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RESEARCH ARTICLE

Systemic treatment for severe atopic dermatitis in children: a case series

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Abstract

Background: *Atopic dermatitis (AD) is children's most frequent chronic inflammatory skin disease. In most patients, this condition is controlled with topical treatments; however, some patients with severe AD do not respond to these treatments, requiring systemic therapy. There is insufficient information about the ideal dose, time of use, clinical response, and safety of systemic therapy in children with severe AD. This study described the clinical characteristics of patients with severe AD who required systemic treatment, drugs used, their clinical course, adverse effects, and associated complications.* **Methods:** *We conducted a retrospective review of the records of pediatric patients with severe AD treated in the Dermatology Clinic, Instituto Nacional de Pediatría (2000 to 2018), who required systemic treatment for more than 3 months.* **Results:** *We included 21 patients. The mean age at disease onset was 3.31 years. The drugs used were methotrexate (57.1%), thalidomide (38%), prednisone (42.8%), azathioprine (19%), mycophenolate mofetil (9.5%), cyclosporine (4.7%), and systemic steroids as bridging therapy (42.8%). Adverse effects were mild and were observed in two patients (9.5%) treated with methotrexate and mycophenolate mofetil.* **Conclusions:** *Methotrexate was the most frequently used drug in > 50% of the patients, and most patients attained remission. Cyclosporine, azathioprine, and mycophenolate mofetil were also effective. Side effects were mild and infrequent. Comparative studies of systemic treatments for severe AD in the pediatric population are necessary.*

Keywords: *Dermatitis. Atopic. Pediatrics. Methotrexate. Thalidomide.*

Tratamiento sistémico para dermatitis atópica grave en niños: una serie de casos

Resumen

Introducción: *La dermatitis atópica (DA) es la enfermedad inflamatoria crónica de la piel más común en niños. En la mayoría de los pacientes la enfermedad se controla con tratamientos tópicos; sin embargo, algunos pacientes con DA grave no responden a estos tratamientos, por lo que requieren de terapia sistémica. Existe poca información acerca de la dosis ideal, tiempo de uso, respuesta clínica y seguridad del tratamiento sistémico en niños con DA grave. Se realizó este estudio para describir las características clínicas de pacientes con DA grave que requirieron un tratamiento sistémico, los medicamentos utilizados, la evolución clínica, los efectos secundarios y las complicaciones asociadas.* **Métodos:** *Se llevó a cabo una revisión retrospectiva de los expedientes de pacientes pediátricos con DA grave atendidos en el Servicio de Dermatología, Instituto Nacional de Pediatría (2000 a 2018), que hayan requerido tratamiento sistémico por más de 3 meses.* **Resultados:** *Se incluyeron 21 pacientes. La media de edad de inicio de la enfermedad fue de 3.31 años. Los fármacos utilizados fueron metotrexato (57.1%), talidomida (38%), prednisona*

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(42.8%), azatioprina (19%), mofetil micofenolato (9.5%), ciclosporina (4.7%) y esteroides sistémicos como terapia puente (42.8%). Se observaron efectos secundarios leves en dos pacientes (9.5%) tratados con metotrexato y mofetil micofenolato. **Conclusiones:** *El metotrexato fue el medicamento utilizado en más del 50% de los pacientes con remisión en la mayoría de ellos. La ciclosporina, azatioprina y mofetil micofenolato también fueron efectivos. Los efectos secundarios fueron leves y poco frecuentes. Es necesario realizar estudios comparativos de tratamientos sistémicos para DA grave en la población pediátrica.*

Palabras clave: *Dermatitis. Atópica. Pediatría. Metotrexato.Talidomida.*

Introduction

Atopic dermatitis (AD) is a highly frequent chronic inflammatory skin disease[1]. Due to its high prevalence, AD is one of the leading public health problems worldwide, affecting approximately 2-20% of children between 6 and 7 years of age[2,3]. Although there are few epidemiological studies on AD in Mexico, a study conducted at the National Institute of Pediatrics (INP, for its Spanish acronym) in 2012 revealed that it was the most frequent dermatosis, constituting 14.59% of consultations[4].

