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CYCLOSPORINE A FOR SEVERE ATOPIC DERMATITIS IN CHILDREN. EFFICACY AND SAFETY IN A RETROSPECTIVE STUDY OF 63 PATIENTS

Running head: Cyclosporin A for atopic dermatitis in children. A series of 63 cases

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ABSTRACT

BACKGROUND: Cyclosporin A (CSA) is an immunosuppressant agent widely used in severe atopic dermatitis (AD). However, experience in children is limited.

OBJECTIVES: To assess the efficacy and adverse events of CSA therapy in children.

METHODS: Retrospective study of children with severe AD treated with CSA between January 2009 and December 2015.

RESULTS: Data from 63 patients were collected. Mean age at the beginning of treatment was 8.4 years (± 3.6). The median starting dose was 4.27 (± 0.61) mg/kg/day. After four weeks of treatment, the outcome was excellent in 35% of cases, good in 29%, and poor in 36% of the patients. The response was better in patients without eosinophilia ($p < 0.05$). The median duration of treatment was 4.6 months (range 1.5-21.6). Side effects were frequent but mild, being more common in patients after longer treatment periods ($p < 0.05$). Mean time of follow-up was 19.4 months (± 12.7). Prolonged remission (> 6 months) was observed in 13 patients (20%).

LIMITS: This is a retrospective review. The follow-up period is limited.

CONCLUSIONS: Our data confirm that CSA is efficacious and acts rapidly in the majority of children with severe AD. CSA therapy can provide sustained remission in some patients. CSA seems to be well tolerated in children, but strict monitoring is mandatory.

Keywords: Cyclosporin A, atopic dermatitis, atopic eczema, immunosuppressant treatment, children

INTRODUCTION

Cyclosporin A (CSA) is a calcineurin inhibitor immunosuppressant agent widely used for the treatment of severe atopic dermatitis (AD) unresponsive to conventional topical therapy both in adults and children¹. CSA is well tolerated in the majority of patients with AD. Its most frequent complication is nephrotoxicity (hypertension, hyperuricemia, hyperkalemia, hypomagnesemia, renal dysfunction and renal failure), which is dose- and time-related. Other adverse effects include gastrointestinal disturbances, liver abnormalities, hypertrichosis, gingival hypertrophy, trembling, headache, paresthesia, myalgia, arthralgia, asthenia and hyperlipidemia, increased risk of opportunistic infections, tuberculosis reactivation and, in the long-term therapy, increased risk of malignancy². The risk increases with increasing dose and duration of CSA therapy and therefore continuous long-term treatment is not recommended in AD.

Although children seem to have a better tolerance against potential CSA side effects^{1, 2}, its use in the pediatric population is still limited. No clear guidelines exist for monitoring adverse effects in this age group; therefore, its administration is reserved to severe AD cases refractory to topical therapies.

OBJECTIVES

To assess the efficacy and side effect profile of CSA in children with severe AD.

PATIENTS AND METHODS

We performed a single-center retrospective observational cohort study of 63 children with severe AD treated with CSA at the Hospital Infantil Niño Jesús of Madrid, Spain from January 2009 through December 2015. Our centre is a Tertiary hospital that receives nationwide patients referred both by pediatricians and dermatologists. Approval from our institutional Ethics Committee and board review was obtained. Children were identified by searching in our electronic databases those children with AD who had attended both Dermatology and Nephrology Clinics during that period. All patients fulfilled Hanifin and Rafka's clinical

criteria of AD³ and showed severe involvement defined as extensive AD refractory to topical steroid therapy affecting children's quality of life. Topical therapy was considered unsuccessful when regular use of moderately potent corticosteroids (class 3) applied twice daily or with the wet-wrap technique did not gain control of the disease. Oral CSA was the first line of immunosuppressive therapy in 60/63 patients. Although no immunosuppressant agent has been licensed to treat severe AD in children, CSA has been approved by the European Medicines Agency for severe AD in adults, favoring its choice. Patients with kidney or liver disease, high blood pressure, systemic infections, immunosuppression or history of malignancy were excluded. Patients were allowed to use topical steroids while on CSA treatment and all of them were assessed monthly in the Dermatology and Nephrology departments by protocol.

