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Efficacy of cyclosporin A in psoriasis: a summary of the United States' experience

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SUMMARY

Since its discovery in 1972, cyclosporin A (CyA) has been widely used in the experimental treatment of multiple inflammatory diseases considered to be of immune-mediated aetiology. In dermatology, oral CyA is most effective in the treatment of psoriasis and has been used successfully for plaque-type, pustular and erythrodermic forms of the disease. While dosages ranging from 1 to 14 mg/kg/day have been used, a starting dose of 4 mg/kg/day gives a rapid response with few side-effects. Nephrotoxicity remains the greatest concern in long-term use of the drug. Although intralesional CyA has proven effective in psoriasis, topical preparations have not. It is hoped that future research will provide effective topical formulations of CyA which are efficacious without the risks inherent in systemic administration.

Cyclosporin A (CyA) is a cyclic polypeptide of fungal origin that was discovered in 1972. Due to its marked immunosuppressive effects and lack of myelotoxicity, the drug rapidly became the mainstay of therapy for organ transplantation. In recent years, the drug has been used in the experimental treatment of rheumatoid and psoriatic arthritis, insulin-dependent diabetes mellitus, inflammatory bowel diseases, myasthenia gravis, Grave's disease and uveitis.[1]

Cyclosporin A has been used as the sole therapy for psoriasis,[2-6] alopecia areata,[7-10] Behçet's disease,[11,12] atopic dermatitis,[13,14] pyoderma gangrenosum[15-17] and lichen planus.[18-20] In combination therapy with other immunosuppressive drugs, CyA has been shown to have a beneficial effect in the treatment of dermatomyositis/polymyositis,[21-23] systemic lupus erythematosus,[24-26] pemphigus and pemphigoid.[27,28]

In dermatology, the most dramatic effect of treatment with CyA is seen in psoriasis. Mueller and Herrmann[29] made the fortuitous discovery in 1979 that plaque-type psoriasis cleared in all four patients who received the drug for psoriatic arthritis. Van Hooff *et al.* [30] reported a renal transplant recipient whose psoriasis cleared after initiation of CyA treatment.

The first controlled study to evaluate the efficacy of CyA in psoriasis was done by us in 1986.[3] Twenty-one patients were enrolled in a double-blind cross-over study. All patients had severe

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plaque-type psoriasis which had been recalcitrant to treatment with topical corticosteroids, anthralin (dithranol) and tar as well as to ultraviolet B (UVB), oral psoralen and ultraviolet A (PUVA), or methotrexate. Patients received either placebo or CyA at a dose of 14 mg/kg/day. Within 4 weeks of therapy, 20 of 21 patients given the drug showed significant to complete clearing of psoriasis. The patients who received placebo showed no response prior to cross-over to active drug treatment.

In an open study, Wentzell *et al.*[31] noted marked improvement to complete clearance in 14 patients given CyA at 5–15 mg/kg/day for 1 month. These excellent responses were seen in patients regardless of whether they had pustular, erythrodermic or plaque-type psoriasis.

Multiple studies conducted both in Europe and in the U.S. have now shown that low-dose CyA can induce clearing of psoriasis. Marks[32] treated nine patients who had plaque-type psoriasis with a starting dose of 1 mg/kg/day of CyA, increasing the dose every 2 weeks as necessary, until improvement was noted or up to a maximum dose of 5 mg/kg/day. Within 20 weeks, all nine patients showed improvement, and clearance was achieved in seven. The average dose required for a clinical response was 3·3 mg/kg/day.

Griffiths *et al.*[4] treated 10 patients with CyA at 2–4 mg/kg/day for 3 months and concluded that the lowest effective dose of the drug was 3 mg/kg/day. Fry *et al.*[33] found that they were able to maintain near-complete remission of psoriasis in eight patients, who were followed for up to 66 weeks, using CyA dosages of 1–4 mg/kg/day. Meinardi and Bos[34] induced remissions of psoriasis in 12 patients with a mean dose of 6 mg/kg/day. On reducing the dose of the drug, each patient had a dose level of CyA below which a flare of psoriasis was inevitable. This dose threshold ranged from 1·6–7 mg/kg/day which, for a given patient, varied with time. Picascia *et al.*[35] used a starting dose of CyA of 7·5 mg/kg/day to treat three patients whose plaque-type psoriasis had failed to respond to other systemic therapies. Two of these patients cleared completely within 3 weeks and one was cleared by 8 weeks. One patient has been maintained on 3·5 mg/kg/day while the other two have been successfully switched to PUVA therapy or etretinate and UVB while maintaining good control of their disease.

We conducted a dose-finding double-blind placebo-controlled trial using CyA in the treatment of severe recalcitrant psoriasis.[36] Eighty-five patients were enrolled in the first phase of this study, during which patients received either placebo, 3 mg, 5 mg or 7·5 mg/kg/day of the drug. Within 1 month of therapy, the percent improvement from baseline in each group was 0%, 42%, 61% and 79%, respectively, for each dose group. By Week 8 of therapy, the percentage improvement was −5%, 54%, 82% and 93%, respectively. In order to achieve a greater than 90% clearance by Week 16, 60% of patients taking 3 mg/kg/day required an increase in dosage compared with 25% of those in the 5 mg/kg/day dosage group and 13% of those receiving 7·5 mg/kg/day. Dosage reduction for side-effects or signs of toxicity was necessary in 0%, 0%, 5% and 33% of each group respectively. In general, the drug was very well tolerated and side-effects were similar to those reported in others taking CyA.

