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SARICAOĞLU, HAYRİYE; YAZICI, SERKAN; ZORLU, ÖZGE; BAŞKAN, EMEL BÜLBÜL; and AYDOĞAN, KENAN (2018) "Cyclosporine-A for severe childhood atopic dermatitis: clinical experience on efficacy and safety profile," Turkish Journal of Medical Sciences: Vol. 48: No. 5, Article 5. https://doi.org/10.3906/sag-1711-7
Available at: https://journals.tubitak.gov.tr/medical/vol48/iss5/5

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Cyclosporine-A for severe childhood atopic dermatitis: clinical experience on efficacy and safety profile

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**Background/aim:** Management of atopic dermatitis (AD) in children is still challenging. The aim of this study was to evaluate the efficacy and safety profile of cyclosporine-A (CsA) treatment in children with severe and recalcitrant AD.

**Materials and methods:** Medical records of 43 children followed between January 2010 and December 2015 and treated with systemic CsA were evaluated retrospectively. Treatment efficacy was assessed according to the physician's global assessment (PGA) score. According to the treatment response, patients were grouped as nonresponder, moderate responder, or good responder. Effects of the variables on treatment response were evaluated by analysis of variance (ANOVA). The safety profile of CsA was assessed by clinical and laboratory findings at each visit.

**Results:** The median initial dose of CsA was 3 mg/kg daily, ranging between 2.5 and 5 mg/kg daily. The mean duration of CsA therapy was 4.9 ± 4.24 months. Seventeen patients (39.5%) achieved good response in a treatment period of 3 to 14 months. After discontinuation of CsA, of the 17 patients, relapse was observed in 4 (23.5%). Moderate response was observed in 12 (27.9%) patients; however, 14 (32.6) patients did not respond to the treatment. Five patients reported mild side effects.

**Conclusion:** Low-dose CsA seems to be an effective and safe treatment option for severe and recalcitrant AD in children.

**Key words:** Atopic dermatitis, cyclosporine-A, treatment

1. **Introduction**

Atopic dermatitis (AD) is a T cell-mediated chronic inflammatory skin disease characterized by relapsing pruritic skin lesions that mostly present in early childhood with an estimated prevalence of 15%–30% in children and 2%–10% in adults (1). Atopic dermatitis is characterized by the complex interaction between multifactorial abnormalities including defects in epidermal barriers, immune dysregulation, and polymorphisms like filaggrin gene mutation. Furthermore, environmental factors have been implicated in the pathogenesis (2,3).

On account of the chronicity of AD, which is mostly seen in childhood, management of AD is still a therapeutic challenge. Restoration of the skin barrier, avoidance of triggers, and reduction of inflammation are aims for the management of AD. Concerning the side effects of systemic therapies in growing children, the majority of patients can be treated effectively with topical agents including emollients, topical corticosteroids, and calcineurin inhibitors or phototherapy with various response rates. However, systemic therapy is required especially in severe and recalcitrant AD, defined as unresponsiveness to conventional topical therapies and phototherapy (4).

Cyclosporine-A (CsA) is an immunosuppressive agent that inhibits calcineurin and blocks T-lymphocyte activation. It has been reported that systemic CsA therapy is as effective and safe in pediatric patients with psoriasis as it is in adults (5). Even though CsA is approved in Europe as a first-line systemic treatment for severe AD in children and adults, data on its efficacy and safety profile in childhood population are scarce (6).

The aim of this study was to evaluate the efficacy and safety profile of CsA treatment in children with severe and recalcitrant AD retrospectively.

2. **Materials and methods**

2.1. **Patients**

Medical records of 43 patients with severe and recalcitrant AD who were under 18 years of age (6–17 years of age) and treated with systemic CsA were retrospectively evaluated. All patients, followed at the tertiary care reference center between January 2010 and December 2015, were admitted...
or referred to us due to severe disease and recalcitrance to conventional therapies. Severe and recalcitrant AD is defined clinically as chronic disease resistant to conventional and adjunctive therapies (6). Patients who did not fulfill the criteria of Hanifin and Rajka were excluded. Patients’ clinic characteristics and demographic features, including age of the patient at the onset of CsA treatment, sex, localization of the lesions, personal and/or family history of atopy, duration of disease, previous therapies and therapeutic parameters of CsA treatment including dosage, duration of therapy, response to therapy, total IgE levels, clinical and laboratory side effects, and follow-up period, were retrieved from medical records. Ethics approval was obtained from the local ethics committee.

