

Severe Atopic Dermatitis In Spain: A Real-Life Observational Study

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Objective: To determine the epidemiology and characterize the treatment prescribed for severe atopic dermatitis (AD) in children/adults in usual clinical practice.

Methods: Observational, retrospective study made through review of medical records of Spanish patients aged ≥ 6 years. Patients diagnosed with severe AD who required care between 2013 and 2017 were included. The study groups were: 6–12 years; 13–18 years; and > 18 years. Patients were followed for 5 years. The main measurements were the prevalence of AD, comorbidity and treatment duration. Statistical significance was established as $p < 0.05$.

Results: We included 2323 patients with severe AD. The overall prevalence was 0.10% (95% CI: 0.09–0.11%) and was 0.39%, 0.23% and 0.07% in the 6–12 years, 13–18 years and > 18 years age groups, respectively ($p < 0.001$), the percentage of males was 58%, 48.6% and 39%, respectively, and general comorbidity was 0.1, 0.2 and 0.9 points, respectively ($p < 0.001$). The most frequent comorbidities were asthma in 49.0%, 44.9% and 20.8%, respectively ($p < 0.001$), and anxiety in 79.7%, 65.8% and 67.3%, respectively ($p < 0.001$). Oral corticosteroids were administered in 97.3%, 90.9% and 81.7%, respectively (concomitant-medication). Cyclosporine (45.3%), azathioprine (15.9%) and methotrexate (9.0%) were the most frequently prescribed drugs; biologic agents were administered in 5.8% of patients (for AD).

Conclusion: In AD the presence of comorbidities was significant, especially in the psychological, immunoallergic and cardiovascular areas. Cyclosporine was the most widely used immunosuppressant. There was a degree of variability in the use and duration of the treatments prescribed.

Keywords: severe atopic dermatitis, epidemiology, comorbidity, treatment, immunosuppressants, biologics

Introduction

Atopic dermatitis (AD) is a recurrent chronic inflammatory skin disease.¹ It is pruritic, and the morphological expression varies with age, although there is a predominance of recurrent eczematous forms.² The aetiology is unknown but involves genetic factors and a combination of allergic and non-allergic-based immune factors, such as epidermal barrier dysfunction, and environmental trigger factors.^{1,2}

The prevalence varies but may affect up to 10% of the general population, of whom up to 15–30% have moderate/severe forms, that may affect up to 10–20% in children and 1–5% in adults, especially in developed countries.^{3–5} Reports suggest that mild infantile forms disappear after puberty in up to 75% of cases. The prevalence incidence is higher in females, although in childhood there is a predominance of males.²

AD has a significant economic impact and affects the quality of life and the psychosocial wellbeing of patients and families, increasing the risk of food allergies,

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asthma, allergic rhinitis, other inflammatory autoimmune diseases, and mental health disorders.^{6–8} Inflammatory flares may affect the entire skin and results in complications such as dehydration, hypernatremia, and cutaneous and systemic infection. Patients with a family history, a late onset, disseminated disease in childhood, females and patients in whom AD is associated with other allergic pathologies, such as asthma and rhinitis, have a worse prognosis. Adult AD is usually severe.^{1,9} In the severe forms of AD, drugs are used systemically and, although there is a considerable variation in the specific drug used, the clinical response is frequently insufficient, in addition to the burden of frequent adverse events.^{10,11}

Topical corticosteroids are the cornerstone of pharmacological treatment.^{1,2} However, in moderate/severe cases, a wide variety of medications is used, some of which do not have an approved indication, including topical immunomodulators (tacrolimus and pimecrolimus), oral corticosteroids, cyclosporine, azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide, biologic agents (omalizumab, rituximab, etanercept, adalimumab, ustekinumab, infliximab, secukinumab), apremilast, intravenous immunoglobulins and/or interferon gamma. Current advances in the long-term treatment of AD suggest that better symptom management may have a greater impact on quality of life. Prevention of the cardiovascular comorbidity associated with severe forms of AD may result in increased longevity and decreased mortality in patients with AD.^{12,13}

Available population-based evidence on the prevalence of severe AD is unclear and poorly documented, with only a few case series reports from specialized care, mainly by dermatologists, but with little evidence on the impact in the population. In Spain, there are no population-based studies. Nowadays, there is a growing need for naturalistic studies, representative of the real clinical conditions of health interventions that adequately reflect the impact on these patients from a population-based perspective. The objective of this study was to determine and characterize the treatment prescribed for severe AD in Spanish children and adults in usual clinical practice and quantify the prevalence of associated comorbidities.

