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NOVELTIES IN DERMATOLOGY

Review and Update of Current Understanding of Childhood Atopic Dermatitis

A. Conde-Taboada,a F.J. González-Barcala,b and J. Toribioc

aServicio de Dermatología, Hospital Clínico San Carlos, Madrid, Spain
bServicio de Neumología and cServicio de Dermatología, Complejo Hospitalario Universitario de Santiago de Compostela, La Coruña, Spain

Abstract. Although childhood atopic dermatitis is reported throughout the world, it has become a health priority in developed countries, where its prevalence is particularly high. Despite extensive study for many years, various aspects of the disease are still subject to debate. This review will discuss the main studies published on the topic and update certain concepts such as the terminology used (the difference between atopic and atopiform), epidemiology, etiopathogenesis (molecular mechanisms, implicated genes, and environmental factors), assessment of severity, influence on the quality of life of the patients and their families, economic impact, and treatment.

Key words: atopic dermatitis, epidemiology, quality of life, costs, costs analysis.

DERMATITIS ATÓPICA INFANTIL: REVISIÓN Y ACTUALIZACIÓN

Resumen. La dermatitis atópica infantil es una enfermedad de distribución mundial, con una elevada prevalencia en los países desarrollados, lo que la ha convertido en una prioridad de salud. A pesar de que es una entidad que ha sido estudiada durante años todavía existen numerosas controversias en distintas áreas. En esta revisión se comentan los principales trabajos publicados sobre el tema, actualizando diversos conceptos: terminología aplicada (diferencia entre atópica y atopiforme), epidemiología, etiopatogenia (estudios moleculares, genes implicados y factores ambientales), medida de la gravedad, influencia en la calidad de vida del paciente y la familia, impacto económico y tratamientos.

Palabras clave: dermatitis atópica, epidemiología, calidad de vida, costos y análisis de costo.

Introduction and Nomenclature

Atopic dermatitis is an inflammatory disease reported throughout the world and its prevalence is particularly high in developed countries. Onset tends to occur during childhood and gradually diminishes with age, although it can persist or even appear in adults.

The terminology employed regarding this subject has led to confusion and debate for more than a century.[1] The term atopic dermatitis was coined by Wise and Sulzberger in 1933[2] to define an entity characterized by dry skin, pruritus, erythematous lesions, and a chronic recurrent course. Currently, the terms atopic dermatitis and atopic eczema are used and both are acceptable.

Conceptual differences have recently reappeared due to attempts to separate those forms of atopic dermatitis that do not present other atopic features. The term "atopiform dermatitis" has been proposed for those symptoms that show the clinical signs of atopic dermatitis but without sensitization to environmental allergens or allergen-specific immunoglobulin (Ig) E; this has also been called "intrinsic" atopic dermatitis.[3,4] According to those who support this approach, this distinction helps to achieve greater reliability regarding studies on the subject that are hindered by selection bias.[4] Other authors consider that the only effect of the new terminology is to confuse physicians and patients, without improving treatment or information, and to increase the number of types of allergy test.[5] We should also clarify the term "atopy," which was employed for the first time by Coco and Cooke[6] in 1923 to denominate a familial entity characterized by hypersensitivity of the skin and mucosa to environmental allergens with elevated IgE

Correspondence:
Alberto Conde-Taboada
Servicio de Dermatología
Hospital Clínico San Carlos
C/ Prof. Martín Lagos
28070 Madrid, Spain
condetaboada@aedv.es

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concentrations. In a consensus statement published by the World Allergy Organization,[7] the term atopy was defined as "a personal or family tendency to become sensitized and produce IgE antibodies in response to exposure to ordinary allergens" and recommended reserving it for the genetic predisposition to develop IgE-specific antibodies against common allergens.

