

ORIGINAL ARTICLE

## Factors determining the effectiveness of oral ciclosporin in the treatment of severe childhood atopic dermatitis

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### Abstract

Ciclosporin is used to treat severe atopic dermatitis (AD) where conventional therapy is either ineffective or inappropriate. Response to treatment is variable and the factors determining responsiveness are currently unclear. The aim of this study was to determine which children with severe AD are most responsive. A cohort of 35 children with severe AD who were given oral ciclosporin was retrospectively surveyed. SCORAD index was used to assess severity prior to and after treatment. Demographic and clinical data were correlated with clinical response. Ciclosporin resulted in a sustained reduction in SCORAD index of 91 (67–100)% in children where clinical skin infection was the main trigger and in whom the infection was effectively eradicated with antibiotics. If infection persisted or recurred the reduction in SCORAD index was only 44 (41–83)%. Children in whom their AD was triggered by other factors had a poor response to ciclosporin with reduction in SCORAD index of 8 (1–39)%. Oral ciclosporin is most effective in children with infection-driven AD in whom the infection is brought under control. In cases where the infection recurs or where the main triggers are non-infectious, response to ciclosporin is poorer.

**Key words:** atopic dermatitis, ciclosporin, children, *Staphylococcus aureus*

### Introduction

Ciclosporin (cyclosporine (USAN), CsA) is a calcineurin antagonist which blocks T-lymphocyte activation. It has been used for up to 8 weeks, but longer under specialist supervision, for the treatment of severe atopic dermatitis (AD) in children and adults where conventional therapy is ineffective or inappropriate (1–7). The first double-blind, crossover study using oral CsA for AD was performed 20 years ago. Oral CsA given for 8 weeks at a dose of 5 mg/kg/day to 33 adults with severe refractory disease significantly reduced the severity and extent of AD, as well as improving the quality of life (1,2). Rapid relapse over 2 weeks occurred when the drug was discontinued. In a larger study of 100 adults with severe AD, CsA taken for up to 48 weeks led to a variable but generally beneficial response, with a mean reduction in surface area affected by AD of 20%.

After stopping treatment the AD flared with an increase in pruritus and disturbed sleep (5). Three-quarters of 40 children with severe AD enrolled in another randomised, open, parallel observational 12-month study showed a significant improvement in symptoms (6).

Variability in the response to the drug was observed in all these studies, with some patients responding better than others. Little information currently exists as to the factors that predict a beneficial outcome. The purpose of this study was to determine which factors are associated with a beneficial response to oral CsA in a cohort of children with severe AD.

### Materials and methods

A retrospective observational cohort survey was performed on 35 children with severe AD who

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had received oral CsA at a single tertiary paediatric AD clinic from one clinician (PDA) between 2003 and 2011. The centre specialises in the management of children with severe AD which is poorly responsive to standard therapy with emollients and topical immunosuppressants. Diagnosis of AD was based on 1994 UK Working Party's diagnostic criteria. All patients who had used CsA over this time were identified from the clinic database. Clinical and laboratory data were obtained from the case notes and reviewed by both authors independently to reduce cofounders and bias. All clinical records were available for review. Clinical AD severity was estimated prior to starting the CsA and at the end of the treatment course using the SCORAD (SCORing Atopic Dermatitis) index (8). Oral CsA was always commenced at a dose of 5 mg/kg/day in divided doses. It was tapered at 1 mg/kg/month depending on response. Where there was no response after 2–4 weeks the medication was discontinued. Full blood count, urea, creatinine and electrolytes were measured at monthly intervals while on therapy. No patient received systemic steroids or other immunosuppressant drugs during the period of being treated. All patients were encouraged to keep applying emollients and topical immunosuppressant ointments.

Infection-associated AD was a clinical diagnosis based on the presence of oozing, crusting and/or pain in addition to xerosis, erythema and lichenification. Presence of *Staphylococcus aureus* was confirmed by skin swabs. In these children, a 2-week course of an anti-staphylococcal antibiotic based on swab antibiotic sensitivities was prescribed prior to or at the same time as starting the oral CsA. Recurrent infective flares are defined as children in whom clinical signs of infection recur or persist after an initial 2-week course of antibiotics.

As this was a retrospective survey not involving any direct patient contact and where clinical and laboratory records were entered into an anonymised database, discussions with the local research ethics committee indicated that a formal ethics approval was not required.