2.2. Cyclosporine-A therapy
In accordance with the current literature, disease severity and recalcitrance to conventional therapies (topical steroids, topical calcineurin inhibitors, and phototherapy) were the indications for systemic CsA therapy in patients with AD in our clinic. Written informed parental consent regarding contraindications of CsA, which are uncontrolled infection, malignancy or history of malignancy, abnormal renal or liver function and hypertension, and unauthorized concomitant medication, was obtained. CsA was supplied as capsules containing 25, 50, or 100 mg. Children unable to swallow the capsules were treated with an oral solution containing 100 mg/mL. The initial dose of CsA was between 2.5 to 5 mg/kg daily, given twice daily. The dosage was maintained until the patient substantially improved. In patients with controlled AD, defined as relief of symptoms as mentioned by the patient, and satisfactory results as reported by the physician, the CsA dose was gradually tapered by 0.5 to 1 mg/kg daily every 2 to 4 weeks according to the therapeutic response. After the initiation of CsA therapy, patients were followed closely with examinations every 2 weeks for the first month and thereafter once a month as suggested (5). All clinical and laboratory side effects were assessed at each visit. Concomitant emollients and topical therapies were permitted during CsA therapy as reported in previous reports (1,10–16). Emollients and topical steroids were permitted during CsA therapy. In patients who had been given phototherapy, CsA therapy was started after a washout period of at least 6 weeks.

2.3. Side effects
Side effects were assessed at each visit. The assessment of side effects included physical examination, blood pressure measurement, full blood count, serum urea, creatinine, electrolytes, magnesium, cholesterol and triglycerides levels, and urine osmolality. Any complaints that were considered to be a clinical adverse effect of CsA were also reported. Serum creatinine levels and blood pressure (BP) were assessed at baseline and at each visit during the follow-up period of therapy. According to our treatment protocol, the CsA dose was reduced or treatment was discontinued if serum creatinine levels were elevated more than 30% above the patient's baseline level on two consecutive occasions, even if the serum creatinine level was still within the normal range as recommended.

2.4. Assessment of treatment response
Treatment efficacy was evaluated retrospectively from the medical records of the patients according to the physician’s global assessment (PGA) scores. Seeing that multitem scales are not routinely used in daily clinical practice, we applied a global assessment on an ordinal scale to measure the clinical response. The PGA is an overall assessment from 0 to 5 of a patient's eczema, evaluating the quality and extent of the lesions relative to the baseline assessment (0 = clear (100%), 1 = almost clear (90% to 99% improvement), 2 = marked improvement (50% to 89%), 3 = modest improvement (<50%), 4 = no change, and 5 = worse). Treatment response was grouped as good response: patients successfully treated (PGA score of 0–2); moderate response: patients with moderate improvement (PGA score of 3); or failure of treatment: no improvement (PGA score of 4–5). Controlled AD was defined as relief of AD symptoms as mentioned by the patient and a satisfactory result as reported by the physician (7).

2.5. Follow-up after discontinuation of cyclosporine-A treatment
In the good to moderate outcome groups, we considered disease to be in clinical remission when the disease was cleared away or could be controlled with topical therapy (moderately potent steroids) and improvement lasted at least 3 months. After discontinuation of CsA therapy, relapse was declared if an exacerbation of clinical symptoms at baseline severity occurred within 3 months, and rebound was declared if an exacerbation of eczema more severe than that at baseline occurred.

2.6. Statistical analysis
SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. Data were summarized and organized in tables. They were analyzed by using descriptive statistics, given as mean ± standard deviation (SD), median, range (minimum–maximum), and percentage. Effects of variables on treatment response including presence of family history of atopy, duration of disease, initial dose, and duration of CsA therapy were evaluated by analysis of variance (ANOVA). P < 0.05 was considered statistically significant.