Epidemiology

Childhood atopic dermatitis has become a public health problem in developed countries, with a prevalence between 20% and 30%.[8] Its prevalence has increased 3-fold or 4-fold in recent decades in these countries.[9] According to the International Study of Asthma and Allergies in Childhood, during a minimum period of 1 year, the prevalence of symptoms of atopic dermatitis in 6- or 7-year-old children presented great variability between different geographic areas. Thus, prevalences were almost 20% in England or Australia but less than 2% in China or Iran.[10] Recent studies suggest that the prevalence of atopic dermatitis may have reached its plateau in some countries, with values remaining stable in recent years, as in the cases of Denmark and Japan.[11,12] Nevertheless, a study conducted in Switzerland in 5- to 7-year-old children confirmed that the prevalence of allergic asthma and rhinoconjunctivitis had stabilized between 1991 and 2001, whereas atopic dermatitis continued to increase, especially among girls.[13]

There is a higher prevalence in urban areas than in rural ones in developed countries, and higher social classes are more affected.[14] Regarding the disease by sex, a study of 12- to 16-year-olds found a higher prevalence among girls (25.7%) than among boys (17%).[15] A recent study of 5- to 7-year-old children differentiated between atopic and nonatopic eczema (the latter only presenting the clinical features of atopic dermatitis, but without sensitization to any allergen). The results showed a greater overall frequency of eczema in girls, whereas the frequency of atopic eczema was the same in both sexes.[16]

The onset of atopic dermatitis occurred during the first 6 months of life in 45% of children, in the first year in 60%, and in the first 5 years in more than 85%.[17] It has been suggested that 30% of children with atopic dermatitis develop asthma and 35% develop rhinoconjunctivitis.[18] However, the popular concept of the "atopic march" (children who begin with atopic eczema and subsequently suffer asthma and rhinitis as they get older) is still in question.[19] A multicenter cohort study conducted in Germany showed that early episodes of wheezing in children and a specific sensitization pattern were the main predictors of asthma at school age, regardless of the presence of dermatitis. Without these 2 associated factors, eczema at early ages by itself did not increase the risk of asthma.[20]

Pathogenesis

The pathogenesis of atopic dermatitis is complex; several factors are involved, many of which are still not well understood. Likewise, it has yet to be determined how these factors might interact with one another. We will classify the implicated factors into 3 different groups to facilitate our understanding of them.

Immunologic and Biochemical Mechanisms

It is commonly accepted that immunologic abnormalities are involved in the development of atopic dermatitis, but debate persists regarding the cause-effect relationship, the type of abnormalities involved, and the relationship between them.[21]

The origin of atopic eczema seems to involve a feedback cycle: pruritus and mechanical damage caused by scratching leads to the production of proinflammatory cytokines (interleukin [IL]-1, IL-18, tumor necrosis factor-α, granulocyte-macrophage colony stimulating factor [GM-CSF]) that recruit leukocytes to the skin.[22] The different leukocyte populations are activated through different processes; on induction by dendritic cells, the lymphocytes differentiate via the T_h2 pathway; these dendritic cells also show increased antigen-presenting capacity and bind to the IgE-antigen complex. The IgE-antigen complex in turn induces mast cell accumulation and activation. The activated T_h2 cells release IL-4 and IL-13, which suppress the production of antimicrobial peptides (β defensins 2 and 3). Viruses, bacteria, and fungi take advantage of these reduced peptide levels, colonizing the skin and releasing proinflammatory products (superantigens, proteoglycans, and lipoteichoic acid) that amplify leukocyte activation. This activation increases the release of inflammatory mediators, such as proteases and IL-31, which perpetuate pruritus (Figure).

Recent studies have made further progress in elucidating the biochemical pathway by relating molecular abnormalities to clinical severity; thus, levels of serum IL-16 (a marker of T_h2 differentiation) have been correlated with the SCORing Atopic Dermatitis (SCORAD) index of clinical severity.[23]

A recent study has shed light on new interrelationships, specifically with obesity. This study included more than 400 children of 10 years old and found lower levels of adiponectin among those with atopic dermatitis.[24] Adiponectin regulates energy metabolism and low values have also been associated with insulin resistance, obesity, and greater risk of cardiovascular disease. Future studies are needed to investigate these correlations, all of which are of great relevance.