Patients And Methods

Design And Study Population

An observational, multicentre, longitudinal retrospective study was performed based on review of medical records (computerized databases, with dissociated data) and complementary databases from seven Spanish Regions. The sample analysed

was of 2.2 million patients, with wide representativeness of the Spanish population. The sample was obtained from health databases of various Spanish centres (unified in the BIG-PAC, Real Life Data dissociated database: <http://www.encepp.eu/encepp/search.htm>). The population analysed was mostly urban, with low-medium socioeconomic status, and predominantly industrial.

Inclusion And Exclusion Criteria

Patients requesting care with regard to AD between 2013 and 2017 were included. For the recruitment period, the last available date was considered the index date. Inclusion criteria were: a) age ≥ 6 years, b) patients with a diagnosis of AD of a least one year prior to the index date, c) patients prescribed of any medication for AD (with verification of the dosage, the time interval and duration of each treatment administered), d) patients receiving ≥ 2 prescriptions during the follow-up period, e) patients who underwent regular monitoring (≥ 2 health records in the computerized system, including ≥ 1 dermatology unit visit). Exclusion criteria were: a) subjects transferred out to other centres or regions or due to change of address, b) permanently-institutionalized patients, and c) patients with a history of seborrhoeic dermatitis, contact dermatitis and/or fungal eczema.

Study Groups

Three age groups were differentiated: 6–12 years, 13–18 years, and > 18 years. Patients were followed retrospectively for 5 years from the date of inclusion/index.

Description Of Severe Atopic Dermatitis

Records of patients with AD were obtained according to the International Classification of Diseases (ninth edition) Clinical Modification (ICD-9-CM; 691.8, 692.9, 706.8), and/or ICD-10-CM (L20, L28, L85.3), which includes AD, allergic dermatitis, allergic eczema, atopic eczema and atopic neurodermatitis. The diagnosis of AD was made by the reference dermatologist according to the Hanifin and Rajka criteria.¹⁴ Severe AD was defined by the following criteria: a) the administration of immunosuppressive treatment, b) the administration of biological treatment, and/or c) hospitalization due to an AD flare.

Sociodemographic And Comorbidity Variables

The following variables were collected: age (continuous and by ranges), sex, time since diagnosis, the history of

hypertension, diabetes, dyslipidaemia, ischemic heart disease, cerebrovascular accident, heart/kidney failure, COPD, bronchial asthma, allergic rhinitis, depressive syndrome, anxiety or agitation, celiac disease, and the body mass index (BMI, Kg/m²). As a summary variable of general comorbidity, the Charlson comorbidity index¹⁵ was used as an approximation to the severity of the patient, and the number of chronic comorbidities. In addition, the comorbidities of patients with severe AD were compared with those of the general population through pairing by age and sex.

Medication Administered

The medication (active ingredients and biological drugs) indicated for the treatment of severe AD were obtained according to the Anatomical Therapeutic Chemical Classification System (ATC).¹⁶ The information was obtained from the records of pharmacological prescriptions of medicines and/or hospital pharmacy services. The choice of drug was at the physician's discretion. The following medications were collected: a) immunosuppressants (*frequent use in AD*): cyclosporine (L04AD01), methotrexate (L04AX03), azathioprine (L04AX01), mycophenolate mofetil (L04AA06), cyclophosphamide (L01AA01); b) biological agents: omalizumab (R03DX05), rituximab (L01XC*), infliximab (L04AB02), secukinumab (L04AC10), ustekinumab (L04AC05), tocilizumab (L04AC07), mepolizumab (R03DX09); and c) other medications (indication not approved): apremilast (L04AA32), immunoglobulins (J06B*), interferon-gamma (L03AB*), hydroxychloroquine (P01BA*), tofacitinib (L04AA29) and baricitinib (L04AA37). Number of treatment cycles of immunosuppressants and the duration of biological therapy were recorded. Systemic corticosteroids (H02A*) administered in patients with severe AD were quantified as rescue treatment (concomitant-medication).

Epidemiology: Prevalence

The prevalence rate was calculated according to patients diagnosed with AD by a dermatologist and prescribed of immunosuppressant or biological agents and/or hospitalized (numerator), as a proportion of patients assigned to primary healthcare centres (denominator). Standardization of the results was not required, due to the similarity of the demographic characteristics of the sample in comparison with general Spanish population.

