The Enigma of Cyclosporin A Treatment for Psoriasis: Systemic Efficacy versus Topical Non-responsiveness

A Review

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Treating patients with various forms of arthritis, Mueller & Herrmann (1) found that in patients with psoriasis arthritis the skin lesions soon cleared after systemic treatment with cyclosporin A (CsA).

This challenging observation led to a series of case reports and smaller open studies confirming the beneficial effect of systemic CsA-treatment for psoriasis (for review see ref. 2).

During the last few years large investigations using double-blind, placebo-controlled as well as open study designs have substantiated the therapeutic effectiveness of systemic CsA-therapy in psoriasis, with special regard to severe forms of this disease including pustular as well as erythrodermic psoriasis (3, 4). Whereas in the first studies high CsA-dosages of up to 14 mg/kg/d were administered (5), recent multicenter investigations have shown that a CsA-dose of 2–3 mg/kg/d given orally is effective in about two thirds of the treated patients with severe chronic plaque-type psoriasis (6–9).

During long-term treatment of organ transplant recipients side-effects of this drug became rapidly evident and were also seen in dermatologic patients treated with CsA. Most importantly, CsA impairs renal function. Other side-effects of CsA consist in the development of hypertension (10) and increased transaminase levels (11). Less frequent and less severe drug-related side-effects include gingival hyperplasia, tremor, hypertrichosis and gastrointestinal discomfort (for review see ref. 11).

All these side-effects of CsA are strictly dose-related, which leads to the therapeutic rationale to reduce CsA-dosage as much as possible.

While in transplant recipients a therapeutic blood level of CsA has been established (trough blood levels measured by RIA 100 to 400 ng/ml), no recommendation for therapeutic blood levels in patients treated with CsA for dermatological disorders can be given so far. However, a first study to estimate therapeutic CsA-blood levels in patients treated for psoriasis revealed a mean blood level of 103 ng/ml (measured by Sandimmune[R]-RIA-kit) when a dose of 2.5 mg/kg were given in two daily portions (12). In this study CsA-levels below 100 ng/ml were associated with decreased efficacy. However, a correlation between CsA-blood levels, efficacy and renal dysfunction could not be established.

Whereas in the treatment of organ transplant recipients no alternative therapy is available, the use of CsA in skin diseases, mainly psoriasis, has to be carefully evaluated, since well-established topical and systemic regimens for treatment already exist.

Low-dose CsA (< 5 mg/kg/d) proved to be an effective drug for severe forms of psoriasis with an acceptable risk/benefit ratio. However, as skin diseases are accessible to topical treatment with the advantage of minimal systemic and side effects drug formulations for topical application may be used whenever possible.

Use of topical cyclosporin A in the therapy of skin disorders

In the past years several groups including our own have tried to use CsA for topical therapy of psoriasis or other skin disorders.

Impact for these studies was given by the work of Aldridge et al. (13) who showed that nickel contact hypersensitivity reaction could be abrogated in approx. 22% of the patients by topical pretreatment of the skin with 5% CsA in unguentum Merck before antigen re-challenge.

Reitamo et al. (14), however, recently showed that CsA-pretreatment of DNCB-sensitized healthy volunteers did not prevent contact hypersensitivity reactions after DNCB-re-challenge.

In psoriasis Schulze et al. (15) demonstrated that CsA prepared as oral solution made up of 5% w/w in an ointment base applied topically onto psoriatic plaques under plastic film occlusion for 6 h daily led to measurable amounts of CsA in the treated skin. The concentration obtained corresponded to tissue levels measured after oral treatment with high-dose CsA (14 mg/kg/d).

Delivery of systemically administered CsA to the skin was substantiated by Meinardi et al. (16), who found measurable amounts of CsA in suction blister fluids of psoriatic patients treated with CsA in low doses (1.8–4.3 mg/kg/d) corresponding to peak and trough blood levels determined simultaneously. Very recently, Ellis et al. (9) found tissue levels of CsA in keratome slices from psoriatic skin lesions being about 10-fold of the CsA-blood levels measured simultaneously using various doses of CsA (3.0 to 14.0 mg/kg/d) for treatment of the patients.

In marked contrast to these experimental observations, all studies using topical CsA prepared in different vehicles for the treatment of psoriatic plaques failed to show any clinical improvement (15, 17–20).

Treatment of alopecia areata with CsA followed the same pattern as observed in psoriasis. Oral treatment of alopecia areata with CsA led to growth of terminal hairs in a number of

treated patients, accompanied by a decrease of the inflammatory infiltrate in the hair follicles (21).