AD presents mild to moderate symptoms that respond to topical treatment and general skin care measures, such as emollients and avoiding detergents and irritants, in most children[1,5]. However, in some patients with AD, adequate disease control is not achieved, requiring systemic therapy to control inflammation, reduce symptoms, prevent relapses, and improve quality of life[5]. Patients with severe AD represent approximately 2% of cases[1]. There is no single criterion for defining severe AD requiring systemic treatment. Still, it should be approached comprehensively, considering objective scales of severity, impact on the patient's quality of life, body surface area, and non-response to topical treatment[5].

Systemic therapeutic options for AD include cyclosporine, methotrexate (MTX), mycophenolate mofetil (MMF), and azathioprine, although none of these drugs were developed explicitly for AD. The most recent guidelines and systematic reviews on the management of AD summarize the existing evidence on the safety and efficacy of systemic agents[6-8]; however, there are few clinical trials or comparative studies on the systemic treatment of choice in children with severe AD, as well as the appropriate dose, time of use, efficacy, and safety[7,9]. Targeted therapies such as dupilumab are relatively new and not yet extensively available for many patients in our country. However, it may become the first-line option for patients requiring systemic therapy[10-12].

This study aimed to describe the clinical characteristics of patients with severe AD who required systemic treatment, the drugs used for their treatment, their clinical course, side effects, and associated complications.

Methods

In this retrospective longitudinal observational study, we reviewed the INP Dermatology Department database from January 1, 2000, to December 31, 2018, to identify patients aged 0-18 years with a diagnosis of AD who required systemic treatment for AD for at least three months. Patients on systemic therapy for any other disease taking the same medication for AD and patients whose records were incomplete (< 75% of the variables to be studied) were excluded.

Clinical characteristics (demographic data, age of AD onset, comorbidities, consequences of the disease on daily life as assessed by the mental health service, and previous treatments) and systemic medications indicated (dosage, time of intake, and side effects), as well as complications secondary to AD were collected from the clinical records. Response to systemic treatment was categorized as follows: no response, partial, or complete remission, according to the medical notes in the clinical records. Descriptive statistics were conducted using measures of central tendency and dispersion for quantitative variables and frequencies and percentages for qualitative variables.

Results

Of the 21 patients included in the study, 11 were female (52.4%), and 10 (47.6%) were male. The mean age of AD onset was 3.31 years (standard deviation (SD) ± 2.97 years).

Regarding comorbidities, allergic rhinitis was reported in 11 patients (52.3%), asthma in six (28.5%), food allergies in two (9.5%), vitiligo in two (9.5%), allergic conjunctivitis in one patient (4.7%), and seven patients had other comorbidities such as autoimmune hypothyroidism, congenital disorders, obesity and hyperuricemia, epilepsy, deafness, testicular teratoma, acne, and attention deficit disorder.

According to the mental health service evaluation, 16 patients presented daily life problems: anxiety or depression (13 patients, 61.9%), social and family life issues (six patients, 28.5%), sleep problems (three patients, 14.2%), and school absenteeism due to the AD severity (one patient, 4.7%). All patients received some treatment before being evaluated at the INP Dermatology Department. The majority had used topical steroids (15 patients, 71.4%), followed by calcineurin inhibitors (five patients, 23.8%), systemic steroids (six patients, 28.5%), antihistamines (three patients, 14.2%); one patient received phototherapy (4.7%), another patient (4.7%) was prescribed transfer factor and one more patient (4.7%) homeopathy. Once evaluated at the INP Dermatology Department, all patients were treated with topical medication before initiating systemic treatment. The most frequent drugs indicated were steroids (100%), followed by antihistamines (61.9%), and calcineurin inhibitors (38%) (Table 1).