Patient demographics included sex, age of onset of AD, age at initiation of treatment, personal history of asthma and/or food allergy (the latter was defined as the presence of a particular food specific IgE levels greater than 95% the positive predictive value), total IgE levels and blood eosinophilia (defined as peripheral eosinophilia higher than >500 eosinophils/ μ L). Drug variables were starting dose of CSA and length of treatment. Outcome measures included clinical response after four weeks of therapy, long-term efficacy (time to relapse and disease-free period after CSA withdrawal) and adverse effect profile. Given that multi-item severity scales are not routinely used in daily practice, to measure clinical response we applied a global assessment on an ordinal scale (*Physician global assessment score* (PGA)⁴), rating overall eczema severity on a 0-5 scale as 0 = clear (100% improvement), 1 = almost clear (90-99% improvement), 2 = mild (50-89% improvement), 3 = very mild improvement (< 50%); 4= without changes, and 5= worse. Based on this ordinal scale we grouped the patients' clinical outcomes in three categorical variables: excellent outcome (0-1), good outcome (2), and poor outcome (3-5).). The outcome was assessed by the dermatologist in charge of each patient and was collected retrospectively. In the good to excellent outcome groups we considered disease in remission when the disease was either cleared or could be controlled with topical therapy (moderately potent steroids/immunomodulators), and recurrence when flares required another course of systemic immunosuppressant therapy.

The assessment of side effects included physical examination, blood pressure measurement, full blood count, serum urea, creatinine, electrolytes, magnesium, uric acid, bilirubin, cholesterol and triglycerides levels, and urine osmolarity. Normal ranges were adjusted according to age and weight of the patients. Any complaints that might be considered a clinical adverse effect of CSA were also reported. Blood pressure was evaluated in a standardized manner and hypertension was considered when values were at or above the 95th percentile after converting systolic and diastolic values to age-, sex-, and height-specific percentiles⁵. Serum creatinine increases below 30% of baseline (or values returned to less than baseline value plus 30% in two weeks) were considered mild and did not require treatment modification.

Statistical analysis

Data are expressed as mean (standard deviation, SD) or as median (range) when the values did not meet the criteria of normal distribution. We evaluated differences between means using student's T-test or Mann-Whitney when variables were not normally distributed. Chi square test or Fisher's exact test were used to determine the association between qualitative variables. The strength of association was assessed using odds ratios. A multivariate logistic regression model for variables with $p < 0.20$ was built. All analyses were performed using SPSS for Windows, version 22 (IBM® SPSS® Statistics). P-values < 0.05 were considered statistically significant.

RESULTS

Data were collected from 63 patients (27 females and 36 males). Their demographic data, drug-related variables and interaction with outcome measures are shown in Table 1. Mean age at starting therapy was 8.4 years (± 3.6). Median starting dose was 4.3 mg/kg/day (± 0.61) given orally in two divided doses. Median length of treatment was 4.6 months (range 1.5-21.6). After four weeks of treatment, outcome was excellent in 35%, good in 29% and poor in 36% of patients (Figure 1). In those with poor outcome in whom CSA was maintained for at least three months, no substantial outcome improvement was observed. CSA was tapered in 45 patients (71%) and stopped in 11 patients (19%). Data was missing in 7

patients. Poor outcome did not show statistically significant association with mean dosage or duration of treatment or the way of CSA withdrawing.

Blood eosinophilia at baseline was present in 80% of patients (70% between 500-1500 Eo/ μ L, 10% >1500 Eo/ μ L). Outcome in patients without blood eosinophilia was significantly better (92% of patients without eosinophilia showed good or excellent outcome while only 58% of patients with eosinophilia had a similarly satisfactory outcome) ($p < 0.05$). Food allergy was found in 24 of 62 patients (Table 1S, supplementary material), but only patients with egg allergy showed a statistically significant association with poor outcome ($p < 0.01$). Fifteen out of 17 patients allergic to egg also had eosinophilia. In a multivariate logistic regression only the absence of egg allergy showed a statistical significance for good to excellent response (OR 5.5 (1.5–20.2), $p = 0.01$) but not eosinophilia (OR 6.5 (0.7–57.4), $p = 0.1$). Outcome and other demographic characteristics were not significantly associated.