Statistical tests were run using the SPSS 19 program. Distribution of discrete variables is quoted as median (inter-quartile range). The  $\chi^2$  analysis was used to assess differences between groups involving discrete variables and Mann–Whitney U test and Student's t-test were used where the variables were continuous. Odds ratios (OR) were calculated using binary logistic regression with age, gender and pre-treatment SCORAD were added to the analysis as cofactors to control for any confounding effects of these variables.

Table I. Clinical features of cohort of 35 children prescribed oral CsA.

| Variable          |                                                                                                                                |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------|
| Gender            | Male 20 (57%)<br>Female 15 (43%)                                                                                               |
| Ethnic origin     | Caucasian 23 (66%)<br>Asian 7 (20%)<br>Afro Caribbean 5 (14%)                                                                  |
| Age               | 8 (6–13) years                                                                                                                 |
| Age at onset      | Infancy (<1 year old) 22 (63%)                                                                                                 |
| Age CsA started   | 6 (3–10) years                                                                                                                 |
| Duration CsA      | 20 (10–32) weeks                                                                                                               |
| Eczema severity   | SCORAD index 78 (65–85); sleep severely disturbed 30 (86%); hospitalisation 26 (74%)                                           |
| Topical treatment | Mildly potent steroids/tacrolimus 3 (8%); moderately potent steroids 22 (63%); potent steroids 10 (29%)                        |
| Trigger           | Skin infection 11 (31%); skin infection and other factors 13 (38%); non-infectious causes 11 (31%)                             |
| Antibiotics       | Nil 4 (11%); flucloxacillin 6 (17%); clindamycin 18 (52%); intravenous teicoplanin 7 (20%)                                     |
| Change in SCORAD  | <b>Group A</b> <45% improvement 18 (51%) (5 (14%) no effect);<br><b>Group B</b> 67–100% improvement 17 (49%) (4 (11%) cleared) |

Number (percentage) for discrete variables; median (inter-quartile range) for continuous variables.

CsA = ciclosporin; SCORAD = SCORing Atopic Dermatitis.

## Results

### *Clinical characteristics of the patients*

The clinical characteristics of the 35 children treated with oral CsA between 2003 and 2011 are shown in Table I. The median SCORAD index of the cohort was 78, with most waking frequently during the night because of pruritus and three-quarters having been hospitalised because of failure of outpatient therapy to control the symptoms. Ninety-two percent were on moderately potent to potent topical corticosteroids because of failure of both mildly potent corticosteroids as well as calcineurin antagonists (tacrolimus 0.03% and 0.1% ointment) to control the disease. Secondary skin infection with *S. aureus* was the major trigger in 11/35 (31%), one of a number of triggers in a further 13/35 (38%) and did not seem to have a significant role in 11/35 (31%). Twenty-five (72%) children received six or more courses of antibiotics in the 12 months prior to commencing on CsA. In 72% there was clinical methicillin-resistance where the

secondary infection (pain, oozing and crusting) failed to completely respond to flucloxacillin but did respond to oral clindamycin 18/35 (52%); 7/35 (20%) with laboratory confirmed MRSA (Methicillin-resistant *S. aureus*) required intravenous teicoplanin to bring the infection under control.

#### *Clinical effectiveness and side effects of oral CsA*

Oral CsA was started at a median age of 6 years and continued for 20 weeks (range 2–52 weeks). The cohort was divided into two equal groups based on whether the improvement in SCORAD index after therapy was greater or less than 50% of pre-treatment scores. Group A showed either no improvement 5 (14%) or minor improvement 13 (37%) (<43% reduction in SCORAD index). Group B showed a major clinical improvement (67–99% reduction in SCORAD index) or complete clearing 4 (11%). Of this latter group, two-thirds had improved within 2 weeks of starting the medicine and all by 4 weeks.

Median maximum CsA trough level was 47 µg/l (only two patients had trough levels >100 µg/l). No children developed hypertension or abnormalities in urea and electrolytes. One patient developed eczema herpeticum requiring treatment with intravenous acyclovir. Two patients were given a second course of CsA when the disease flared again.

