

Retrospective Review of Relapse after Systemic Cyclosporine in Children with Atopic Dermatitis

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Abstract: Cyclosporine is a systemic therapy used for control of severe atopic dermatitis (AD) in children. Although traditionally recommended at a dose of 5 mg/kg/day for 6 months, a longer duration of treatment may be necessary to bring a child with active and severe disease into remission. There are few data on the short- and long-term effectiveness of longer courses of therapy. This was a retrospective chart review of children treated with cyclosporine at a Canadian hospital-affiliated clinic between 2000 and 2013. Fifteen patients with adequate follow-up were identified. Twelve (80%) were male and the mean age at initiation of cyclosporine was 11.2 ± 3.4 years. The mean duration of cyclosporine therapy was 10.9 ± 2.7 months (range 7–15 months) at a starting dose of 2.8 ± 0.6 mg/kg/day. Of 12 patients (80%) who responded to cyclosporine, 5 patients (42%) had relapsed at a follow-up of 22.7 ± 15.0 months. The duration of therapy was longer in patients who did not relapse (17.7 ± 10.7 months) than in those who did (10.2 ± 2.7 months) ($p = 0.06$). Adverse events led to discontinuation in three patients (20%) and included infection-related complications in two patients and reversible renal toxicity in one. These results suggest that a longer duration of low-dose cyclosporine may help decrease the risk of relapse in patients with severe AD who are resistant to topical therapies.

Atopic dermatitis (AD) is a common condition in children, with prevalence rates varying from 8.2% to 10.2% in five large Canadian cities (1). The physical changes of this condition have a great effect on quality of life in children and on family dynamics. Children with AD often have trouble sleeping, which affects their school performance and leads to behavioral

problems. Low self-esteem, anxiety, and bullying further compound the disease burden and lead to social isolation (2). The majority of children with AD can be treated effectively with topical agents, including emollients, moisturizing agents, corticosteroids, and calcineurin inhibitors, but severe AD can be refractory to these modalities, thus systemic immu-

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nosuppressive therapies are occasionally required to control and modify the disease (3).

Cyclosporine is a systemic immunosuppressive drug that acts selectively on T-cells and is indicated for many dermatologic conditions, including dermatitis, psoriasis, and chronic idiopathic pruritus (4). Because the pathophysiology of AD involves T-helper cell 2 (Th2) infiltrates in acute lesions and Th1 cells in chronic states, cyclosporine's mechanism of action can inhibit these activated T-cells (3). Although it is sometimes used for treatment of severe AD in children, data on its effectiveness and safety in this population are scarce and there is almost no information on long-term outcomes.

Our aim was to report on the relapse rate of AD and the time to relapse after treatment with cyclosporine in a pediatric cohort and to determine any predictors of sustained remission. Our secondary objectives were to describe the characteristics and safety outcomes of patients treated with cyclosporine at our facility.

MATERIALS AND METHODS

This was a single-center retrospective cohort study of children at the Hospital for Sick Children, a tertiary health care center in Toronto, Ontario, Canada. Ethics approval was obtained from the Hospital for Sick Children Research Ethics Board. All children prescribed cyclosporine to treat AD from 2000 to 2012 were identified through a medication

search of the clinic electronic database. Patients were excluded from the analysis if there was an absence of follow-up data, they were still receiving cyclosporine, or they had been treated with cyclosporine for <6 months.

Data were collected on patient demographic characteristics, previous documented therapies, and details about cyclosporine treatment courses, with a focus on duration, effectiveness, and safety. The main outcome measure was relapse, defined as a need for systemic therapy after a minimum of 1 month after discontinuation of cyclosporine.

Data were compiled in Microsoft Excel and analyzed using Stata Data Analysis and Statistical Software version 11 (StataCorp, College Station, TX), with a *p* value of 0.05 set for statistical significance. Unpaired *t*-tests were used to compare means of continuous variables and Fisher's exact tests for categorical variables.

RESULTS

Fifteen patients were eligible for analysis, as outlined in Fig. 1. Of these patients, 80% (*n* = 12) were male and the mean age at diagnosis of AD was 4.2 ± 3.9 years. The mean age of initiation of cyclosporine was 11.2 ± 3.4 years. All patients had previously been treated with high-potency steroids, 46.7% (*n* = 7) had tried topical calcineurin inhibitors, and two had been treated with other systemic therapies (methotrexate and ultraviolet B light).