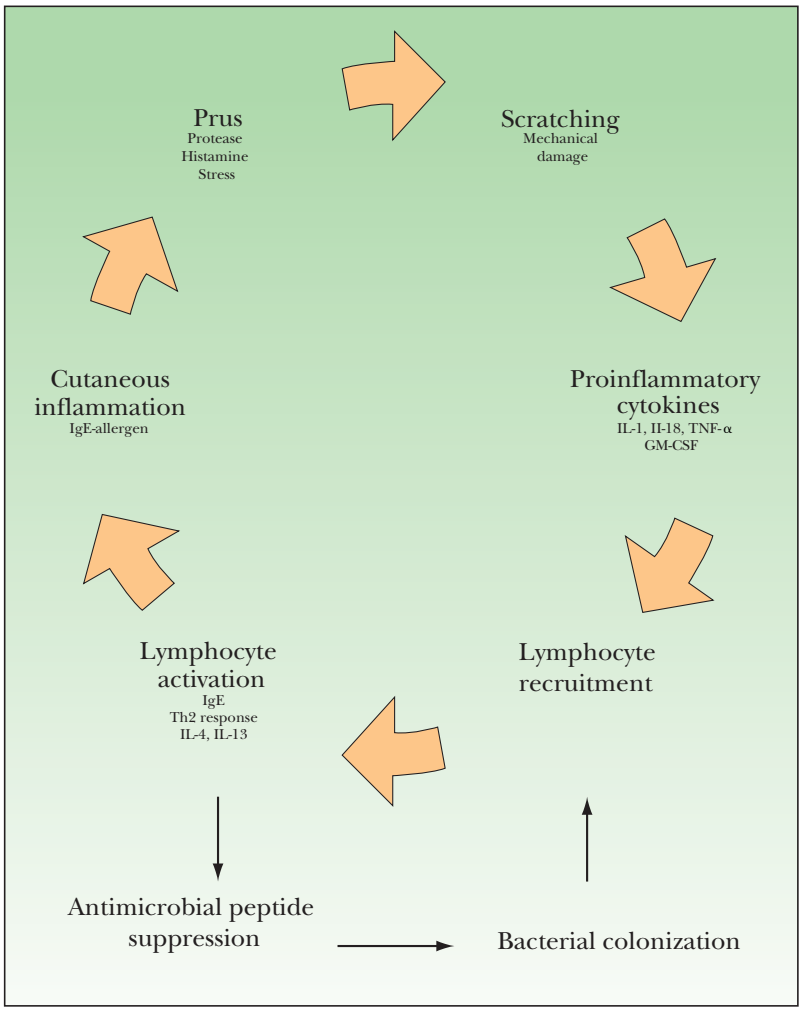

Figure. Self-sustaining atopic dermatitis feedback loop

A recently published investigation extended the study of exhaled nitric oxide beyond patients with asthma. Until now, elevated nitric oxide levels had been observed in patients with asthma and these were used as a marker of bronchial inflammation. A study conducted in children in the Netherlands found that those who had atopic dermatitis had lower exhaled nitric oxide levels than those who did not have dermatitis, regardless of the presence of asthma.[25] This should stimulate research into the role of nitric oxide beyond bronchial pathology.

Genetics

The familial association of atopic dermatitis and the high level of concordance in identical twins indicate the relevance of genetic abnormalities in its pathogenesis. Furthermore, the association with allergic asthma and rhinitis points to genetic abnormalities that correlate with T_h2 immune system imbalances. A group of genes located on chromosome 5q31-33 have been implicated in regulating the production, via the T_h2 pathway, of interleukins such as IL-3, IL-4, IL-5 and IL-13, as well as GM-CSF.[26] Investigators have also managed to identify polymorphisms in the region that codes for the IL-4 receptor (16q12), as well as mutations in the promotor region of the RANTES gene (17q11), that could influence the expression of atopic dermatitis.[8]

Similarly, SPINK5 gene polymorphisms (causing Netherton syndrome) have been associated with atopic eczema,[27] as well as mutations in the filaggrin gene which is implicated in ichthyosis vulgaris and which has a high number of carriers in the European population.[28]

In addition, genetic analysis has shown an overlap between atopic dermatitis and psoriasis, specifically at loci 1q21, 17q25, and 20p12, an observation which could indicate some type of association between these 2 inflammatory diseases.[29]

Environmental Factors

The increased prevalence of childhood atopic dermatitis in developed countries has led to the appearance of many theories on the possible involvement of environmental factors.