#### *Factors associated with good response to oral CsA*

The cohort was divided into two equal groups based on whether the children had a poor (group A) or good (group B) response to CsA (Table II). Factors such as age, gender and ethnicity did not influence response. Using regression analysis with age of starting CsA, initial SCORAD index, trigger and recurrent infective flares as cofactors, the only factor associated with a good response to CsA was whether or not the AD had an infective trigger. Compared with children where there was no obvious secondary skin infection, the chance of improvement (OR (95% confidence

Table II. Clinical features in subgroups of children who did and did not improve with oral CsA.

| Variable                      | Group A<br><50% improvement<br><i>n</i> = 18              | Group B<br>≥50% improvement<br><i>n</i> = 17              | <i>p</i> -Value |
|-------------------------------|-----------------------------------------------------------|-----------------------------------------------------------|-----------------|
| Current age (years)           | 12 (7–14)                                                 | 8 (6–11)                                                  | 0.2             |
| AD onset in infancy (<1 year) | 12 (67%)                                                  | 10 (59%)                                                  | 0.9             |
| Age CsA started (years)       | 8 (6–11)                                                  | 4 (3–6)                                                   | 0.01            |
| Duration CsA (weeks)          | 15 (5–35)                                                 | 20 (12–32)                                                | 0.2             |
| CsA trough level (µg/l)       | 38 (19–56)                                                | 48 (12–65)                                                | 0.7             |
| Gender (male)                 | 10 (56%)                                                  | 10 (58%)                                                  | 0.8             |
| Ethnic origin (Caucasian)     | 12 (67%)                                                  | 11 (65%)                                                  | 0.8             |
| SCORAD (pre-CsA)              | 84 (70–90)                                                | 70 (62–79)                                                | 0.03            |
| SCORAD (post-CsA)             | 56 (49–80)                                                | 6 (2–14)                                                  | < 0.001         |
| SCORAD % decrease             | 23 (4–41)%                                                | 89 (81–98)%                                               | < 0.001         |
| Hospitalisation               | 15 (84%)                                                  | 11 (65%)                                                  | 0.2             |
| Topical treatment             | Mild/tacro 0<br>Moderate 12 (67%)<br>Potent 6 (33%)       | Mild/tacro 3 (18%)<br>Moderate 10 (59%)<br>Potent 4 (23%) | 0.3             |
| Trigger                       | Infection 2 (11%)<br>Infection + 7 (39%)<br>Other 9 (50%) | Infection 9 (52%)<br>Infection + 6 (35%)<br>Other 2 (11%) | 0.01            |
| Antibiotic use at any time    | None 2 (11%)<br>Fluclo 3 (17%)<br>Clinda/teico 13 (72%)   | None 2 (11%)<br>Fluclo 3 (18%)<br>Clinda/teico 12 (71%)   | 0.3             |
| Recurrent infective flares    | 8 (44%)                                                   | 1 (6%)                                                    | 0.01            |

Number (percentage) for discrete variables; median (inter-quartile range) for continuous variables. Statistics: discrete variables  $\chi^2$  test; continuous variable Mann–Whitney U test. Infection+ = infectious and non-infectious triggers. tacro = tacrolimus ointment; fluclo = flucloxacillin; clinda = clindamycin; teico = teicoplanin.

interval (CI) where secondary infection was the key trigger was 364 (5–26,176) and where secondary infection was one of a number of factors the OR (95% CI) was 17 (1.2–233).

Median reduction in SCORAD index in children whose AD was triggered by infection was 91 (67–100)%; by infection and other factors was 44 (41–83)%; non-infectious triggers 8 (1–39)% ( $p = 0.001$ ) (Figure 1). Where secondary skin infection was eradicated the reduction in SCORAD index was 85 (71–95)% compared with 40 (40–43)% where the secondary infection was not completely controlled ( $p = 0.05$ ).

## Discussion

This study demonstrates that oral CsA is most effective in children with evidence of infection-driven AD where the infection is brought under control with oral antibiotics. Concomitant use of appropriate antibiotics based on skin swab sensitivities is thus an important aspect of management of these patients. Where the AD has both infectious and non-infectious triggers CsA is only partial. In cases where the AD

is not associated with evidence of clinical infection the, response to CsA is poor. Using multivariate analysis other factors such as age of the children, gender, ethnicity and duration of CsA therapy and SCORAD index prior to commencing CsA was not found to influence outcome.

No abnormalities in renal function were observed, although one patient developed eczema herpeticum on the skin of her back requiring temporary discontinuation of CsA and a course of intravenous acyclovir.

