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REVIEW ARTICLE

Cyclosporin A treatment in severe childhood psoriasis

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Abstract

Though used occasionally, systemic therapies in severe childhood psoriasis have not been systematically investigated. Cyclosporin A (CysA) is effective in adults with severe psoriasis but there are no extensive data regarding the efficacy and safety of its use in childhood psoriasis. In this paper, we describe six children aged between 11 months and 13 years (average: 7.6 years) treated with CysA microemulsion formulation for severe psoriasis, who had been unresponsive to other treatments. The CysA dose ranged from 2 to 4 mg/kg/day, for periods varying from 8 to 105 weeks (mean: 54 weeks). Dose tapering was gradual after lesion improvement and adjusted according to clinical response. Adjuvant therapy with topical steroids, vitamin D3 ointments, coal tar preparations or anthralin was used in all children. Acitretin was used in three patients for short periods. The children were regularly monitored for serum renal and liver function and blood pressure. Improvement of skin lesions was achieved after between 4 and 30 (mean: 12) weeks of treatment, with complete remission in three children. Relapse of lesions occurred in the other children during CysA reduction, but they responded to a dose increase. The treatment was found to be well tolerated and with no significant side-effects. CysA can be used in carefully selected and monitored patients and may represent an alternative tool for severe episodes of psoriasis in children, when other therapies are unsuccessful.

Introduction

Childhood psoriasis has many clinical facets that may change over time. Although its exact incidence is unknown[1] it has been calculated to range from 0.1 to 3%[2] in various parts of the world. In children, psoriasis usually both follows a benign course and is successfully managed with topical agents. In severe forms of the disease, such as generalized pustular psoriasis, extensive psoriasis vulgar, psoriatic erythroderma or psoriatic arthropathy, more aggressive treatments, such as phototherapy or systemic therapy, are required.[3] However, because of the uncommon nature of these psoriasis types, the clinical experience with systemic agents is limited.

Primary systemic treatments for severe psoriasis include phototherapy, retinoids, methotrexate (MTX), cyclosporin (CyA) and new biological therapies. Psoralen plus ultraviolet A (PUVA) therapy is not indicated in children, although narrowband ultraviolet B (UVB) in older children has recently proven to be a safer alternative to maintain long-term disease control.[4] Retinoids are the most commonly used oral medication, but the risk of skeletal toxicity, derangement of hepatic enzymes and serum lipids and mucocutaneous side-effects are a limiting factor.[5–7] MTX remains one of the most effective antipsoriatic drugs, but previous experience of its use in childhood psoriasis is scarce and there are concerns over long-term safety concerning its hepatotoxic potential and the risk of bone marrow suppression.[8,9]

The safety and efficacy of CyA therapy has been extensively studied in severe adult and childhood atopic dermatitis and in adult psoriasis. The most troublesome side-effects of CyA are nephrotoxicity and hypertension, both of which are of particular concern in long-term use. These side-effects are dose-dependant and, in almost all cases, reversible after discontinuation of CyA. Provided the patient is monitored for side-effects, treatment can be continued for up to 2 years.[10]

Previous experience with CyA use in childhood psoriasis has been controversial. Mahé *et al.*[11] described four children, aged between 2 and 10 years, who were treated with CyA for severe drug resistant psoriasis and in whom the results were unsatisfactory. Only one child inadvertently treated with 10 mg/kg/day showed response, but the therapy was discontinued due to relapse. Perret *et al.*[12] describe three children, aged between 7 and 11 years, with generalized plaque psoriasis, who responded well to CyA without side-effects, except for nausea and diarrhoea in one child at the beginning of treatment. Most of the case reports of successful use of CyA in paediatric groups involve patients with pustular psoriasis, with a well tolerated and effective treatment.[13–15]

We describe six children, five boys and one girl, aged between 11 months and 13 years (average: 7.6 years), with severe psoriasis, refractory to conventional therapy and treated with CyA microemulsion formulation. Five children presented generalized plaque psoriasis and one, pustular psoriasis. All children had previously failed to respond to topical treatments and two did not respond to UVB (one in association with acitretin). In all children the treatment was considered to be well tolerated and with no significant side-effects.

