleogel formulation was not tested in atopic dermatitis.

Allergic contact dermatitis

Seven female patients (age range 24–64 years) suffering from allergic contact (nickel) dermatitis were included. After 48 h of simultaneous application of topical CsA formulations and 4% nickel sulphate, no significant inhibition of elicitation of contact dermatitis was found. Other patch areas were exposed to 4% nickel sulphate and controls, and subsequently treated during the next 5 days with topical CsA: no significant effect of topical CsA was seen. After pre-treatment with topical CsA for 48 h, 4% nickel sulphate was applied for 48 h. Again no effect of topical CsA therapeutics was found. CsA trough levels were determined in 6 of these allergic contact dermatitis patients: in one patient a CsA level of 12 ng/ml was found. Again, no adverse events were observed.

DISCUSSION

In Table I we have summarized previously published data on topical CsA in allergic contact dermatitis and atopic dermatitis. From Table I it can be seen that the response rate of topical CsA in allergic contact dermatitis is very low (< 25%), and limited to only two independent studies. Except for one study by de Prost et al. (16) (see Table I), no data are available regarding topical CsA and atopic dermatitis. Our data also indicate that the value of topical CsA in allergic contact dermatitis (n = 7) and atopic dermatitis (n = 16) was very limited.

To date, several studies (1, 3, 18) have been presented indicating that in atopic dermatitis at least, orally administered CsA is effective. CsA is metabolized by P450-dependent enzymes in the liver, thus generating several metabolites, two of which (1, 17) may be additionally immunosuppressive (19). The presence of a potent P450-enzyme system in the skin generating these metabolites has not been demonstrated yet. Alternatively, it can be speculated that CsA is neutralized in the skin by a specific or non-specific enzyme system, or by binding to a compartment in which CsA does not exert any immunosuppressive action. No data are available to substantiate these speculations.

The lack of efficacy of topical CsA in previous studies is not related to a specific allergen or to the CsA formulation used (see Table I). The most obvious reason for inefficacy of the presently available CsA formulations is lack of adequate skin penetration. CsA is a hydrophobic cyclic undecapeptide

with a molecular weight of 1202.6. When using human cadaver skin, only 0.33% of a 10% CsA solution in Labrafil was found to penetrate (13). Although we did not measure the actual skin penetration of CsA, the observed lack of clinical response, low but mostly absent CsA trough blood levels and the currently available literature, suggest that insufficient CsA skin penetration is probably responsible for these failures. This is supported by the observation that maximum clinical response is achieved when high (100 ng/ml) topical CsA concentrations are used (16). Duncan (9) recently used a topical CsA (5%) formulation with a new penetration enhancer (propylene glycol 18%, azone 2%) but was also unable to demonstrate a clinical effect.

In conclusion, new studies should be initiated, aimed at the development of adequate CsA skin penetration.

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