When used topically, CsA-formulations applied onto hairless areas for 4 to 6 months induced growth of terminal hairs in 16 to 25% of the patients, but no complete hair growth was observed (22, 23). However, hair growth was also observed in some patients of the placebo group treated with the vehicle alone, thus making a drug-related effect questionable.

Evidence for a possible therapeutic effect of CsA in the topical treatment of atopic dermatitis was given by De Prost et al. (24), showing improvement of pruritus, vesicles and crusts but no complete remission when CsA in an oily alcohol gel preparation was used.

Recent reports have demonstrated CsA to be effective in the treatment of oral lichen planus when administered topically using the peroral CsA-preparation (25). CsA-concentrations in the treated mucosal tissue reached levels found in psoriatic plaques when patients were treated systemically with high doses of CsA (14 mg/kg/d) given orally. Blood levels of CsA above the detection limit as measured after treatment of oral lichen planus could not solely be attributed to mucosal absorption but also to gastrointestinal uptake according to the patient's skill of performing the "splish and spit"-technique (25).

Intralesional application of cyclosporin A

Intralesional injection of drugs seems to be an unsuccessful therapeutic approach to chronic relapsing and widespread skin disorders such as psoriasis. Nevertheless, as has been clearly shown by Powles et al. (26) and Ho et al. (27), intralesional injection of the i.v.-preparation of CsA diluted 1:3 with isotonic saline into psoriatic plaques resulted in rapid clearing of the treated lesions. Blood levels of CsA were slightly above detection limit soon after injection but were not detectable 12 h later (27).

Apart from these findings in psoriasis, our own investigations have shown that intralesional CsA (i.v.-preparation diluted 1:3 with isotonic saline) proved to be effective in the treatment of pyoderma gangrenosum (28) as it has been reported for systemic CsA-treatment (29–31).

Cyclosporin drug delivery in topical systems

As mentioned above percutaneous absorption of CsA in an ointment base could be demonstrated (15). Using the hairless mouse skin model Egbaria et al. (32) found penetration of CsA into the skin in a time-dependent fashion the amount of detectable CsA in the skin being in relation to the drug delivery system. In their study hydroalcoholic solution proved to be the best solvent to obtain the highest amounts of CsA in subcorneal layers.

Enhanced percutaneous absorption of CsA in the guinea pig system has been observed using CsA-formulations employing propylene glycol and azone as penetration enhancers (33).

Indirect evidence for percutaneous absorbtion of CsA was given by the studies of Aldridge et al. (13) and Nakagawa et al. (34), demonstrating inhibition of contact hypersensitivity reactions in man and in guinea pigs. However, CsA was not detectable in the blood after topical application (13), which

may indicate that topical CsA did not penetrate to the region of dermal papillae to pass into blood vessels.

On the other hand, Hermann et al. (35) did not observe penetration of CsA-preparations through the skin using a two-compartment diffusion cell. In their experiments penetration enhancers like azone or polyvinylpyrrolidone/ethanol were without effect.

Effect of cyclosporin A on keratinocytes

In psoriasis epidermal hyperproliferation is a main characteristic, and keratinocyte abnormality has been discussed as a crucial pathologic feature.

Numerous studies have focussed on an inhibitory effect of CsA on keratinocyte DNA synthesis and proliferation, but this issue is still a matter of controversy.

Using human keratinocyte cultures Fisher et al. (36) found an inhibitory effect of CsA on keratinocyte proliferation only when cells were cultured in low calcium and serum-free medium. Under these conditions CsA inhibited growth with an ED_{50} of 5 µg/ml, whereas no effect of CsA was found using culture medium containing high calcium and fetal calf serum (FCS). These results were confirmed by Ramirez-Bosca et al. (37) under the same experimental conditions. However, an inhibitory effect of CsA was only observed after 48 and 72 h of culture and with an ED_{50} of about 10 µg/ml. Using a similar assay and culture media containing FCS, Dykes et al. (38) found growth inhibition of human keratinocytes with an ED_{50} of 10 µg/ml CsA.

In murine systems as well as by employing transformed cell lines Furue et al. (39) showed CsA-induced inhibition of growth and ^{3}H-thymidine uptake with an ED_{50} between 2 and 5 µg/ml CsA, depending on time of culture using serum-containing media.

On the other hand, Kato et al. (40), employing a pig skin explant technique, did not find inhibition of keratinocyte outgrowth in the presence of CsA up to 6 µg/ml. Inhibition was only achieved when CsA-concentrations higher than 12 µg/ml were used.