Clinical cases

Patient 1

A 6-year-old boy with a 12 month widespread psoriasis affecting the upper and lower limbs, trunk, face and scalp (fig. 1). The initial PASI was 22.9. His psoriasis was precipitated by surgery (circumcision). There was no history of sore throat or other focal infections that might have precipitated exacerbations of the disease. He had been treated with topical preparations (emollients, coal tar, calcipotriol and anthralin), with no response. CysA was started at a dose of 3.8 mg/kg daily and, after 45 days of treatment, a marked lesion improvement was observed (fig. 2). The dosage was reduced, with complete remission of lesions after 60 days of treatment and without relapses during the 1 year of follow-up. During CyA treatment, no abnormalities were found in blood pressure or renal function.

Patient 2

A 12-year-old boy with generalized plaque psoriasis involving the trunk, limbs and scalp, over the last 12 months. The initial PASI was 29. There was no history of sore throat or other focal infections that might have precipitated exacerbations of the disease. He had been treated with various topical preparations, including emollients, betamethasone valerate, tacalcitol and anthralin, without remission. A course of ultraviolet B for 2 months resulted in little improvement of lesions. He then started CyA treatment at a dose of 2.7 mg/kg daily. Two months after starting CyA, his skin significantly improved and the dosage was gradually reduced. He remained in almost complete remission for the following 12 months, with only a few localized lesions on the scalp, which is managed well with topical coal tar and steroid lotion. His renal function and blood pressure remained stable throughout the course of treatment.

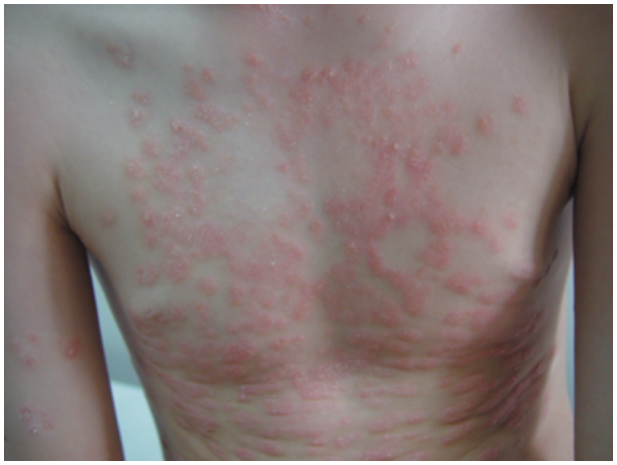

fig. 1 Psoriasis unresponsive to topical therapy (patient 1).

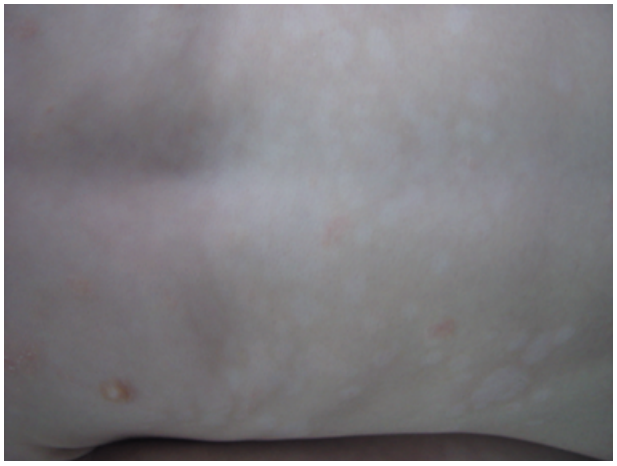

fig. 2 Lesion resolution after 45 days of cyclosporin A treatment.