Mean time of follow-up of the group of good and excellent responders was 19.4 months (± 12.7). Prolonged remission (>6 months, with a range of 6 to 33 months) was observed in 9 non-relapsing patients (Figure 1). Five patients were still on CSA treatment at the end of this study, and were excluded from the final count of recurrences/disease-free period patients.

Side effects were recorded in 70% of patients. Hypertrichosis and gingival hypertrophy were the most frequent findings (52% and 22% respectively) whereas no patient showed proteinuria or hypertension (Table 2). The appearance of hypertrichosis and gingival hypertrophy was statistically significant associated with a longer time of treatment ($p < 0.05$). No patient showed concurrent severe infection requiring CSA therapy interruption or withdrawal. Four patients required CSA cessation: one for a combination of important asthenia and poor outcome, one for worsening of preexisting headaches and two more due to mild hyposthenuria (318 mOsm/kg) and urea increase (59 mmol/l, normal value <50). The appearance of side effects was significantly associated with a longer time of treatment ($p < 0.05$) (Table 2S, supplementary material). All side-effects resolved within a month after CSA withdrawal.

DISCUSSION

While everybody caring for a child with severe AD wants to alleviate his suffering, it is inevitable to fear systemic immunosuppressant side effects. In this scenario, the most frequently asked questions by parents and caregivers are 1) *is this strong treatment going to be effective in my child?*; 2) *for how long will my child be on CSA?*, 3) *what are the side effects of CSA?*, and 4) *what will it happen after CSA withdrawal?* This is the largest series of children with severe AD CSA-treated that has been published so far, allowing us to draw valuable conclusions about the efficacy and tolerability of CSA and making it possible to provide reliable answers to these uncertainties.

According to our results and in agreement with prior studies that assessed the efficacy and tolerability of CSA in children with severe AD⁶⁻¹¹, most patients will show a good to excellent response shortly after initiating CSA therapy with a very low incidence of severe side effects. We observed a good to excellent outcome in 64% of our patients, a slightly lower figure than previously reported in other studies^{6, 8-10} (Table 3). However, as it has been pointed out recently, global assessment on severity scales in AD lack standardized definitions making it difficult to compare studies¹². Also, the smaller size of these series may account for the outcome differences. It is clear though that CSA therapy shows satisfactory results in the majority of patients with severe AD. In agreement with other studies, side-effects in our series were mostly mild.

Assessed drug-related variables were CSA dosage and length of treatment. We did not find a statistically significant association with either outcome or relapse rate. Two main different CSA dosage regimens have proven equally efficacious, low doses (2-3 mg/kg/day) and high doses (5 mg/Kg/day)^{7, 8, 13}, the latter seeming to achieve a faster response^{1, 14}. On a mean dose of 4.27 mg/kg/day, patients with a good or excellent outcome showed a rapid response after only 4 weeks of treatment. Prompt response in 2 to 4 weeks of starting CSA treatment was also found in other studies^{6-8, 10}. Interestingly, we observed that in those patients with poor outcome in whom CSA was maintained for longer than 4 weeks, no substantial outcome improvement was observed over time. This finding is of particular relevance when making the decision as to whether or not to continue CSA therapy when the patient fails to show quick satisfactory results.

Ideally, associated findings might help us to predict which patients will show a better response. We assessed patients' demographic characteristics and biologic markers but failed to show any statistically significant association with outcome except for the presence of blood eosinophilia at baseline or egg allergy, which were independently associated with a poor outcome ($p>0.05$). Blood eosinophilia is a frequent unspecific finding in children with AD¹⁵, and correlates in some studies with disease severity but not necessarily in every patient¹⁶. Also, it has been shown that egg allergy is a predictive factor for more persistent AD¹⁷, that severe AD can be a precursor of food allergy¹⁸ and that peripheral eosinophilia occurs with an associated allergic sensitization in children¹⁹. However, although peripheral eosinophilia and egg allergy seem to be related to a more severe AD course, we cannot explain why this subset of children responded worse to CSA therapy. To our knowledge, this issue has never been raised before and we do not know whether children with egg allergy might benefit from a different immunosuppressant agent.