3. Results
3.1. Demographic features
A total of 43 children were treated with systemic CsA (capsule or oral solution) with the diagnosis of severe and recalcitrant atopic dermatitis. Of the patients, 24 were male and 19 were female. The age of the patients during
CsA treatment ranged from 6 to 17 years (mean: 10.94 ± 4.48 years). A positive family history of atopy was found in 10 (23%) patients. The median total IgE level was 336.5 (21.2–6126.0) kU/L. All patients had been previously treated with emollients, topical corticosteroids, and topical calcineurin inhibitors, and 8 of them were treated with phototherapy (7 with narrow-band UVB and 1 with UVA-1). The demographic and clinical features of the patients are summarized in Table 1. Baseline BP measurement, serum creatinine, urinalysis, complete blood cell count, and renal and liver function tests were all within normal limits in all patients. None of the patients had a history of an infectious disease as a trigger.

3.2. Therapeutic parameters of cyclosporine-A

The median initial dose of CsA was 3 mg/kg daily (range: 2.5–5). The mean duration of CsA therapy was 4.9 ± 4.24 months. The therapeutic parameters are presented in Table 1. Seventeen patients (39.5%) achieved good response in a treatment period that varied between 3 and 14 months. Fourteen patients who did not respond to CsA were treated for 3 months or less. Treatment duration varied between 3 and 18 months with a mean of 7.01 ± 3.96 months and the median was 6 months in patients with moderate to good response. The mean duration of the disease was 2.71 months, 7.25 months, and 6.18 months in the nonresponder, moderate responder, and good responder groups, respectively. Moreover, the mean duration of CsA therapy was 2.64 months in the nonresponder group, but 4.33 months in moderate responders and 7.44 months in good responders. The associations between the duration of treatment and the treatment response (P = 0.04) and the duration of disease and the treatment response (P = 0.046) were statistically significant and may be attributable to the small sample size. There was no other statistically significant difference regarding criteria including family history of atopy, initial dose of CsA therapy, age at the onset of disease, sex, and total IgE levels between good, moderate, and nonresponder groups.

3.3. Follow-up

Four of the 17 patients who were in the good responders group relapsed. One of them relapsed within a month and 2 within a year after discontinuation of CsA therapy. The other patient was lost to follow-up. We did not find any statistically significant difference regarding the duration of the disease, duration of the treatment, and dose of CsA between relapsed and nonrelapsed groups. Two of 14 patients who did not respond to CsA were given CsA (3–4 mg/kg daily) again for 3 months with moderate response. In the nonresponder group, CsA therapy was stopped due to nonadherence to treatment in 3 patients. In the other patients who were unresponsive to CsA therapy, CsA was switched to systemic steroid or methotrexate therapy with variable response rates. Five patients (11.6%) reported mild to moderate tolerable side effects including dyspepsia, hypertrichosis, sore gums, and flu-like symptoms. Renal and/or hepatic dysfunction was not observed in any patients.

| Table 1. Demographic and clinical features of the patients and cyclosporine-A (CsA) therapeutic parameters. |
|-------------------------------------------------|
| n                              | 43                                      |
| Sex, n (%)                      |                                         |
| Male                           | 24 (55.8%)                              |
| Female                         | 19 (44.2%)                              |
| Age at onset of CsA therapy, years | 10.94 ± 4.48                           |
| Mean ± SD                      | 12; 6–17                                |
| Median; min–max                |                                         |
| Lesion localizations, n (%)     |                                         |
| Flexural                       | 8 (18.6%)                               |
| Trunk and extremities          | 25 (58.1%)                              |
| Generalized                    | 10 (23.3%)                              |
| Duration of disease, years     | 5.34 ± 5.03                             |
| Mean ± SD                      | 3.0; 1–17                               |
| Median; min–max                |                                         |
| IgE levels (kU/L)              | 965.9 ± 1483.8                          |
| Mean ± SD                      | 336.5; 21.2–6126.0                      |
| Median; min–max                |                                         |
| Family history of atopy, n (%) | 10 (23.3%)                              |
| Initial dose of CsA therapy, mg/kg daily | 3.26 ± 0.76                           |
| Mean ± SD                      | 3; 2.5–5                                |
| Median; min–max                |                                         |
| Duration of CsA therapy, months | 4.9 ± 4.24                             |
| Mean ± SD                      | 4.0; 1.0–18.0                           |
| Median; min–max                |                                         |
| Response to therapy, n (%)     | 17 (39.5%)                              |
| Good responder                 | 12 (27.9%)                              |
| Moderate responder             | 14 (32.6%)                              |
| Nonresponder                   |                                         |
| Follow-up (n = 17), n (%)      | 13 (76.5%)                              |
| Complete remission             | 4 (23.5%)                               |
| Relapse                        | 5 (11.6%)                               |
| Adverse effects, n (%)         | 1 (2.3%)                                |
| Dyspepsia                      | 2 (4.7%)                                |
| Sore gums                      | 1 (2.3%)                                |
| Hypertrichosis                 |                                         |
| Flu-like symptoms              |                                         |