Our results are in keeping with a small observational study of 11 children with AD by Bunikowski et al. who found that the six children with ongoing clinically apparent skin infections responded less well to oral CsA than the five patients with evidence of bacterial colonisation but no infection (9). The observed lack of response to CsA in children with non-infectious triggers argues against CsA being universally effective in the treatment of severe AD. It suggests that T-lymphocytes may play a more prominent role in the pathogenesis of infection-triggered AD. CsA suppresses T-lymphocyte activity and in patients with AD has previously been shown to inhibit the production of inflammatory Th2 cytokines (10,11). Skin bacteria are known to produce superantigens that trigger polyclonal T-cell activation and Schlievert et al. previously demonstrated that refractory AD is associated with *S. aureus* isolates with high superantigen production (12). CsA would be expected to block T-lymphocyte activation and turn off the inflammatory process so long as the primary trigger (bacteria-producing exotoxins) is also eradicated. CsA has recently been found to be useful in the treatment of refractory Kawasaki disease, another superantigen-driven inflammatory disorder (13). It is possible that other T-cell immunosuppressants such as azathioprine and methotrexate would have a similar beneficial effect to CsA. Direct comparison of these drugs in a double-blind, placebo-controlled trial of patients with severe AD would be useful.

As the reduction in SCORAD index was significantly greater in children in whom infection was completely rather than partly eradicated one might argue that in this subgroup CsA was superfluous and what was required was more effective antibiotic therapy. However, 72% of patients had received six or more courses of antibiotics in the year prior to commencing on CsA, implying that although antimicrobial therapy was important, it was insufficient to induce a sustained remission. Antibiotics may remove the source of superantigens by killing skin bacteria, but CsA suppresses superantigen-activated T-cells that drive the underlying inflammation. We conclude from the results of this study that CsA synergises with antibiotics to induce

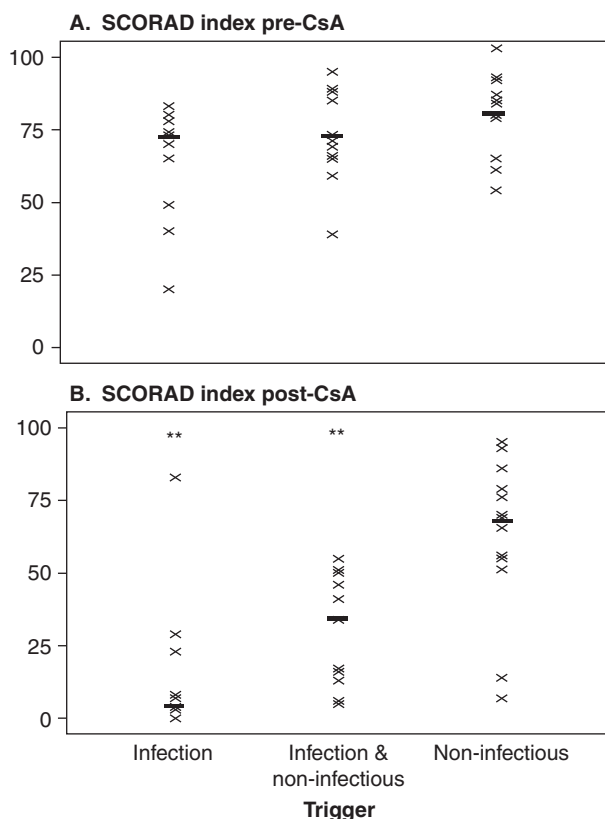


Figure 1. SCORAD index before and at the end of the course of CsA in groups of children based on whether or not infection triggered the disease. Bars represent medians. \*\* $p < 0.001$  (two-tailed) compared with pre-CsA SCORAD index using paired Student's t-test.

remission, breaking the infection–eczema cycle by reducing pruritus and further skin damage. Although potent topical immunosuppressants may have a similar beneficial effect to CsA, in many children with severe AD, they are difficult or impossible to effectively apply because of the pain and distress the child is experiencing.

We suggest that management of children with severe AD unresponsive to topical ointments should include identification of patients with infection-driven disease and systemic antibiotic treatment of the secondary skin infection in these patients. If symptoms do not settle, then oral CsA should be considered, weaning the dose to maintain control of disease activity. Where CsA is ineffective, antimicrobial therapy should be re-evaluated based on skin swab sensitivities and non-infectious triggers considered. Larger prospective multicentre studies would be useful to confirm and extend these findings with a view to updating the current indications and recommendations for use of CsA in AD.

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