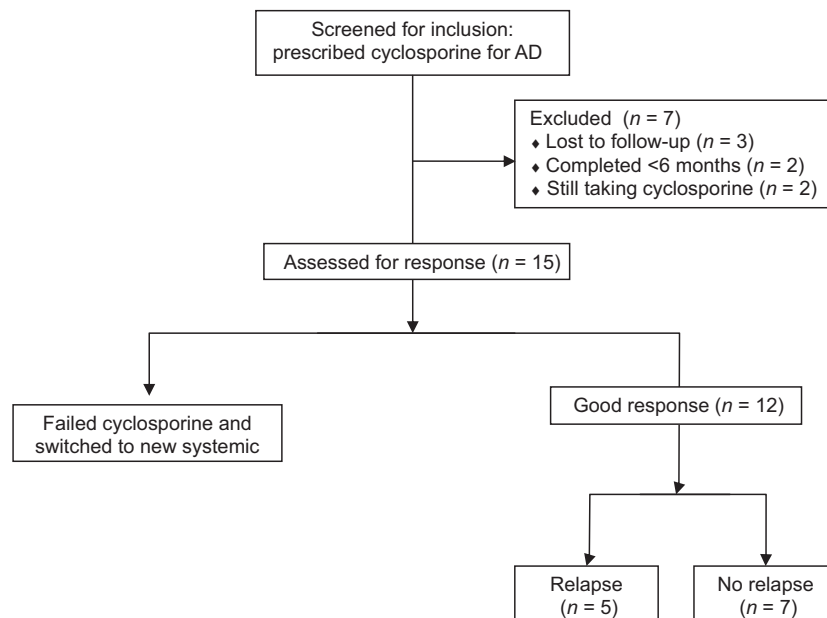


Figure 1. Patient selection.

The average duration of cyclosporine therapy was 10.9 ± 2.7 months (range 7–15 months), at a mean starting dose of 2.8 ± 0.6 mg/kg/day.

Twelve of the 15 patients (80%) had improvement in surface area, intensity, and symptoms of disease after therapy and were in remission when cyclosporine was discontinued. Seven patients (58.3%) remained relapse free for a minimum follow-up of 15 months. Comparative data for the groups are summarized in Table 1. Subsequent systemic therapies for the patients who relapsed are listed in Table 2. The most common treatments were phototherapy, azathioprine, and additional courses of cyclosporine. The time until subsequent therapies ranged from 2 to 12 months.

Six patients (40%) reported adverse events during therapy and four patients discontinued therapy

because of adverse events (Table 3). Patients who reported side effects were younger (mean 9.7 ± 3.4 yrs vs 12.5 ± 3.0 yrs, $p = 0.06$). In the patient with evidence of renal dysfunction, laboratory indices normalized with discontinuation of therapy.

DISCUSSION

Our results suggest that a course of cyclosporine often helps control the manifestations of AD and decreases the need for future systemic therapies in a subset of children resistant to optimized topical therapy. The benefit of cyclosporine in treating severe AD has been demonstrated in several trials with a total of 602 patients, with cyclosporine consistently decreasing disease severity (5), although there is a paucity of data

TABLE 1. Demographic and Clinical Characteristics of Patients With and Without Relapses After Completing a Course of Cyclosporine ($N = 12$)

Characteristic	Relapse ($n = 5$)	No relapse ($n = 7$)	p
Age at diagnosis, years, mean $\pm$ SD (range)	5.1 ± 4.1 (1.5–12)	3.2 ± 2.9 (0–8)	0.80
Age at initiation, years, mean $\pm$ SD (range)	10.2 ± 4.21 (5–15)	10.7 ± 3.7 (6–15)	0.41
Male, %	80	85.7	>0.99*
Initial cyclosporine dose, mg/kg/day, mean $\pm$ SD (range)	2.9 ± 0.6 (2–3.75)	3.0 ± 0.8 (2–4)	0.36
Cyclosporine duration, months, mean $\pm$ SD (range)	10.2 ± 2.7 (7–15)	17.7 ± 10.7 (6–32)	0.06
Taper used to discontinue, %	60	43	>0.99*
Follow-up, months, mean $\pm$ SD (range)	27.2 ± 15.5 (10–50)	23.9 ± 13.5 (15–43)	0.66

*Double-sided Fisher's exact test.

SD, standard deviation.

TABLE 2. Subsequent Therapies in Patients with Relapses ($N = 5$)

Sex	Age at diagnosis of AD, Years	Age at cyclosporine initiation, years	Duration of cyclosporine therapy, months	Subsequent systemic therapies (in chronological order)	Time to subsequent systemic therapy, months
Male	3	9	7	UVB, cyclosporine	12
Female	1.5	14	9	Cyclosporine, methotrexate, UVB	8
Male	5	8	9	Azathioprine, UVB	5
Male	12	15	11	UVB	6
Male	4	5	15	UVB	2

AD, atopic dermatitis; UVB, ultraviolet B.