As found in the study of Fisher et al. (36), the CsA-content of involved epidermis of psoriatic patients treated with the formerly used high-dose CsA of 14 mg/kg/d was about 3 µg/ml, which makes an anti-proliferative effect of CsA on keratinocytes in vivo using low-dose CsA-regimen unlikely.

Effect of cyclosporin A on cells of the inflammatory infiltrate in psoriasis

Beside epidermal hyperproliferation psoriasis is characterized by inflammation.

The inflammatory infiltrate within a psoriatic lesion consists mainly of mononuclear cells and neutrophil granulocytes (41, 42).

Mononuclear cells are mainly found close to the blood vessels and consist mainly of T-helper and -suppressor cells and monocytes (41).

In an early lesion of psoriasis found in guttate psoriasis there is an influx T-helper and -suppressor cells, but activation was found preferential for T-helper cells (43). In chronic plaque

type psoriasis there appears to be a balance between T-helper and -suppressor cells (44).

Systemic treatment of psoriasis with CsA causes a reduction in the density of all T-cell subsets in both the dermis and the epidermis of lesions (5, 45). The striking effect of CsA on T-cell function has already been mentioned and will be discussed later on.

As recently reviewed by Cooper et al. (46), antigen-presenting cells in lesional psoriatic skin can be identified as CD 1[+] DR^{+} Langerhans cells and a CD 1[-] DR[+] subpopulation of macrophages. Latter cells may be responsible for the increased antigen-presenting activity found in psoriatic skin (47). Although the antigen-presenting capacity of the non-Langerhans subpopulation seemed to be resistant to CsA-treatment their number decreased during therapy and could be correlated to clinical improvement (48), whereas epidermal Langerhans cells remained unchanged in number.

As known so far, monocytes are not affected by CsA. Neither monocyte functions nor the release of cytokines can be inhibited at therapeutic concentrations (17, 49–52).

Neutrophil granulocytes are the most prominent cells within epidermis and stratum corneum forming microabscesses (Munro) (42, 53). Little is known about the *in vitro* or *in vivo* effects of CsA on these cells.

Pigatto et al. (54) found a slight and not significant decrease of neutrophil chemotaxis in vivo when psoriatic patients were treated systemically with CsA. Our own experiments failed to demonstrate effects of CsA on neutrophil chemotaxis, enzyme degranulation and respiratory burst activity at therapeutical concentrations (Mrowietz & Schröder, unpublished observations). During CsA-therapy neutrophils disappear from the psoriatic lesion in the same manner as seen for T-cells (55).

CONCLUSION

The results of the numerous studies described above reveal a number of discrepancies:

1. Systemic as well as intralesional CsA is effective in clearing psoriasis, while topical application of CsA is without effect in psoriasis but improves oral lichen planus and may inhibit delayed type hypersensitivity reaction.
2. CsA can be measured in the psoriatic epidermis after systemic as well as topical application and
3. Systemic CsA is effective in psoriasis in low dosages (< 5 mg/kg/d), whereas very high tissue levels are necessary to induce inhibition of keratinocyte proliferation in vitro using serum-free, low calcium culture.

The results further clarify that although CsA can be found in the psoriatic epidermis after oral and topical application only oral treatment is effective.

A discussion about the possible mode of action of CsA in psoriasis is difficult because the pathogenesis of this disease is still unclear. The therapeutic effectiveness of CsA, however, challenged new approaches of research investigating the etiology of psoriasis.

As known so far, T-cell activation (inhibition of IL-2, IL-4 and interferon-gamma production) and proliferation are the only processes where CsA is effective at a very low dose (ED_{50} 10–50 ng/ml) (56).

In comparison, inhibition of keratinocyte proliferation can only be achieved using a 200–500-fold concentration of the drug (36, 37).

Since topical CsA has been shown to clear oral lichen planus the question arises whether there is a psoriasis-specific phenomenon related to the mode of action of CsA in this disease.

As one of the early changes following CsA-treatment in psoriasis consists in a decrease of the inflammatory infiltrate, the action of this drug may be restricted to an inhibition of immune cell functions.

T-cells are part of the dermal inflammatory infiltrate within a psoriatic plaque which disappear after CsA-therapy, and these cells may be regarded as the main target cells for CsA.

CsA potently inhibits IL-2 and interferon-gamma production from T-cells. These mediators were thought to play a pathogenic role in diseases responding well to CsA-therapy.

In psoriasis and atopic dermatitis increased levels of soluble IL-2 receptor (sIL-2r) have been found, suggesting an increased T-cell activity in these disease (57, 58). Circumstantial evidence for a pathophysiological role of IL-2 in psoriasis was given by the observation that treatment with IL-2 for renal cell carcinoma in psoriatic patients caused an exacerbation of psoriasis (59).