Confidentiality Of Information

Data confidentiality (anonymous and dissociated) was respected according to the Spanish Organic Law on Data

Protection (Law 15/1999 of December 13). The study was classified by the Spanish Agency for Medicines and Health Products (EPA-OD), and was approved by the Clinical Research Ethics Committee, International University of Catalonia (Barcelona).

Statistical Analysis

A data validation was carried out to ensure the quality of the results. Descriptive statistics were expressed as absolute and relative frequencies. Qualitative data was presented in percentage and 95% confidence intervals (CI). Data was retrieved according to the total number of subjects with non-missing records. Means and standard deviation (SD) were used to describe quantitative data. A bivariate analysis was made according to the distribution of data (chi-square test or ANOVA). Comorbidities in patients with severe AD were compared with those in the general population using propensity score matching (pairing). The estimators were age and sex. The tolerance of the model was 2, with sampling with substitution and giving priority to exact matches (1:2). Statistical significance was established as $p < 0.05$. The statistical analysis was performed using SPSSWIN v. 23.

Results

Of the 2.2 million patients aged ≥ 6 years assigned to the centres, 62,849 received a diagnosis of AD (Table 1), of which 2323 (3.69%) were severe. 28 patients were excluded from the study (reasons: inclusion/exclusion criteria, 8; missing data: 14; loss follow-up: 6). The overall prevalence of severe AD, according to the defined criteria, was 0.10% (95% CI: 0.09–0.11%). The prevalence in the different age groups was 0.39%, 0.23% and 0.07% in the 6–12 years ($N = 600$), 13–18 years ($N = 244$) and >18 years ($N = 1479$), respectively ($p < 0.001$). In all age groups asthma frequency was higher than in the general population (49%, 44.9% and 20.8%, respectively, $p < 0.001$). Asthma severity (intermittent, mildly persistent, moderately persistent and severely persistent) was 16.1%, 25.4%, 45.0% and 13.5%, respectively, in patients aged 6–12 years, 14.5%, 30.4%, 44.3% and 10.8%, respectively, in those aged 13–18 years, and 12%, 36.7%, 42.8% and 8.5%, respectively, in patients aged > 18 years ($p = 0.013$). Anxiety/agitation diagnosis was higher in severe atopic patients than in general population in all age groups. In adults, the most frequent comorbidities were dyslipidaemia (46.0%), hypertension (38.9%), obesity (27.7%), and diabetes mellitus (14.9%), which were higher than in the general population (Table 2).

Table 1 Prevalence Of Atopic Dermatitis According To Age Group

Age Groups	6–12 Years	13–18 Years	> 18 Years	p
Patients with severe AD	600	244	1479	<0.001
Patients with AD	17,533	6841	38,475	
General population	151,910	106,346	1,973,278	
Estimated prevalence of AD, %	11.5%	6.4%	1.9%	
95% CI	11.0–12.0%	5.8–7.0%	1.8–2.0%	<0.001
Estimated prevalence of severe AD, %	0.39%	0.23%	0.07%	
95% CI	0.23–0.54%	0.04–0.41%	0.06–0.08%	

Note: p: statistical significance.

Abbreviation: AD, atopic dermatitis.

Cyclosporine (N = 1053, 45.3%), azathioprine (N = 370, 15.9%) and methotrexate (N = 209, 9.0%) were the most frequently used drugs; biological agents were used by 5.8% (in AD), Table 3. Cyclosporine (38.5%), immunoglobulins (34.3%) and azathioprine (25.0%) were the most frequent in patients aged 6–12 years; cyclosporine (45.5%), azathioprine (20.9%) and immunoglobulins (18%) in patients aged 13–18

years; and cyclosporine (48.1%), methotrexate (13.5%) and azathioprine (11.4%) in patients aged > 18 years. The most frequently used biological agent was omalizumab (3.7% in patients aged 13–18 years and 3.0% in those aged > 18 years). Three or more treatment cycles were administered in 34.2%, 10.3% and 10.0% of patients, respectively (p <0.001). Systemic corticosteroids were administered in 97.3%, 90.9%

Table 2 Baseline Characteristics And Comorbidities Of The Study Population And The General Population By Age Group