Different relapse rates after CSA withdrawal ranging from 42% to 100% have been reported in children⁶⁻¹¹. Thirty-six out of 41 patients who responded well had withdrawn CSA therapy at the end of our study; 19 of them relapsed after CSA cessation, while the remaining 17 could manage their disease with topical treatments after CSA withdrawal. All but one⁹ of the other pediatric series reported a remarkably higher relapse rate^{6-8, 10, 11}. However, some of our patients still had a short follow-up and the relapse rate could change over time. Notably, 4 patients relapsed 6 months after withdrawing CSA therapy and 9 more demonstrated a sustained remission 6 months after CSA cessation, meaning that in at least 13 patients (20% of the total) CSA induced sustained disease remission. In agreement with our results, three other pediatric series showed prolonged remission in some patients^{6, 8, 10} and therefore, such possibility should be kept in mind, as already pointed out by other authors^{4, 20}.

The main CSA drawback is dose-dependent nephrotoxicity²¹. Acute nephrotoxicity appears during the first weeks or months of treatment and is reversible after lowering the dose or withdrawing CSA, while chronic nephrotoxicity usually occurs from the first year of treatment and is associated with irreversible damage to the kidneys due to tubular atrophy and interstitial fibrosis. In children, CSA is well tolerated and the profile of adverse effects in our series is comparable with other studies^{6, 7, 9, 10}. Only two of our patients needed to

withdraw from treatment due to pronounced clinical side effects (headache and asthenia) but neither showed relevant analytical anomalies. Two more who presented mild hyposthenuria (318 mOsm/kg) and urea increase (59 mmol/l, normal value <50) could have been maintained on CSA under strict monitoring.

Our study has some limitations. First, this is a retrospective study and some data are missing. Thus, there may be an underestimation of the reported adverse events if patients were not actively asked for all possible side-effects. Second, we do not have an individual score of each patient prior to treatment, and therefore some of them showing good to excellent response might have had a milder AD at baseline than the ones showing a worse outcome. However, all patients fulfilled the same clinical criteria of AD severity. Also, the PGA was retrospectively performed and could not be validated. Third, the limited follow-up prevents us from making any definite conclusions about the remission length and long-term safety of CSA treatment.

In conclusion, our results along with the review of the literature allow us to answer the questions most frequently asked by parents and caregivers before starting CSA treatment (Table 4). Our data confirm the efficacy and tolerability of CSA in the treatment of severe AD in children. CSA shows an excellent to good response in the majority of patients with severe AD refractory to topical treatment and can provide sustained remission in up to 20% of them. Although CSA seems to have no serious adverse effects in children in the short term, strict monitoring in this group age is mandatory.

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LEGENDS

Figure 1. Outcome, relapse rate and disease-free period after CSA withdrawal in our series of patients.

Table 1. Patients' demographic data. drug-related variables and interaction with clinical outcome.

	Total N (%)	Poor outcome	Good to excellent outcome	p
Patients	63 (100)	22 (34.9)	41 (65.1)	
Sex Male / Female	36 (57.1) / 27 (42.9)	11 (30.6) / 11 (40.7)	25 (69.4) / 16 (59.3)	0.4
Age at AD onset Median (Range)	0.5 (0 – 9)	0.55 (0 – 9)	0.5 (0 -3.5)	0.68
Blood eosinophilia * > 500 / < 500 Eo/ μ L	12 (19.4) / 50 (80.6)	1 (8.3) / 21 (42)	11 (91.7) / 29 (58)	0.04
Food allergy No / Yes	38 (61.3) / 24 (38.7)	10 (26.3) / 12 (50)	28 (73.7) / 12 (50)	0.06
Egg Allergy * No / Yes	44 (72.1) / 17 (27.9)	11 (25) / 11 (64.7)	33 (75) / 6 (35.3)	0.004
Asthma No / Yes	36 (57.1) / 27 (42.9)	14 (38.9) / 8(29.6)	22 (61.1) / 19 (70.4)	0.59
Age at CSA initiation (months) Mean (DT)	8.4 (3.6)	8.4 (4.2)	8.4 (3.3)	1
Time of disease evolution (years) Mean (DT)	7.3 (4.0)	6.8 (4.5)	7.5 (3.8)	1
Treatment length (months) Median (range)	4.7 (1.5 – 21.6)	3.9 (1.5 – 21.6)	5.3 (2.8 – 21)	0.09
Starting dose (mg/kg/day) Median (range)	4.2 (2.6 – 5.8)	4.0 (3.0 – 5.0)	4.4 (2.6 – 5.8)	0.09