Interestingly, Johnson et al. (60) reported exacerbation of psoriasis in patients with AIDS where impairment of T-helper cell number and function is a main characteristic.

The localization of the T-cell infiltrate in the dermis close to the dermal microvasculature would explain the observations that oral as well as intralesional administration of CsA is effective while topical application fails to clear psoriasis.

CsA may inhibit antigen-presenting function of human monocytes (61) but is without effect both on monocyte functions such as chemotaxis, respiratory burst activity or enzyme release (17) and IL-1, IL-6, TNFα and NAP-1/IL-8 synthesis and release (50–52, 62). Furthermore, no inhibition of neutrophil functions has yet been described.

A very important factor for the pharmacological effects of CsA in psoriasis is the chemical nature of the substance itself and the structure of the stratum corneum. CsA is a highly lipophilic drug and binding of the molecule to the lipid-rich stratum corneum and to epidermal cells when used topically may lead to a reduction of drug levels needed to inhibit leukocyte-dependent processes in the deeper (dermal/epidermal) region of the skin.

The effectiveness of topical CsA in the treatment of oral lichen planus where a cornified layer of the mucosal epithelium is lacking may further substantiate the role of the stratum corneum as a barrier for CsA-penetration.

Metabolism of CsA in the skin may not account for the lacking effect of topical preparations. CsA is mainly metabolised in the liver by the cytochrome P-450 III2 A enzyme (63). In the skin of normal persons and psoriatic patients mRNA of the cytochrome P-450 III gene family is absent, indicating no conversion of CsA in human epidermis by this enzymatic system (64).

Support for the assumption that the pharmacological effect of CsA may be "local" was given by the work of Takashima & Morita (45). They showed that peripheral blood T-cells of psoriatic patients were not significantly different in genomic, phenotypic and functional analyses before and after systemic CsA-treatment. The authors conclude that skin-specific effects of CsA-therapy may be more likely than systemic changes.

The vascular endothelium as a possible target for the pharmacological effects of CsA has been discussed in connection with recent findings concerning adhesion of T-cells to human umbilical vein endothelial cells as well as to endothelium in human skin organ culture via the endothelial leukocyte adhesion molecule-1 (ELAM-1). T-cells were shown to bind to endothelial cells by ELAM-1 (65–67). This process can be inhibited by CsA (67). ELAM-1 is expressed in minimal levels in normal skin. However, in psoriasis, atopic dermatitis and allergic contact eczema ELAM-1 expression proved to be intense and widespread, particularly so for vessels in the dermal papillae (68).

The role of adhesion molecules in clearing psoriatic plaques by systemic treatment with CsA was further substantiated by recent observations of Petzelbauer et al. (69). The authors described pronounced suppression of intercellular adhesion molecule-1 (ICAM-1) expression on endothelial cells of the papillary vessels in CsA-treated psoriatic patients during clearing of the lesions. Interestingly, in two patients who did not respond to CsA-therapy (5 mg/kg/d) decreased ICAM-1 expression could not be seen. Furthermore, Petzelbauer et al. (69) were able to show that only endothelial cells of the papillary vessels within the elongated ("squorting") papillae showed reduced ICAM-1 expression during systemic CsA-treatment, whereas endothelial cells of the dermal and reticular plexus remained unaffected. Interestingly, ICAM-1 expression on keratinocytes and dermal endothelial cells could be induced after intradermal injection of interferon-gamma, a cytokine secreted by activated T-cells, this secretion being potently inhibited by CsA (70).

As recently reviewed by Nickoloff & Griffiths (71), the same pattern of expression of ICAM-1 and ELAM-1 as described above is found in alopecia areata where the perifollicular dermal vessels strongly expressed these adhesion molecules not found in normal skin. Moreover, enhanced expression of ICAM-1 ceased when patients underwent systemic treatment with CsA, the reduction of expression being correlated to the regrowth of hairs. As in psoriasis, topical CsA-treatment of alopecia areata did not lead to major improvement (22, 23) in comparison to systemic CsA-therapy (21).

From these findings it may hypothesised that systemic and intralesional administration of CsA, even using low-dose regimen, may lead to local concentrations effectively inhibiting ELAM-1 as well as ICAM-1 expression, whereas topical administration due to the above mentioned problems of penetration may not.

The observations found in the numerous clinical and experimental studies described concerning the mode of action of CsA in psoriasis and the pathogenesis of this disease may challenge future work in psoriasis research. Creation of new drug delivery systems enabling CsA to penetrate into skin may be a future perspective to optimize CsA therapy in psoriasis.

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