Age Groups	6–12 Years		13–18 Years		> 18 Years	
Comparison By PS	Severe AD	Population	Severe AD	Population	Severe AD	Population
Number of patients, PS	600	1200	244	488	1479	2958
Demographic characteristics						
Mean age, years	9.1 (2.0)	9.0 (2.0)	14.8 (1.6)	14.9 (1.7)	51.4 (14.7)	50.9 (14.8)
Sex (male)	58%	57.7%	48.6%	48.1%	39.0%	39.8%
Time since diagnosis, years	8.6 (3.1)	–	10.9 (3.9)	–	27.6 (4.3)	–
General comorbidity						
Mean Charlson Index	0.1 (0.2)	0.1 (0.2)	0.2 (0.2)	0.2 (0.2)	0.9 (0.3)	0.8 (0.3)
Mean comorbidities	1.1 (0.9)	1.0 (0.8)	1.5 (0.9)	1.2 (0.8)	3.2 (2.2)	2.8 (2.2)
Specific comorbidity						
Hypertension	0.5%	0.4%	0.4%	0.3%	38.9%	36.1%*
Mellitus diabetes	0.3%	0.4%	1.2%	1.0%	14.9%	11.5% [‡]
Dyslipidaemia	2.5%	2.0%	2.1%	2.9%	46.0%	44% [‡]
Obesity	19.5%	17.5%	19.8%	18.8%	27.7%	24.1% [†]
Ischemic heart disease	0.5%	0.4%	0.8%	0.6%	5.7%	4.0%
Cerebrovascular accident	0.2%	0.3%	1.2%	0.7%	7.4%	5.5%
Heart/kidney failure	0.0%	0.0%	0.0%	0.0%	7.4%	6.2%
COPD	0.0%	0.0%	0.0%	0.0%	10.9%	9.3%
Bronchial asthma	49.0%	18.6% [‡]	44.9%	11.9% [†]	20.8%	6.5% [‡]
Allergic rhinitis	25.0%	19.4%*	22.2%	17.2%	22.9%	10.2% [‡]
Depressive syndrome	0.3%	0.3%	0.8%	0.5%	12.6%	10.3%*
Anxiety or agitation	79.7%	32.4% [‡]	65.8%	20.8% [†]	67.3%	35.3% [‡]
Celiac disease	0.5%	0.2%	1.3%	0.7%	2.2%	1.1% [†]
Body mass index, Kg/m ²	15.2 (2.3)	14.1 (2.5)	19.5 (3.1)	17.8 (3.2)	28.6 (3.2)	27.5 (3.2) [†]

Notes: Values expressed in percentages or mean (standard deviation). Statistical significance: [‡]p <0.001, [†]p <0.01, *p <0.05 in the pairwise comparison. PS, pairing by age and sex.

Abbreviations: AD, atopic dermatitis; PS, Propensity Score Matching; COPD, chronic obstructive pulmonary disease.

Table 3 Medication Administered For Severe Atopic Dermatitis According To Age Group

Age Groups	6–12 Years	13–18 Years	> 18 Years	p
Immunosuppressants				
Cyclosporine	38.5%	45.5%	48.1%	<0.001
Azathioprine	25.0%	20.9%	11.4%	0.001
Methotrexate	1.2%	0.8%	13.5%	<0.001
Mycophenolate mofetil	0.5%	6.2%	9.6%	<0.001
Cyclophosphamide	0.2%	2.5%	2.2%	0.003
Other medications*				
Hydroxychloroquine	0.0%	1.2%	4.2%	<0.001
Interferon	0.0%	0.0%	1.4%	0.002
Immunoglobulins	34.3%	18.0%	1.5%	<0.001
Apremilast	0.0%	0.4%	1.3%	0.001
Biological agents				
Omalizumab	0.3%	3.7%	3.0%	<0.001
Rituximab	0.0%	0.0%	0.6%	0.001
Secukinumab	0.0%	0.4%	1.8%	0.001
Infliximab	0.0%	0.4%	1.4%	0.007
Treatment cycles				
Mean cycles	1.9 (0.9)	1.4 (0.7)	1.4 (0.7)	<0.001
1	46.2%	73.3%	74.7%	<0.001
2	19.7%	16.5%	15.3%	
3+	34.2%	10.3%	10.0%	
Other variables				
Systemic corticosteroids**	97.3%	90.9%	81.7%	<0.001
Hospitalization	0.8%	1.0%	1.8%	0.040

Notes: Values expressed in percentages or means (standard deviation). p: statistical significance. *Indication not approved. **Concomitant-medication.

and 81.7% of patients, respectively ($p < 0.001$; concomitant-medication). The mean number of cycles of systemic corticosteroids administered during the 5 years of follow-up was 7.5 (SD: 3.3), with a mean duration of 12.1 (SD: 3.8) days; 1.1% of patients were hospitalized due to atopic dermatitis.