TABLE 3. Adverse Events ($N = 6$)

Sex	Age at cyclosporine initiation, years	Description of adverse event	Onset after cyclosporine start, months	Duration of cyclosporine therapy, months	Effect of event on cyclosporine treatment
Male	9	Three infections*	2	6	Discontinued
Male	14	Pharyngitis	20	20	Held and not restarted
Female	12	Eczema herpeticum	1	6	No interruption
Male	5	Renal dysfunction†	2	15	Dose reduced then discontinued
Male	9	Stomach upset, headache	24	24	Discontinued
Female	13	Headaches	1	14	No interruption

*Strep throat, cellulitis around a percutaneous gastric feeding tube site, and upper respiratory tract infection due to respiratory syncytial virus.

†High potassium and serum creatinine.

TABLE 4. *Published Studies of Cyclosporine for Atopic Dermatitis in Children*

Author	Year	Study Design	Location	N	Age, years	Dose of cyclosporine, mg/kg/day	Length of treatment	Length of follow-up
Berth-Jones et al (19)	1996	Open uncontrolled	United Kingdom	27	2–16	5	6 wks	10 mos
Zaki et al (20)	1996	Open uncontrolled	United Kingdom	18	3–16	5–6	4–12 wks	Until first relapse (0–8 mos)
Harper et al (6)	2000	Open-label RCT	United Kingdom	43	2–16	5	Continuous (1 yr) vs intermittent (12 wks)	1 yr
Bunikowski et al (12)	2001	Open uncontrolled	Germany	10	2–16	2.5	8 wks	12 wks
Haw et al (11)	2010	Retrospective cohort	Korea	61	9–68	Mean 2.7	Mean 13.5 ± 8.4 mos	Minimum 6 mos

RCT, randomized controlled trial.

on the efficacy and safety of cyclosporine in pediatric AD. The five reviews published to date are summarized in Table 4. None of these studies were based in North America and none examined the sustained remission of patients after cyclosporine was withdrawn. Our study adds longer follow-up times in a purely pediatric North American population.

Most patients had a good immediate response to cyclosporine, and only three did not demonstrate improvement after treatment. These findings are in keeping with evidence of the short-term effectiveness of cyclosporine and reinforce the recommendation of its use as a first-line systemic option in severe AD. The three patients who did not respond were older (13–15 yrs at initiation of cyclosporine), and adherence may have affected efficacy in one patient who admitted missing doses intermittently. Larger cohorts would help determine whether any distinguishing characteristics in these patients could predict resistance.

Almost half of the patients in our cohort did not need further systemic therapy by the end of data collection. Spontaneous resolution of AD is common, especially in children, but the rate of relapse in our cohort is lower than previously reported rates of 75% to 86% in three pediatric and adult studies (6–8). Although a starting dose of 5 mg/kg/day of cyclosporine for a maximum of 6 months has been traditionally recommended (9,10), the lower starting dose and longer duration of cyclosporine treatment in this cohort has previously been shown to be a safe and effective treatment approach (11,12). Patients who did not relapse tended to have longer treatment durations, although the difference was not significant, and the sample was small. It has been proposed that low-dose cyclosporine may have an immunomodulatory effect, in contrast to the immunosuppressive effects of higher doses, based on the observation that lower doses allow continued production of interleukin 2 and thus persisting cell activation with consecutive regulatory

T-cell induction and expansion (13,14). In adults, case reports have suggested that cyclosporine can induce permanent remission in select patients (15,16). A recent review of 167 patients with AD in Korea found that higher doses of cyclosporine were associated with a lower relapse rate, contrary to our findings (17). The difference in our results highlights the need for more data in pediatric populations to evaluate the effect of dose on relapse as well as other predictors such as serum immunoglobulin E levels.

Concern regarding cyclosporine's side effects, including acute and chronic kidney failure, gum hyperplasia, hypertrichosis, hyperkalemia and hypertriglyceridemia, headaches, and paresthesias often limited its use. Although many patients in our sample reported side effects, all were reversible. Regular blood pressure checks revealed that no patient developed hypertension, a common concern with adult patients. Only one patient developed evidence of renal toxicity, and this was reversible with discontinuation of therapy. The incidence of renal toxicity may have been minimized in our population by using a lower dose, because this adverse effect is generally dose and time dependent (10). Concurrent infections are more common with high-dose cyclosporine in the literature, with rates of 5.9% per month compared with 1.8% with low doses (5). Although infections may be coincidental, some recommendations suggest temporary suspension of cyclosporine (9). Eczema herpeticum only occurred in one patient and resolved without therapy disruption, suggesting that this may not be a significant concern. Although the number of infections in our sample seems high (five infections in three patients), when adjusted for the total length of therapy, the incidence of infections was low (2.4% per month) and comparable with that in the existing literature (5). This adds to the appeal of lower-dose therapy, especially in patients more susceptible to infections because of comorbidities.

