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Novel topical and oral treatment for dermatitis and psoriasis

Rebecca Lawrence, News & Features Editor

Positive clinical results have been recently announced for the first of a new class of drugs for atopic dermatitis and psoriasis that could provide the first new treatment option for these conditions for 40 years. SDZ ASM981, developed by Novartis Pharma AG (Basle, Switzerland), is an ascomycin derivative providing a new approach. It specifically targets the skin and selectively inhibits the release of inflammatory cytokines, therefore preventing the inflammatory cascade pathway.

Pathophysiology

Atopic dermatitis is the most common skin condition and its prevalence has increased by 30% in the past 30 years, affecting 5–12% of the US population. Most cases are diagnosed within the first two years of life and are characterized by itchy, inflamed, dry and cracked skin. Current therapies include short-term corticosteroid treatment usually in combination with emollients. However, there are many concerns over the long-term use of corticosteroids, including skin atrophy caused by downregulation of collagen synthesis in the dermis, telangiectasia (appearance of visible blood vessels on the skin) and systemic uptake leading to conditions such as Cushing's syndrome and HPA (hypothalamo-pituitary-adrenal)-axis suppression, leading to growth retardation. These side effects prevent the application of corticosteroids to the eyelids, face and other sensitive parts of the body and also mean that treatment can only be short term. This has led to a search for compounds that circumvent these selectivity problems while maintaining similar efficacy.

T cells appear to play a key part in the pathomechanism of inflammatory skin diseases such as atopic dermatitis, psoriasis and allergic contact dermatitis. In atopic dermatitis, allergens are presented to antigen-specific T cells, mostly of the Th2 phenotype, where the activation of these cells leads to interleukin (IL)-4 and IL-5 secretion, stimulating immunoglobulin E (IgE) production, mast cell activation and degranulation as well as eosinophilia, respectively. A Th1 response is also stimulated in the later phases of development of the inflammatory skin lesion.

The ascomycins

In the 1980s, researchers showed that the immunosuppressant drug cyclosporin A is highly effective in inflammatory skin diseases such as psoriasis. However, cyclosporin A is administered systemically and has a number of side effects, especially on kidney function and blood pressure. All efforts to develop a clinically effective topical cyclosporin A formulation failed, despite considerable efforts by researchers at the Novartis (formerly Sandoz) Research Institute (Vienna, Austria) and elsewhere.

The next step was to establish clinically relevant animal models of inflammatory skin diseases to enable research into new agents. In particular, a novel model of allergic contact dermatitis was developed using pigs, which have similar skin characteristics to humans. In this model, topical corticosteroids of different potencies were similarly efficacious while topical cyclosporin A was ineffective, these results being confirmed by clinical findings. Furthermore, macrophilin-interacting drugs such as FK506 and ascomycin were shown to be topically highly effective in the pig, indicating for the first time therapeutic dermatological potential for these compounds in inflammatory skin diseases[1–3].

Ascomycin (from the microorganism *Streptomyces hygroscopicus ascomyceticum*) is known to work through a similar mechanism to cyclosporin A by inhibiting the phosphatase calcineurin via binding to macrophilin-12 (Ref. 3). However, says Stütz, ascomycin does not have skin specificity. 'We therefore embarked on two efforts. The first was to explore the therapeutic potential of an ascomycin derivative in a clinical proof-of-concept study in inflammatory skin diseases. Indeed, SDZ281240 was highly efficacious in patients with chronic plaque psoriasis when applied topically under Finn-chamber occlusion[4]. The second effort was an intensive medicinal chemistry program where we synthesized and tested 300 ascomycin derivatives in *in vitro* and *in vivo* assays[3],' he continues. SDZ ASM981 was found to have the best skin selectivity in pharmacological models, and the best safety profile, and was therefore selected for development[3].

SDZ ASM981

SDZ ASM981 (33-epi-chloro-33-deoxy-ascomycin) was shown to have a high affinity for the immunophilin, macrophilin-12 and to inhibit calcineurin[5]. As a consequence, nuclear factor of activated T cells (NF-AT)-dependent cellular processes are abrogated and the production and release of pro-inflammatory cytokines after antigen-specific or non-specific stimulation in T cells and mast cells is

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blocked[5]. More specifically, the compound downregulates the production of Th1 [IL-2 and interferon γ (IFNγ)] and Th2-type (IL-4 and IL-10) cytokines in a human cell line isolated from the skin of an atopic dermatitis patient.

A significant feature of SDZ ASM981 is its skin specificity, says Stütz. 'We have shown that in skin inflammation models, SDZ ASM981 has a high efficacy when administered either topically or orally[6,7]. However, in contrast to commonly used immunosuppressants such as cyclosporin A and FK506, SDZ ASM981 has little effect on systemic immune responses, as shown in the graft-versus-host reaction and the kidney transplantation model in rats[6,8],' he explains.

Clinical studies

Two 26-week multicentre vehicle-controlled Phase III studies in 403 paediatric patients (aged 2–17 years) with mild to moderate atopic dermatitis have now confirmed these results in patients[9]. Both studies consisted of a six-week randomized, double-blind, parallel-group phase, with the primary endpoint being clear of any signs of atopic dermatitis, followed by a 20-week open-label phase.

The combined trials showed that 40% of the group treated with topical SDZ ASM981 achieved clearance, which was significantly more than the control group, and 62% of the treated group showed improvement. Transient application site burning was found in 10% of treated patients. There was no increased incidence of infection noted and only low levels of systemic exposure to the drug (<2 ng ml^{-1}) observed[10]. Longer-term studies of >1 year in adults also showed a good side effect profile with no evidence of skin atrophy, showing that chronic treatment is also well tolerated[11]. The absence of skin atrophy was further demonstrated in a double-blind comparison with cream vehicle and topical corticosteroids as a positive control[12,13].

A pilot multi-rising-dose study, examining the pharmacokinetics, safety and efficacy of oral SDZ ASM981 in psoriasis patients demonstrated high efficacy, reducing the standard psoriasis score (PASI) by 75% at the highest dose tested (60 mg daily)[14]. The drug had no effect on kidney parameters such as creatinine levels, glomerular filtration rate or blood pressure, the only reported side effect being a feeling of warmth during the first few hours after dosing. Although the researchers are excited about these results, Stütz warns that: 'These results will now need to be confirmed in follow-up studies.'

Future studies

Current ongoing Phase III studies using SDZ ASM981 are now examining the effects of topical administration of the drug on infants of 3–23 months of age with atopic dermatitis. Stütz says that early results are looking very encouraging and appear to be at least as good, if not better, than the results obtained in the study in older children. If all goes according to plan, the group hopes that topical SDZ ASM981 will reach the market by late 2001 to early 2002, with the oral preparation of the compound following in the next 3–4 years.

Stütz and his colleagues are continuing to investigate the mechanism of the selectivity of SDZ ASM981. The scientists at Novartis Research Institute are also exploring a number of other novel targets for atopic dermatitis and psoriasis treatments and are currently in the process of validating them.

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