Table 4 shows the medication administered and the duration of the cycles. The two most frequently used immunosuppressants represented 61.2% of the consumption. Cyclosporine was the most frequently used second-line immunosuppressant. There were variations in the duration of each cycle in each of the drugs administered.

Discussion

There is a lack of evidence on the prevalence of severe AD, although some authors place it at around 5%^{17,18,20} We found a lower figure, which may be due to the method of measurement. The severity of AD was classified

according to the treatment administered, instead of the use of a clinical scale. The fact is that AD has a fluctuating course and the degree of severity is not substantially modified over time in most patients, and the possible classification bias (depending on the treatment) may substantially disappear. In moderate/severe cases a wide variety of drugs are used in combination; therefore, these results may reflect the type of systemic prescription used in usual clinical practice of the most severe/recurrent forms.

The results show a close association between AD and other immunoallergic expressions such as asthma and rhinitis. Patients with a late-onset, females, and patients with AD associated with other allergic diseases (asthma and rhinitis) have a worse prognosis.^{1,2} The percentage of patients with allergic comorbidity (asthma and rhinitis) may have been underdiagnosed compared with other reports.^{1,2} This might be because the comorbidities of these patients are not always included in the computerized medical record. We also found an association between AD and anxiety in all age groups and with depression in adults, in line with other reports.^{1,19,21,22} It is known that.^{10,19} Comparison of comorbidity in adult patients with severe AD with that of the general population showed a marked association with various metabolic/cardiovascular risk factors, such as hypertension, diabetes, dyslipidaemia and obesity. Although our results are similar to those of other studies,²³ more data is required to reinforce the consistency of our results and identify associations between chronic severe AD and cardiovascular risk, which reduces life expectancy.^{24,25}

In our study, after 5 years of follow up, all patients had received at least two types of systemic treatments for the treatment of AD, with a frequent need for several cycles of immunosuppressive treatment due to recurrences.

Management of signs and symptoms of AD with immunosuppressive agents has been widely described.^{26,27} Despite the difficulty in making comparisons, our results are also consistent with previous publications, agreeing that cyclosporine stands out as the most effective drug. However, the treatments administered by physicians in our study were short- or medium-term, showing a conservative attitude despite the existing variability.

However, data on the efficacy of systemic treatment and the long-term safety of immunosuppressants are limited, and further studies are needed to standardize and agree on their use. Cyclosporine is the only first-line immunosuppressant approved by the EMA for the systemic treatment of AD.^{28,29} There is ample evidence on the lack of control of

Table 4 Medication Administered And Duration Of Cycles In Patients With Severe Atopic Dermatitis