Patient 3

An 11-year-old boy with a 2-year history of chronic plaque psoriasis covering most of his body, arms, legs and scalp. The initial PASI was 36.4. The child came from a

difficult social background and there was a family history of psoriasis from his father's side. There was no history of sore throat or other focal infections that might have precipitated exacerbations of the disease. He had been treated with various topical preparations, including emollients, calcipotriol, betamethason and coal tar. None of these resulted in satisfactory control of his psoriasis. CyA was started at a dose of 2.5 mg/kg/day. He showed a transitory improvement of lesions, but 6 months later, during dose reducing, he was admitted because of the development of a generalized exfoliative erytroderma. The CyA dose was increased to 4 mg/kg/day, with great improvement of lesions after 5 weeks of treatment. Tapering of the dosage resulted in a relapse of psoriasis. The dosage was reverted and acitretin associated at a dose of 0.2 mg/kg/day, with good response after 6 weeks. Dose tapering was gradual with good control of the disease. During CyA treatment no abnormalities were found in blood pressure, complete blood count, liver function, serum electrolytes, serum urea and creatinine tests.

Patient 4

A 3-year-old boy with generalized plaque psoriasis, involving the trunk, the limbs and the scalp, poorly controlled with topical corticosteroids over the last 12 months (fig. 3). He had a history of atopic dermatitis from the age of 10 months, which responded well to topical corticosteroids, emollients and antihistamines. The initial PASI was 31.6. There was no history of sore throat or other focal infections that might have precipitated exacerbations of the disease. CyA was initiated at a dose of 3.5 mg/kg/day, with significant improvement after 3 months (fig. 4). The dosage was then gradually reduced, with no relapse. He is currently almost disease-free, after 24 months of follow-up, with no adverse effects on blood pressure or renal function.

Patient 5

A 13-year-old boy with widespread erythematous plaques of psoriasis affecting the trunk, limbs and scalp over the last 12 months. The initial PASI was 41.3. There was no history of sore throat or other focal infections that might have precipitated exacerbations of the disease. He had previously failed to respond to topical therapy. He was then started on CyA at a dose of 3.5 mg/kg/day, with improvement of lesions after 2 months. The dosage was discontinued, but the lesions promptly began to relapse. The dosage was reverted to 3.5 mg/kg daily and his lesions cleared after 6 weeks of treatment. Six months later, he had a lesion relapse that responded to a course of CyA at a dose of 3.5 mg/kg/day and acitretin at 0.2 mg/kg/day and control of his disease was achieved after 5 months of treatment. He was disease-free for 6 months. He experienced no side-effects and his liver and renal function, serum lipids and blood pressure remain stable.

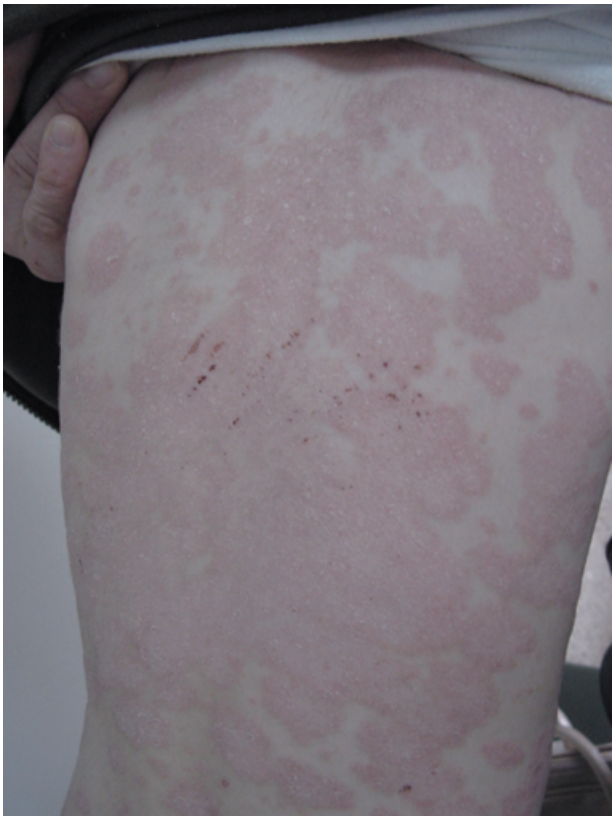

fig. 3 Psoriasis unresponsive to topical therapy (patient 4).