*P-values <0.05 were considered statistically significant.

Table 2. Most frequent side effects in our series of 63 patients.

Hypertrichosis	33 (52%)
Gingival hyperthrophy	14 (22%)
Hyperazotemia	5 (8%)
Asthenia	5 (8%)
Decrease osmolarity	4 (6%)
Headache	4 (6%)
Muscle cramps	2 (3%)
Elevated creatinine	1 (1.5%)
Tremors	1 (1.5%)
Hypertension	None
Proteinuria	None

Table 3. Summary of main data in studies of CSA in children with severe AD

	Berth-Jones ⁶	Zaki ¹⁰	Harper ¹⁴	Bunikowski ⁷	Haw ¹¹	Sibbald ⁹	Our study
Study type	Prospective	NS	Prospective	Prospective	Retrospective	Retrospective	Retrospective
N	27	18	40	10	13	15	63
Age	2-16	3-16	2-16	2-16	5-14	5-15	8.4 ±3.6 yr.
Dosage	5 mg/kg/d	5-6 mg/kg/d	5 mg/kg/d	2.5 mg/kg/d	Mean 2.7 mg/kg/d	Mean 2.8 mg/kg/d	Mean 4.27 mg/kg/d
Length of treatment	6 weeks	4-12 weeks	1 year (continuous) vs 3 months (intermittent)	8 weeks	Mean 13.5 ± 8.4 months	Mean 10.9 ±2.7 months (1.5-21.6)	Median 4.6 months (1.5-21.6)
Time to efficacy assessment	6 weeks	NS	12 weeks	8 weeks	6 months	NS	4 weeks
Outcome	Complete or marked improvement 22/27 (81%)	Good to excellent 16/18 (88%)	Good or very good 30/40 (75%) (no statistically significant differences between groups)	Decrease of 50% of affected body surface in 9/10	Decrease of the mean SCORAD in all patients	Good 12/15 (80%)	Good to excellent 40/63 (64%)
Relapse	17/20 (85%)	16/18 (89%)	Continuous regimen: NS Short course: 17/19 (89%)	7/9 (78%)	100%	5/12 (42%)	21/40 (51%)

Disease-free period	Up to 6 months in 3 (11%) patients	Up to six months in 2 (11%) patients	Continuous regimen: NS Short course: 3 pts with sustained remission after a 3-month course (9%)	4 weeks	4.5±2.9 months	Min 15 months	Up to 6 months in 9 (14%) pts
Follow-up	10 months	Max 8 months	1 year	3 months	Min 6 months	Min 15 months	Up to 21 months
Side effects	Mild	Mild	57% mild. 37% moderate. 6% severe	Mild	Mild/moderate	Mild	Mild

Table 4. Answers to the questions most commonly asked by parents and caregivers before starting CSA treatment in a child with severe AD

- ☐ *Is this strong treatment going to be effective in my child?*

The majority of children with severe AD will show good to excellent results with CSA treatment (particularly if they do not have blood eosinophilia or egg allergy).

- ☐ *For how long will my child be on CSA?*

CSA acts rapidly, improving AD significantly in four weeks in those cases with good to excellent response.

- ☐ *Does it have important side effects?*

CSA is well tolerated and adverse effects are usually mild (but need to be strictly monitored).

- ☐ *What will happen after CSA withdrawal?*

CSA does not cure AD and most patients will relapse after CSA withdrawal, but some of them will show a sustained remission for longer than 6 months.