Table 1. Treatments used before starting systemic therapy for atopic dermatitis

Treatment	Frequency (n)	Percentage (%)
Topical steroids	21	100
Oral antihistamines	13	61.9
Topical calcineurin inhibitors	8	38
Wet wrap or wet pajamas with topical steroid or cold cream	7	33.3
Topical coal tar master preparation	4	19
Oral antibiotics	2	9.5
Topical antibiotics	1	4.7
Dilute liquid bleach baths (1 in 1000)	1	4.7
Phototherapy	1	4.7

Systemic treatments used for these AD patients are summarized in Table 2. Eleven patients (52.3%) received more than one systemic drug, although not concomitantly, except for six patients (28.5%) who received a systemic steroid used as bridge therapy at the time of initiating a steroid-sparing immunosuppressant. These patients showed partial disease remission at a mean dose of 0.6 mg/kg per day, with a mean treatment duration of 5.5 months. Regarding immunosuppressive therapy, six patients required two or more steroid-sparing systemic immunosuppressants. Twelve patients were treated with MTX for a mean duration of 16.5 months; three showed complete clinical remission, and six showed partial remission. Eight patients received thalidomide treatment with a mean duration of 16.8 months; only one showed complete remission (Figure 1), but seven patients were reported to have poor adherence to treatment. Four patients were treated with azathioprine, of which two showed complete remission with a mean treatment duration of 12.5 months. Of two patients treated with MMF, one showed complete clinical remission with a mean treatment duration of 8.5 months. Near full disease control was observed in the patient on cyclosporine treatment after 14 months (Figure 2). Two patients showed mild side effects, one treated with MTX and the other with MMF.

Along with systemic treatment, the following adjuvant therapies were indicated: topical steroids (14 patients, 66.6%), topical calcineurin inhibitors (seven patients, 33.3%), oral antibiotics or antivirals (seven patients (33.3%), one of them for recurrent eczema *herpeticum*), oral antihistamines (six patients, 28.5%), moisturizing therapy with wet pajamas (six patients, 28.5%), topical antibiotics (five patients, 23.8%), oral antidepressants/anxiolytics (four patients, 19.04%), diluted liquid bleach (1:1000) baths (four patients, 19.04%), transfer factor (prescribed by health care providers external to the authors' institution) (three patients, 14.2%), and topical coal tar/liquor carbonis formulations (two patients, 9.5%).

Complications secondary to AD identified in the patients are summarized in Table 3. The most frequent complication was impetiginization, followed by Kaposi's varioliform rash and erythroderma.

Discussion

In this study, the clinical records of 21 pediatric patients with severe DA were analyzed; MTX was the most used systemic treatment, and most patients showed complete or partial remission with this drug. Although there is little information on the use of MTX in children with AD, the experience of its administration in children with psoriasis is extensive. Among the main adverse effects reported in children are stomatitis, nausea, and vomiting[13], elevated liver enzymes (34%), and hematological abnormalities (23%), such as mild lymphopenia, neutropenia, and normocytic anemia[14]. In this study, one patient presented a mild elevation of cholesterol and triglyceride concentrations that did not require discontinuation of the drug.

Table 2. Systemic treatments for severe atopic dermatitis in the patients studied

Drug	n (%)	Dose (mean ± SD)	Duration (mean ± SD)	Evolution	Cause of discontinuation	Side effects or alterations in lab results
Methotrexate (oral administration)	12 (57.1)	14 ± 4.3 mg/week	16.5 ± 9.8 months	Three patients (25%) complete remission Six patients (50%) were still taking it at the time of the study with partial remission Three patients (25%) with poor treatment adherence and loss of follow-up	Three patients (25%): complete remission Three patients (25%): loss of follow-up	Elevation of cholesterol and triglycerides in one patient, which did not require discontinuation of the drug
Systemic steroid Prednisone (oral administration)	9 (42.8)	0.6 ± 0.27 mg/kg/day	5.5 ± 4.7 months	All patients (100%) presented partial remission and were changed to an immunosuppressive drug	Change to another drug	Not reported
Thalidomide (oral administration)	8 (38)	115.62 ± 64 mg/day	16.87 ± 15.52 months	One patient with total remission	Four patients (50%): economic reasons Three patients (37.5%): poor adherence to treatment One patient (12.5%): total clinical improvement	—
Azathioprine (oral administration)	4 (19)	112.5 ± 25 mg/day	12.5 ± 9.7 months	One patient (25%) with total remission, and one patient (25%) with partial remission	One patient (25%): poor adherence to treatment One patient (25%): came of age with partial remission at discharge One patient (25%): economic reasons One patient (25%): medical indication due to total remission	—
Mycophenolate mofetil (oral administration)	2 (9)	30 ± 14.14 mg/kg/day	8.5 ± 2.1 months	One patient (50%): total remission	One patient (50%): total remission One patient (50%): side effects and discontinued the treatment	One patient reported severe headache that required discontinuation of the drug
Cyclosporine (oral administration)	1 (4.7)	4.8 mg/kg/day	14 months	Almost total remission	Remission	Not reported