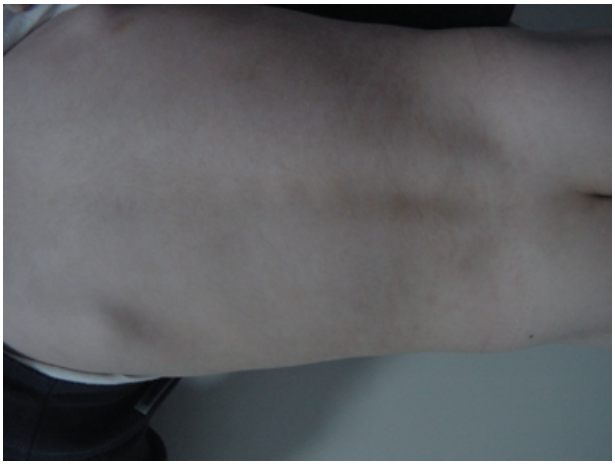

fig. 4 Lesion resolution after 12 weeks of cyclosporin A treatment.

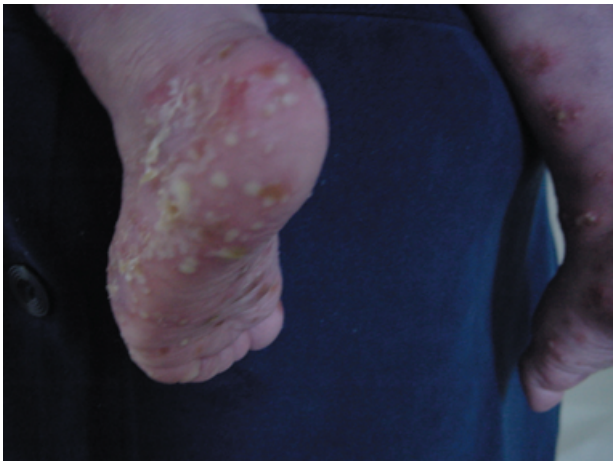

fig. 5 Pustular psoriasis in an 11-month-old child (patient 6).

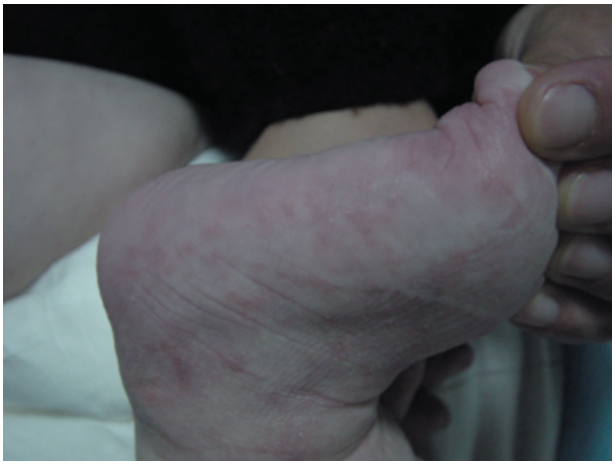

fig. 6 Lesion improvement after 12 weeks of cyclosporin A treatment.