In general, children have been demonstrated to tolerate cyclosporine better than adults, with a lower incidence of adverse effects (10). In our cohort, children who developed adverse effects tended to be younger, but this difference was not significant. In all five patients who discontinued therapy because of adverse effects, cyclosporine had been taken for many months before stopping (three patients for more than 1 yr). These patients were able to tolerate cyclosporine for many months before stopping, and most of them remained in remission after completing their course of cyclosporine, with only one requiring subsequent systemic therapies.

The long-term risk of malignancy has been associated with cyclosporine, more commonly in people who have undergone organ transplantation who are undergoing lifelong multidrug immunosuppressive treatment. In adults with psoriasis, cyclosporine therapy for more than 2 years was associated with a six times greater risk of nonmelanoma skin cancers (18), but this was still lower than the risk associated with ultraviolet light therapy in this cohort. It is unclear whether this greater risk would be translated to children with AD using lower doses of cyclosporine.

Our study has several limitations, namely the small sample size and the retrospective nature that limited the data available for analysis. In addition, longer follow-up would help clarify whether there is a greater risk of malignancy. Nevertheless, our results are promising, with the data suggesting that a longer course of low-dose cyclosporine may make it more likely that patients will remain in remission after a course of cyclosporine. Future research would help determine whether current cyclosporine protocols should be adapted to optimize long-term outcomes in children with AD.

REFERENCES

1. Wang HY, Pizzichini MM, Becker AB et al. Disparate geographic prevalences of asthma, allergic rhinoconjunctivitis and atopic eczema among adolescents in five Canadian cities. *Pediatr Allergy Immunol* 2010;21:867–877.
2. Krakowski AC, Eichenfield LF, Dohil MA. Management of atopic dermatitis in the pediatric population. *Pediatrics* 2008;122:812–824.
3. Tan A, Gonzalez M. Management of severe atopic dermatitis in children. *J Drugs Dermatol* 2012;11:1158–1165.
4. Amor KT, Ryan C, Menter A. The use of cyclosporine in dermatology: part I. *J Am Acad Dermatol* 2010;63:925–946; quiz 947–948.
5. Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema: a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2007;21:606–619.
6. Harper JI, Ahmed I, Barclay G et al. Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *Br J Dermatol* 2000;142:52–58.
7. Granlund H, Erkkö P, Sinisalo M et al. Cyclosporin in atopic dermatitis: time to relapse and effect of intermittent therapy. *Br J Dermatol* 1995;132:106–112.
8. Atakan N, Erdem C. The efficacy, tolerability and safety of a new oral formulation of Sandimmun—Sandimmun Neoral in severe refractory atopic dermatitis. *J Eur Acad Dermatol Venereol* 1998;11:240–246.
9. Harper JI, Berth-Jones J, Camp RD et al. Cyclosporin for atopic dermatitis in children. *Dermatology* 2001;203:3–6.
10. Ricci G, Dondi A, Patrizi A, Masi M. Systemic therapy of atopic dermatitis in children. *Drugs* 2009;69:297–306.
11. Haw S, Shin MK, Haw CR. The efficacy and safety of long-term oral cyclosporine treatment for patients with atopic dermatitis. *Ann Dermatol* 2010;22:9–15.
12. Bunikowski R, Staab D, Kussebi F et al. Low-dose cyclosporin A microemulsion in children with severe atopic dermatitis: clinical and immunological effects. *Pediatr Allergy Immunol* 2001;12:216–223.
13. Brandt C, Pavlovic V, Radbruch A et al. Low-dose cyclosporine A therapy increases the regulatory T cell population in patients with atopic dermatitis. *Allergy* 2009;64:1588–1596.
14. Baumgrass R, Brandt C, Wegner F et al. Low-dose, but not high-dose, cyclosporin A promotes regulatory T-cell induction, expansion, or both. *J Allergy Clin Immunol* 2010;126:183–184; author reply 184.
15. Sepp N, Fritsch PO. Can cyclosporin A induce permanent remission of atopic dermatitis? *Br J Dermatol* 1993;128:213–216.
16. Wong SS. Permanent remission of severe atopic dermatitis in a Chinese patient after cyclosporin A therapy. *Acta Derm Venereol* 1995;75:168.
17. Roh HS, Kim JE, Ko JY, YS Ro. A retrospective analysis of cyclosporine dose regimens and contributing factors for relapse in atopic dermatitis. *Korean J Dermatol* 2012;50:773–780.
18. Paul CF, Ho VC, McGeown C et al. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. *J Invest Dermatol* 2003;120:211–216.
19. Berth-Jones J, Finlay AY, Zaki I et al. Cyclosporine in severe childhood atopic dermatitis: a multicenter study. *J Am Acad Dermatol* 1996;34:1016–1021.
20. Zaki I, Emerson R, Allen BR. Treatment of severe atopic dermatitis in childhood with cyclosporin. *Br J Dermatol* 1996;135(Suppl 48):21–24.