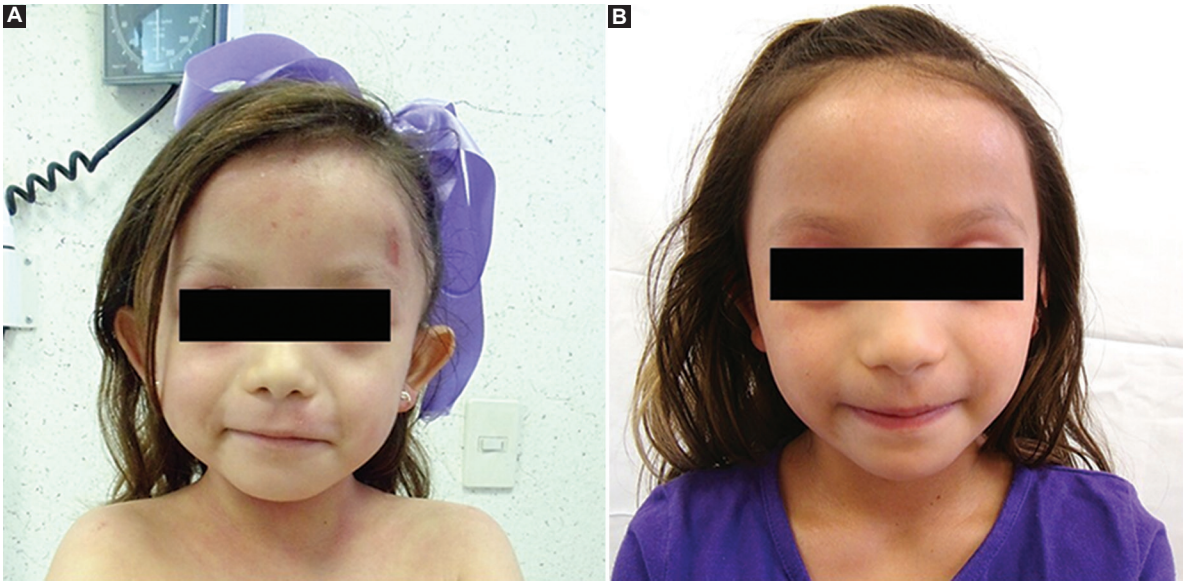

Figure 1. **A:** before treatment. **B:** after 18 months of treatment with thalidomide at a dose of 50 mg daily.

