Development of new treatment modalities for atopic dermatitis

van Leent, E.J.M.

Publication date
2002

Citation for published version (APA):
Chapter 7

In contrast to pimecrolimus (Elidel®, SDZ ASM 981), the ascomycin derivative SDZ ASD 732 is not effective in atopic dermatitis


submitted for publication
Topical cyclosporin is not effective in most dermatological diseases tested\(^1\), probably because its molecular weight (1202 dalton) is too high to allow penetration through the corneal layer of the human epidermis. The advantage of tacrolimus and ascomycin derivatives is that their molecular weight is smaller (around 800 dalton), so that they might be effective as topical agents. In psoriasis, tacrolimus\(^2\) and the ascomycin derivatives ASM 281-240\(^3\) and ASM 981\(^4\) have been found to be effective topically, but only under plastic occlusion. We have previously suggested the concept of the 500 dalton rule, which says that in normal human skin as well as in most dermatological diseases, the corneal layer does not allow penetration of molecules with a molecular weight over 500 dalton\(^5\). Destruction of the corneal layer, for example by disruption with ultrasound (phonopheresis) is one of the few but complicated ways to get large molecules into the skin from outside inwards. Patients with atopic dermatitis seem to form the only exception to the 500 dalton rule. The apparent efficacy of both topical tacrolimus\(^6\) and topical pimecrolimus\(^7\) (Elidel\(^8\), SDZ ASM 981) in clearing lesions of atopic dermatitis indicated that there is something intrinsically wrong with the corneal layer in atopic dermatitis.

Pimecrolimus is a selective inhibitor of inflammatory cytokine synthesis in T cells and mast cells, which has proven to be safe und highly effective in the treatment of atopic dermatitis and other inflammatory skin diseases. It was selected from a large pool of derivatives of the macrolactam ascomycin. Together with pimecrolimus, SDZ ASD 732, another ascomycin derivative, was identified featuring not only an innovative chemical structure but also interesting pharmacological activities\(^8\). SDZ ASD 732 was found like pimecrolimus and its parent compound to inhibit the inflammatory response to allergens in animal models of allergic contact dermatitis, but had in contrast to pimecrolimus and ascomycin no \textit{in vitro} effect on T cells and mast cells. Despite considerable efforts, the mechanism of its anti-inflammatory could not be identified so far. It was intriguing to explore whether this novel ascomycin derivative would have clinical efficacy in patients with inflammatory skin diseases. Therefore the effect of SDZ ASD 732 2% cream formulation was studied in a pilot trial in patients with atopic dermatitis.

A total of 10 adult patients with atopic dermatitis as defined by the Hanifin and Rajka criteria\(^9\) was included in the study, after obtaining permission from the Medical Ethical Committee and informed consent from the patients. Patients had to have at least 1-2% of their total body surface area involved in test area, being the arms. Lesional severity was measured using the ADSI (atopic dermatitis severity index). The ADSI is the sum of 5 items (erythema, pruritus, exudations, excoriation and lichenification) each scored on a scale of 0 (absence) to 3 (severe). ADSI had to be minimally 6 at inclusion. ASD 732 2% cream or its vehicle control was applied twice daily for three weeks on the test
area’s. Patients were allowed to use 1% hydrocortisone acetate cream and/or emollients, but simply not on the test area’s.

Results: Of the 10 patients participating, 8 could be included in the per protocol evaluation. The other 2 were not analysed because of protocol violations (poor compliance, prohibited medication). Using matched-paired, signed rank sum testing for the difference between treatments (last observation carried forward), no statistical difference could be observed. The mean ADSI before treatment was 7.3 at the placebo side and 7.4 at the site to be actively treated. After 3 weeks of topical therapy, ADSI was 6.9 at the placebo side and 6.8 at the actively treated ASD 732 exposed side.

One might argue that the lack of effect might be due to the concentration of the active compound chosen, or perhaps due to the composition of the vehicle, which might not be optimal for skin delivery of the drug. Although this is difficult to deny, in all probability it seems reasonable to accept the interpretation of our results that there is simply lack of efficacy. This lack of a therapeutic effect suggests that the mechanism of anti-inflammatory activity observed in animal models might not be relevant for the pathomechanism of atopic dermatitis.
References