Medication Administered	N	%	Mean age, Years	Sex (Male)	Time Since Diagnosis, Years	General Comorbidity	Systemic Corticosteroids	Mean Cycles Over 5 Years	Duration Cycle 1, Days	Cycle Duration 2, Days	Cycle Duration 3, Days	Second Line*
Immunosuppressants												
Cyclosporine	1053	45.3%	45.4 (22.6)	40.1%	23.4 (8.7)	3.4 (2.4)	87.8%	1.4 (0.7)	60.7 (60.0)	71.7 (88.8)	66.3 (76.0)	Methotrexate
Azathioprine	370	15.9%	31.7 (21.0)	47.7%	20.1 (9.7)	1.7 (1.4)	84.7%	1.5 (0.7)	84.4 (72.0)	80.6 (82.8)	89.1 (68.0)	Methotrexate
Methotrexate	209	9.0%	48.7 (14.9)	41.7%	27.0 (6.0)	2.6 (2.0)	72.2%	1.4 (0.7)	54.0 (13.3)	52.9 (13.8)	53.5 (15.1)	Cyclosporine
Mycophenolate mofetil	160	6.9%	50.2 (16.7)	52.8%	26.6 (5.6)	2.6 (1.8)	90.7%	1.3 (0.5)	92.0 (70.0)	82.7 (87.6)	82.9 (47.4)	Cyclosporine
Cyclophosphamide	40	1.7%	52.2 (18.9)	54.3%	26.5 (5.8)	2.2 (1.1)	100.0%	1.4 (0.7)	53.6 (55.9)	28.3 (14.8)	20.8 (13.2)	Cyclosporine
Other medications**												
Hydroxychloroquine	65	2.8%	47.5 (14.1)	42.4%	27.9 (4.6)	2.6 (2.0)	79.0%	1.3 (0.6)	90.3 (62.3)	97.2 (97.0)	81.1 (79.5)	Cyclosporine
Interferon	21	0.9%	49.8 (12.3)	46.7%	27.1 (3.1)	2.2 (1.7)	86.7%	1.2 (0.4)	53.6 (48.9)	71.7 (90.1)	–	Cyclosporine
Immunoglobulins	272	11.7%	10.9 (5.4)	55.8%	10.1 (6.0)	1.2 (0.9)	94.9%	2.2 (0.9)	34.1 (26.9)	32.0 (16.4)	33.1 (18.3)	Cyclosporine
Biological agents												
Omalizumab	55	2.4%	38.0 (13.7)	44.2%	24.6 (7.1)	2.3 (1.8)	92.6%	–	51.3 (50.5)			
Rituximab	9	0.4%	41.5 (7.6)	42.4%	27.0 (4.1)	2.3 (1.9)	100.0%	–	32.0 (17.6)			
Apremilast	20	0.9%	42.3 (12.3)	45.0%	25.9 (4.4)	1.8 (1.2)	100.0%	–	40.5 (39.6)			
Secukinumab	28	1.2%	45.9 (13.1)	48.5%	27.0 (7.2)	2.7 (1.6)	97.0%	–	47.2 (48.3)			
Infliximab	21	0.9%	48.0 (15.2)	34.5%	26.5 (4.0)	2.1 (1.4)	100.0%	–	41.6 (45.6)			

Notes: Values expressed in percentage or mean (standard deviation). *Drug used for second line treatment. **Indication not approved.

AD with current treatments and the need for rescue medication,^{6,30} which was confirmed in our study by the high use of concomitant systemic corticosteroids.

Recently, dupilumab, a biological agent, has been suggested as a reference treatment for AD. The safety profile was more effective to conventional immunosuppressants (cyclosporine or methotrexate). Dupilumab was approved by the EMA in September 2017 for the treatment of adult patients with moderate/severe AD not adequately controlled with topical therapies or when these are not advisable.³¹

It should be noted that the prevalence of AD (total and severe) decreases according to the increase in the age of the patients (temporary follow-up).³² Two studies published in our country conclude that moderate to severe AD requiring treatment with systemic immunosuppressants has a low prevalence in adults and children; and that more studies will be needed to determine the real epidemiology of the disease. Our results are consistent with these publications.^{33,34}

The possible limitations of the study affect the categorization of the disease and the possible aforementioned classification bias (treatment vs. scales), attributable to the information system used. Therefore, the study shows the usual limitations of retrospective studies, such as, for example, disease underreporting and variability in the physicians and patients, due to the observational design. In this regard, the possible inaccuracy of the diagnostic coding of moderate/severe AD and other comorbidities, or the non-inclusion of variables that could influence the final results (socioeconomic level, evolution of the pharmacological dose prescribed, therapeutic adherence, phenotypes, etc.) should also be considered as limitations. Likewise, we did not detail the possible overlap of medications between flares or maintenance phase due to difficulties in their measurement. The main limitation is shown in the evaluation method, the lack of measurement of clinical effectiveness and/or the lack of measurement of adverse reactions. Conversely, conducting the study in children, adolescents and adults simultaneously, and the large number of patients diagnosed with AD included, may be considered as the strengths of the study.

This disease results in a substantial comorbidities burden, including psychological and immunoallergic and, in adults, metabolic/cardiovascular components. Management of severe AD may become challenging, as many treatments have not received approval for use in severe AD, and the clinical control is inadequate, as shown by the high use of

systemic corticosteroids. These difficulties in the disease control show the unmet medical need of these patients. Cyclosporine is the most widely used immunosuppressant.

The treatment of AD in general and of severe AD in particular may require more-personalized therapy depending on the phenotype. At present, clinical trials of biological agents that may revolutionize the evolution and treatment of AD are ongoing. Further studies are needed to determine the real effectiveness of many of these treatments. Moreover, future studies will require cost-effectiveness analyses and improved diagnostic and severity measurement tools. In addition, coordination strategies between the different health levels and effective prevention programs are necessary to delay the progression to more advanced stages of AD and reduce flares.

Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

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