Patient 6

An 11-month-old girl with generalized pustular psoriasis since the age of 2 months. She had recurrent episodes of multiple erythematous and scaly plaques with overlying pustules on the scalp, face, trunk and extremities (fig. 5). During acute flares the child was ill, with malaise, anorexia and pain secondary to her exfoliating skin. She also had a history of severe erythematous nappy rash and complete dystrophic finger nails and toenails. A lesional biopsy showed changes consistent with pustular psoriasis. Other investigations, including full blood count and biochemical profile, were at normal range and her HLA type was A24, B35, 58, CW 07,12. Various topical treatments were unhelpful. She started CyA at a lower dosage of 2 mg/kg/day, with improvement of lesions after 3 months (fig. 6). Over the next year the child had three episodes of disease exacerbation, responding well to CyA. In the later episode, we added acitretin at 0.3 mg/kg/day for 2 months, with faster improvement of lesions and no side-effects. Two years after starting CyA, the treatment was discontinued because she had an acute flare that did not respond to conventional doses of CyA. During CyA treatment, no abnormalities were found in blood pressure, complete blood count and liver or renal function.

Discussion

Systemic treatment is usually reserved for the management of children with severe subtypes of psoriasis, including those with recalcitrant plaque psoriasis, which does not respond to topical and phototherapy. Usually, in these cases, we tend to first use retinoids, based on the experience acquired with this drug in children with keratinization disorders. However, patients receiving oral retinoids are at risk of several skeletal complications including hyperostotic changes, calcification of tendons and ligaments and premature closure of epiphysis.[7] Skeletal abnormalities may be asymptomatic, irreversible and not associated with laboratory alterations.[16] Therefore, close monitoring of growth parameters and yearly radiology studies are recommended during the duration of retinoid treatment. Other adverse effects observed are mucocutaneous (chapped lips, dry skin, nose bleeds), and elevation of lipid and liver enzymes, and these parameters must be regularly monitored. If used carefully, the retinoids are probably safe but, in monotherapy, is only partially effective and rarely clears the disease. In fact, two of our children did not respond to UVB, one in association with acitretin.

Compared with other current systemic therapies, such as acitretin in monotherapy, CyA proved to be significantly more efficacious.[17] CyA has not been systematically investigated in paediatric populations with psoriasis, but the drug has been studied extensively in paediatric atopic dermatitis.[18–20] There is also accumulated experience on the prevention and treatment of organ transplant rejection.[21] CyA has been shown to be well tolerated in children with connective tissue disease[22] and diabetes mellitus.[23] Some of these studies, carried out in children with atopic dermatitis, are open and blind clinical trials that show that the drug is consistently safe. These studies also suggest that CyA is well tolerated both by children and by adults. In addition, the most serious side-effects, nephrotoxicity and hypertension, can be controlled by patient monitoring, with appropriate dose adjustment or pharmacological intervention. Prevention or reversibility of side-effects may be achieved by discontinuation of therapy after the induction of clearing.

The dosage for childhood psoriasis has been empirically developed and extrapolated from results in adults, which have recommended an initial dose of 3–4 mg/kg/day. If no significant response is found after 6–8 weeks, the dose can be titrated up to 5 mg/kg/day. In our experience, the initial doses within 2–4 mg/kg/day have offered good results; these are in a similar range to those used by other authors.[12,14] None of our children took a dose higher than 4 mg/kg/day and all the children had a good initial response. Therefore, we found that low to moderate doses can be effective in clearing psoriasis. In fact, with these doses, we observed a satisfactory improvement of skin lesions and, indeed, three children maintained a good response to CyA, without relapses after reduction of dosage. The other children experienced deterioration in their psoriasis on tapering of the CyA, but control of the disease was rapidly achieved after reverting to the original dosage. Although some children had relapse after treatment, it was particularly encouraging that the treatment period could provide a useful period of remission. In fact, three children had complete remission during the subsequent 12–24 months follow-up period and two children that relapsed with the tapering doses have not suffered any major relapses 6–12 months after discontinuation of CyA. Patient 6 had had an atypical and particularly severe form of pustular psoriasis (complete nail dystrophy, continued flares since the age of 2 months) that responded to CyA during two consecutive years.