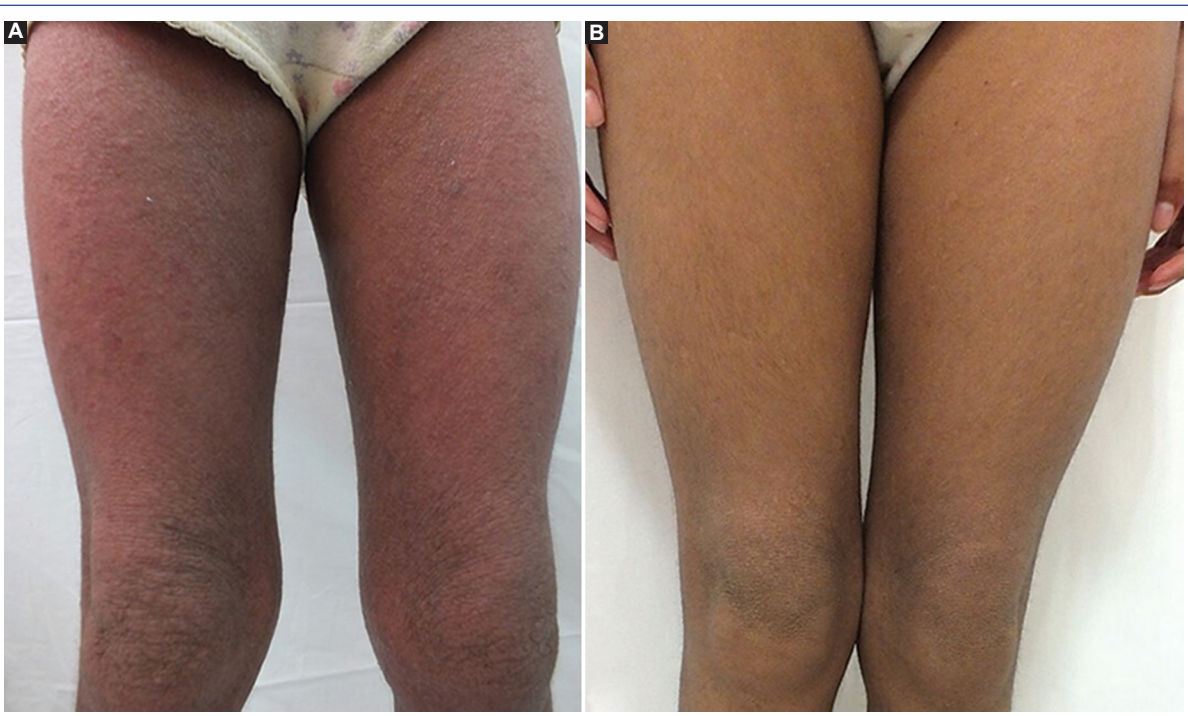

Figure 2. **A:** before treatment. **B:** after 12 months of treatment with cyclosporine at 4.8 mg/kg/day.

A retrospective study found that MTX was effective in 75% of patients with AD (children and adolescents) at a dose of 5-10 mg/week and a mean drug treatment duration of 16.5 months[15]. In the population studied here, 75% of patients showed complete or partial remission with a mean dose of 14 mg/week and a mean treatment duration of 16.5 months.

Thalidomide has historically been used to treat multiple inflammatory skin conditions. Some small studies reported good results in AD because of its

Table 3. Complications secondary to atopic dermatitis

Complication	n (%)
Secondary impetiginization	6 (28.5)
Eczema *herpeticum*/Kaposi's varioliform eruption	3 (14.2)
Hospitalization for erythroderma	3 (14.2)
Bilateral retinal detachment	2 (9.5)
Staphylococcal scalded skin syndrome	1 (4.7)

immunomodulatory, anti-inflammatory, and antipruritic properties[16-18]. Eight patients in this study received thalidomide, and only one showed complete remission, although poor adherence to treatment was reported in the remaining patients.

Mendes et al. studied 14 patients (aged 3 to 30 years) with refractory AD who were treated with thalidomide at doses of 3-5 mg/kg/day (maximum 200 mg/day) for three months. These authors found 71% of patients with a significant decrease in pruritus[16]. The most feared side effect of thalidomide use is peripheral sensory neuropathy; its occurrence is dose-related, but most cases are reversible. In our study, the mean dose was 115.6 mg daily, and none of the patients presented clinical data compatible with peripheral sensory neuropathy on interrogation. Only one patient adhered adequately to the drug for 18 months, although no electrophysiological studies or directed neurological examinations were performed. Children on thalidomide treatment should be monitored every three months for neuropathic changes, either by electrophysiological studies or neurologic physical examination, particularly in patients >12 years since they are more susceptible than younger patients[16], as well as in patients who reach a cumulative dose of 20 g of thalidomide[19]. Another recommendation is contraceptives in women of reproductive age, as thalidomide has teratogenic effects[19]. Figure 1B shows the complete remission of a patient treated with thalidomide for 18 months.

Evidence has demonstrated the efficacy of azathioprine in children with AD[20,21]. In a prospective study of 28 children with recurrent AD treated with azathioprine at a dose of 1-3 mg/kg/day, depending on their thiopurine methyltransferase levels, 61% showed significant improvement in AD. However, 25% showed laboratory alterations (elevated liver enzymes, decreased hemoglobin and leukocytes), and 57% developed skin infections (cellulitis or folliculitis); the mean duration of drug intake was 13 months, compared to 12.5 months in our population[22].