SD, Standard deviation
4. Discussion
Data on the efficacy and safety of CsA in the childhood population are scarce. Therefore, CsA should only be used in severe and recalcitrant cases and only if there is a significant negative impact on the patient’s quality of life. A review of the literature revealed a total of eight articles including one of an open-label randomized controlled trial regarding the use of CsA in pediatric patients with AD with varied good remission rates, ranging between 11% and 95% (Table 2) (8–15). The initial dose of CsA has

| Author                  | Year | Study design     | Number of cases, n | Dosage, mg/kg daily | Duration, months | Response                              | Adverse effects                                                                 |
|-------------------------|------|------------------|--------------------|---------------------|-----------------|----------------------------------------|---------------------------------------------------------------------------------|
| Berth-Jones et al. (8)  | 1996 | OUC              | 27                 | 5                   | 1.5             | Complete remission 81.5%               | Headache (7), abdominal pain (6), nausea (4)                                      |
| Zaki et al. (9)         | 1996 | OUC              | 18                 | 5–6                 | 1–3             | Good or very good response 89%         | Nausea (1)                                                                      |
| Harper et al. (10)      | 2000 | Open-label RCT   | 43                 | 5                   | Continuous (12mos) vs intermittent (3mos) | Good or very good clinical response ≥75% | Rhinitis (19), infected eczema (15), bronchospasm (13), *URTI (13), headache (9), folliculitis (1) |
| Bunikowski et al. (11)  | 2001 | OUC              | 10                 | 2.5–5               | 2               | Significant improvement 90%           | Elevated creatinine (1), elevated bilirubin (1)                                    |
| Haws et al. (12)        | 2010 | Retrospective cohort | 13               | Mean 2.7            | Mean 13.5       | Prolonged remission 95%               | Hypertension (8), renal dysfunction (1), nausea and abdominal discomfort (3), hypertrichosis (1) |
| Sibbald et al. (13)     | 2015 | Retrospective cohort | 15               | Mean 2.8            | Mean 10.9       | Complete remission 80%               | Headache (1), dyspepsia (1), eczema herpeticum (1), renal dysfunction (1), pharyngitis (1), three infections (1) |
| Beaumont et al. (14)    | 2012 | Retrospective cohort | 35               | 5                   | 5               | Complete remission (11%)             | Eczema herpeticum (1)                                                        |
| Hernandez-Martin et al. (15) | 2016 | Retrospective cohort | 63               | Mean 4.27           | Median 4.6      | Good to excellent response (64%)      | Hypertrichosis (33), gingival hypertrophy (14), hyperazotemia (5), headache (4), muscle cramps (2), elevated creatinine (1), tremors (1) |
| Present study           |      | Retrospective cohort | 43               | Mean 3.26           | Mean 4.9        | Good responder (39.5%)                | Dyspepsia (1), sore gums (2), hypertrichosis (1), flu-like symptoms (1)         |

OUC, Open uncontrolled; RCT, randomized controlled trial; *URTI, upper respiratory tract infections.
been varied between 2 and 5–6 mg/kg daily. Two different CsA doses have been used, low doses (2–3 mg/kg daily) and high doses (5–6 mg/kg daily). It has been reported that high doses achieve a faster response. Sibbald et al. (13) suggested that longer duration of low-dose cyclosporine may help decrease the risk of relapse. Our initial doses of CsA (2.5–5 mg/kg daily) were similar to the doses used in previous reports. We suggest that faster responses may be achieved with higher doses of CsA.