We suggest that CyA at 4 mg/kg/day may be the best starting dose as this can be expected to produce a significant improvement within 1–2 months of therapy with minimal risk of short-term toxicity. If an increase in dosage is required, most patients can be expected to tolerate 5 mg/kg/day, at least for several weeks to months.

Cyclosporin A has also been shown to be effective in non-plaque-type psoriasis. Picascia *et al.*[5] treated two patients who had erythrodermic psoriasis with CyA at approximately 8 mg/kg/day; complete clearance was noted in both patients within 3 weeks. After clearance was achieved, one patient was maintained on CyA 2 mg/kg/day and had plaque-type psoriasis on less than 20% of her body. The second patient was controlled with PUVA therapy and CyA

at 1·7 mg/kg/day.[35] Meinardi *et al.*[37] reported successfully treating a patient with generalized von Zumbusch pustular psoriasis using CyA at 5–12 mg/kg/day. We treated one patient, who had a 30-year intermittent history of pustular psoriasis, with CyA at a starting dose of 7·5 mg/kg/day.[38] Due to his excellent clinical response, we were able to gradually taper his dose to 1·5 mg/kg/day over 5 months. A mild flare of disease at this dose required a gradual dosage increase of 3·5 mg/kg/day, which again resulted in a remission.

A recalcitrant case of acrodermatitis continua cleared for the first time in 10 years after therapy was initiated with CyA at 14 mg/kg/day, followed by gradual tapering to a dose of 5 mg/kg/day.[39] Six patients with palmoplantar pustulosis showed a dramatic improvement with CyA at 2·5 mg/kg/day.[40] We treated two patients who had acrodermatitis continua with CyA at 6 mg/kg/day.[41] One patient cleared completely and the other showed no new pustulation within 8 weeks of initiating therapy.

Intralesional CyA can be effective in the treatment of plaque-type psoriasis. Ho *et al.*[42] conducted a double-blind trial of six patients with plaque-type psoriasis which compared intralesional injections of CyA (17 mg/ml), vehicle and saline which were given three times per week. Within 4 weeks, significant improvement to complete clearing was seen in all CyA-treated plaques in contrast to vehicle- or saline-treated plaques, which showed minimal to no improvement. Both the solution of CyA and its vehicle caused pain on injection in all the patients, apparently as the result of the vehicle rather than the drug itself. In contrast, CyA administered once weekly was no better than its vehicle in improving the plaques of psoriasis. Systemic absorption of the drug was negligible, suggesting that CyA need not be given systemically to be effective in the treatment of psoriasis. Similar results were also found in a study of 10 patients.[43]

In contrast, topical CyA has, so far, been ineffective in the treatment of psoriasis. In a placebo-controlled study, Griffiths *et al.*[44] treated six patients twice daily for 4 weeks with a 2% CyA ointment. No difference was noted in efficacy between the drug and placebo. In an open trial, we treated 10 patients with a 10% CyA solution, which was also found to be ineffective,[45] and a similar lack of response was noted in six patients treated with a 5% topical CyA solution.[46] Bousema *et al.*[47] found 10% topical CyA gel to be ineffective.

Schulze *et al.*[48] treated six patients in a placebo-controlled trial using a 5% CyA ointment, under plastic-film occlusion, for 2–3 weeks. Immunostaining revealed a marked decrease in the number of infiltrating neutrophils in the epidermis and papillary dermis, but no change in the helper/suppressor T-cell ratio. Despite drug levels in CyA-treated plaques comparable to those observed in patients given oral CyA, no change in epidermal cell kinetics was noted after topical application of the drug, and no clinical improvement was seen. This is in contrast to our study of intralesional CyA in which a clinical response was preceded, in many cases, by a significant reduction in the number of antigen-presenting cells, epidermal and dermal monocytes, and keratinocyte intercellular adhesion molecule-1 expression.[42]

It is not known why topical CyA formulations have been ineffective in the treatment of psoriasis. The clearing in response to intralesional CyA demonstrates that systemic administration should not be required for efficacy. The failure of psoriasis to improve in response to topical applications of the drug may be due to an inadequate concentration of the drug reaching the necessary site(s), poor percutaneous absorption,[49] rapid redistribution of the drug, drug inactivation or by non-specific binding to proteins in the skin.

The discovery of CyA in 1972 and the subsequent demonstration of its marked efficacy in psoriasis have ushered in a new era of both research and therapy for this chronic disease. The dramatic effects of CyA in many dermatological diseases has not only provided new therapeutic

options, but has also expanded our understanding of the pathophysiology of many diseases and opened up new avenues of research. It is hoped that, in the future, effective CyA topical formulations or oral analogues with less toxicity will be discovered.

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