Four patients received azathioprine but had inadequate follow-up; the only patient with adequate follow-up showed promising results and no laboratory alterations.

MMF is less toxic than other immunosuppressants and is used off-label for AD. Although little has been studied on the use of MMF in children with AD, Waxweiler et al. found that the most frequent side effects were gastrointestinal involvement (nausea, vomiting, and diarrhea), leukopenia, hypertension, and nephrotoxicity[22]. In two patients treated with MMF, we found complete remission in one with a dose of 30 mg/kg/day at 10 months of use, and in the other, it was necessary to discontinue the drug due to severe headaches. Accordingly, a retrospective study reported that 29% of pediatric patients with severe AD showed > 90% clinical improvement with a dose of 40-50 mg/kg/day; the mean duration of treatment was eight months[23]. As side effects, gastrointestinal alterations were reported in two patients, eczema *herpeticum* in one patient, and impetiginization and folliculitis in two patients. In contrast to our patients, none of them presented laboratory alterations.

Cyclosporine is an approved drug for the treatment of AD in Europe. However, there is little information on the efficacy and safety of cyclosporine in children with AD. In a retrospective cohort of 15 children with AD treated with cyclosporine, 80% improved, although five patients relapsed at 22.7 ± 15.0 months of follow-up. The mean period of use of this drug was 10.9 ± 2.7 months, and the mean dose was 2.8 ± 0.6 mg/kg/day. Six patients (40%) reported adverse effects (recurrent pharyngitis, eczema *herpeticum*, infections, renal failure, stomach malaise, headache), and three patients discontinued the drug (two due to infection and one due to acute renal failure)[24].

In this population, the only patient treated with cyclosporine was eight years old at the time of the study (Figure 2). This patient had been treated with cyclosporine for 14 months and showed almost complete remission. Previously, this patient had been treated with MTX for two years with no response. No alterations were found in the laboratory studies, and no adverse effects as those reported in the literature were observed.

As for the complications in patients with severe AD, the most frequent were secondary impetiginization, Kaposi's varioliform rash due to herpes simplex superinfection, and erythroderma. Many ophthalmologic complications are associated with AD, such as keratoconjunctivitis, keratoconus, and cataracts. In this study, we identified two patients with bilateral retinal detachment. Keratoconus is

associated with chronic scratching, and ophthalmologic studies report that retinal detachment in patients with AD is also secondary to chronic scratching[25]. The incidence may have decreased in recent years due to new treatments and better control of AD[26].

Among the limitations of our study is the small number number of patients since it was necessary to exclude some with incomplete medical records or concomitant intake of other drugs. Another limitation is that not all laboratory results were available for each patient. In some cases, only indirect information reported in the patients' notes was available since some patients underwent studies in laboratories outside our institution, and these data were inaccessible.

Although this is a small case series, it is relevant as it revealed that only 2% of patients with AD required systemic treatment. We identified the clinical characteristics of 21 patients with severe AD who required systemic treatment and information on the drugs used, doses, time of use, and associated complications. This information is extremely valuable for the medical community treating patients with AD who require systemic treatment. Furthermore, the importance of adequate follow-up and monitoring studies to corroborate the safety of the medicines should be emphasized.

New AD-specific target therapy drugs are being developed; however, they are expensive and not widely available for a large part of the population in our country. Conversely, the systemic drugs analyzed in this study (MTX, azathioprine, and cyclosporine) as therapeutic options for AD are widely available, affordable for the population, and, according to our results, effective and safe. Comparative studies of systemic treatments for severe AD in the pediatric population are required to determine the best therapeutic option based on each patient's clinical characteristics.

In conclusion, this descriptive study in children with severe AD found that MTX was the most frequently used drug (> 50% of patients), was effective in 75% and had a good safety profile. The use of thalidomide was frequent, although only one patient completed treatment and had complete remission. Cyclosporine, azathioprine, and MMF were effective for treating severe AD in children with no significant side effects; however, only a few patients received these drugs.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. This study involved a retrospective review of medical records, for which approval was obtained from a formally constituted review board (Institutional Review Board or Institutional Ethics Committee).

Conflicts of interest

The authors declare no conflict of interest.

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