The treatment duration is still inconclusive. A starting dose of 5 mg/kg daily of CsA for a maximum of 6 months has been traditionally recommended, but in the literature, two different treatment regimens, which were multiple short courses and continuous therapy, were compared. Harper et al. (10) reported that almost 50% clinical remission was observed in most patients who were given short-term (multiple courses of 12 weeks) and 5 mg/kg daily of CsA. Furthermore, the authors suggested that CsA is effective for controlling severe AD in children over a 1-year period and is well tolerated. The authors observed that a short course of therapy was adequate for some patients, and also reduced the cumulative exposure to the drug. Nonetheless, they concluded that duration of treatment (mean duration of therapy varied between 1.5 and 13.5 months) should be tailored according to the patients' needs (10). It is noteworthy that the reports in which CsA was used for less than 3 months were published before 2000 (8,9,11). This may be explained by limited experience of CsA use because of concern about potential side effects. Hijnen et al. (7) reported that CsA was an effective treatment option for recalcitrant cases with a dose of 2.5–5 mg/kg daily with more than a 7-year safety profile. We observed that 39.5% of the patients achieved good responses in a period that varied up to 14 months. There are limited data about variables impacting treatment response. Although Hernandez-Martin et al. (15) reported that poor outcome did not show a statistically significant association with mean dosage or duration of therapy, we found statistically significant associations of both duration of treatment and duration of disease with treatment response (P = 0.04, P = 0.046, respectively). Increase in clinical response rates with longer durations of CsA therapy indicates that long-term therapy with lower CsA doses is an effective treatment method in severe AD, compatible with the findings of Haws et al. (12) and Sibbald et al. (13). Better clinical responses in patients with longer duration of disease may predict that higher doses of CsA are needed in the management of acute severe disease. Although Bunikowski et al. (11) reported that the therapeutic effect of low-dose CsA was independent of the patients' baseline clinical disease severity, Hamid et al. (16) reported that acute AD skin lesions expressed a higher number of inflammatory cells than observed in chronic AD skin lesions. It is evident that acute severe disease needs a more aggressive approach, as in our observation.

Relapse was observed in 4/17 (24%) patients after discontinuation of CsA, which was similar to what Hijnen et al. (7) reported (34%). We realized that 14 patients who did not respond to CsA were treated for 3 months or less. Those cases being unresponsive may be ascribed to the short course of treatment. Long remission after withdrawal of treatment was seen in some patients, although most relapsed within a few weeks.

It is proposed that children tolerate CsA better than adults and the incidence of side effects is lower in children (17). In our study, only five patients (11.6%) reported side effects, which were tolerable. All side effects were similar to those of previous reports and no serious organ toxicity was observed. Haws et al. (12) reported that the development of adverse events was related to a higher initial dose of CsA. Only one patient discontinued therapy because of reversible hypertrichosis.

Studies reported that the pharmacokinetics of CsA may be different in children compared to adults, as children generally have higher CsA clearance rates and absorption of CsA is reduced in young children (18). According to the literature, CsA is suggested to be an effective treatment for pediatric patients with AD at the same dose that is used in adult patients with psoriasis (5). In our experience and also based on previous research, clinical improvement is rapid and generally occurs within the first few weeks of CsA therapy.

Our study has several limitations. Owing to the retrospective nature of this study, available data for analysis were limited. In addition, our sample size was small, and the limited follow-up prevented us from making any definite conclusions about the remission length and long-term safety of CsA treatment.

In conclusion, we suggest that low-dose CsA is an effective and safe treatment option for children with severe and recalcitrant AD. However, higher doses may be required in acute and severe disease. Further prospective and controlled studies with large sample sizes are required to confirm and extend these findings and recommendations for use of CsA in AD.
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