Some studies have demonstrated pharmacokinetic differences between children and adults. In children, oral absorption may be lower, clearance is more rapid and volume distribution at a steady state is greater.[11,24] Because of a dose-dependant effect, cases of childhood psoriasis may require higher dosages of CyA, or doses should be administered three times per day.[11,24] However, in cases of atopic dermatitis, despite the pharmacokinetic differences between adults and children, the same dosage of CyA, 2.5–5 mg/kg/day, is equally effective.[18]

Adverse effects of CyA are common, usually dose-related and can be serious. Consequently, the lowest possible maintenance dose and shortest treatment period should be implemented. The side-effects of most concern are decreased renal function and hypertension. The risk of CyA-induced nephropathy can be reduced by avoiding doses exceeding 5 mg/kg/day and elevations in serum creatinine greater than 30% above baseline.[25] These side-effects are relatively infrequent and rarely require withdrawal of treatment. Our children tolerated CyA extremely well, with no significant side-effects. The length of time during which our children took CyA varied from 8 to 105 weeks (mean: 54 weeks); one child took CyA for more than a year and two children continued maintenance therapy for 2 years. None of our children experienced a persistent elevation of blood pressure or serum creatinine. Moreover, we did not observe other possible side-effects associated with the use of CyA, such as nausea, diarrhoea, joint pains, muscle aches tremors, headache, paresthesias, gingival hyperplasia or hypertrichosis.

In childhood atopic dermatitis, there is limited experience in long-term use of CyA. One study demonstrated that CyA was effective and safe in controlling severe atopic dermatitis in children over a 1-year period.[19] There were no significant changes in either blood pressure or serum creatinine levels with a dosage of 5 mg/kg/day. Although children seem to tolerate CyA better than adults, treatment for periods of longer than 2 years should be avoided because of cumulative toxicity.

The risk of developing malignancies, skin cancers and lymphoproliferative disorders, an especially worrisome prospect for children, is increased in transplant patients treated with high-dose, long-term CyA.[26] For dermatological conditions, the risk of malignancies does not appear to be increased in patients receiving doses of 5 mg/kg/day or less in patients who are not on concomitant immunosuppressives.[27] However, this risk is another reason to minimize the dose and duration of treatment.

Concomitant treatment, either with topical steroids, vitamin D3 ointments, coal tar preparations or anthralin, was used in all children in our study. Combination with topical agents has been used with varying efficacy and safety, with the potential benefit of reducing the dosage and/or the treatment duration. Although the number of studies that show the efficacy of CyA in combination with other agents is limited, topical steroid[28] anthralin[29] and calcipotriol[30] have been reported as improving its efficacy. It is our opinion that the child should be encouraged to maintain topical therapy.

In three children that relapsed with the tapering dose, we added acitretine for short periods, with the view of improving the treatment efficacy without CyA dose increase. This combination was associated with significant clinical improvement and did not increase its toxicity. Combination with retinoids is not only effective but may also protect against cutaneous malignancies.[31] Moreover, this combination can potentially reduce the dosage of CyA required or the duration of the treatment and therefore minimize the risk of side-effects.

We suggest that, when systemic treatment is indicated in childhood psoriasis, CyA should be considered as a treatment option, along with retinoids and MTX. CyA can be used in carefully selected and monitored patients and represents an alternative tool for severe episodes of psoriasis in children, refractory to topical therapy. In its favour, it appears to be more effective than other current therapies, has less side-effects than the retinoids, which are

poorly tolerated because of mucocutaneous side-effects, and is therefore more acceptable to patients. In view of the potential toxicity of CyA use, further studies are needed to find out more about the optimal dosage, treatment duration and appropriate monitoring. Gradual tapering is the most appropriate method of withdrawing CyA and this is also worthy of further investigation.

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