Increases in the prevalence of allergic disease probably depend more on environmental factors than on other individual characteristics. This possibility seems to be supported by studies such as that conducted in Germany, where significantly different prevalences of allergic diseases were found between former East Germany and West Germany.[30] Although the genetic characteristics of individuals are similar, there were striking environmental and socioeconomic differences, especially before unification.[30]

Around 33% of children with moderate-to-severe atopic dermatitis are positive for some food-specific IgE. This value is much higher than in the normal population; nevertheless, only a minority of these allergens are clinically relevant, as shown by food challenge tests.[17,31] Moreover, a recent study correlated allergy to eggs with a greater severity of atopic eczema and with longer healing time.[32]

Breast feeding has been repeatedly cited as a protective factor against atopic dermatitis; a metaanalysis performed by Gdalevich et al[33] showed that feeding exclusively with breast milk during the first 3 months of life is associated with a lower incidence of atopic dermatitis, but only in children with first-degree family members with a history of the disease.

Much attention has been given to the "hygiene hypothesis" which suggests that the low exposure of children to germs in developed countries can prevent the immune system from developing correctly. Thus, a lower incidence of infection at young ages will increase the probability of suffering from atopic dermatitis. This theory has led to many studies, most of which have been recently reviewed by Flohr et al.[34] They were unable to establish a clear causal relationship between infection due to a specific pathogen and the lower incidence of atopic dermatitis. On the other hand, Zutavern et al,[35] in a historical cohort study with more than 4000 children, analyzed exposure to respiratory infections (whether or not the child developed clinical infection). The study showed that exposure to respiratory infection during pregnancy and during the first year of life had a protective effect on the later development of atopy (both dermatitis and asthma or rhinitis).

Two cohort studies[36,37] have shown that children sent to a day-care center have a lower incidence of atopic dermatitis. Contact with animals is an area of debate, since some authors have reported no differences, whereas others suggest they offer a preventive effect against developing atopic eczema, and even a reduction in IgE concentrations in some cases.[34]

Similarly, it has been suggested that growing up in a rural area, especially on farms, could have a protective effect against the development of atopy. Several studies have found no association,[34] but a Swedish cohort study conducted over 3 decades found a reduction in the incidence of atopic dermatitis among those born after 1971 who had grown up on farms.[38]

The effect of exposure to endotoxins, a lipopolysaccharide group in the outer membrane of gram-negative bacteria, has also been studied. These could induce IL-10 and interferon-α production, as well as providing an explanation as to how pets and a farming environment might influence the frequency of atopic dermatitis. Two cohort studies[39,40] have shown that children who are in contact with endotoxins during the first months of life develop atopic dermatitis less frequently.

Clinical Presentation

There is a wide spectrum in the clinical presentation of atopic eczema, ranging from minimal lesions on flexural surfaces to erythroderma. The skin of the child usually presents severe xerosis and pruritus is a constant feature. Lesions can appear anywhere on the skin, but have a typical pattern that varies with age.[41] In infant atopic dermatitis (up to 2 years old), lesions tend to be more acute, with papules and vesicles that erode early. These usually appear on the face, especially on the forehead and cheeks, although the perioral area is usually spared. There may be extensor as well as scalp involvement. From 2 years old onward the lesions change and tend to become more chronic, with lichenification and epidermal thickening. Furthermore, the areas where they are located become more specific, with a preference for the inner folds of the elbows and knees, flexural surfaces of the wrists, anterior side of the feet, and the first finger. The lips are also often affected, and in many cases this is worsened by sucking and the constant moisture in the area.[42]

Severity and Quality of Life

Assessing the severity of atopic dermatitis has been and continues to be a subject of debate and several indexes have been designed to measure this objectively. The best known and most used is SCORAD, which combines measuring the affected surface with the rule of nines and the presence of 6 clinical features: erythema/darkening, edema/papulation, oozing/crusting, excoriation, lichenification/prurigo, and xerosis. Assessing pruritus and sleep disturbance has also been added to this index. Higher scores indicate greater severity, with 3 main grades defined: mild, scores less than 15; moderate, between 15 and 40; and severe, above 40.[43]

This index has been questioned by patients and their families, especially regarding its relationship to their subjective symptoms.[44] Other parameters have been suggested to assess the severity of the symptoms, such as combining 3 clinical signs shown to be independent predictors of severity, namely, excoriation, erythema, and edema/papulation.[45]

On the other hand, several noninvasive tests have been developed for the objective measurement of severity,[46] such as transepidermal water loss, assessment of erythema and darkening using spectroscopy, ultrasonography to identify edema, or examination of the epidermis for scaling and wrinkling. All these studies may prove useful in assessing severity and in researching the pathophysiology of the disease.

Quality of life is also a relevant parameter when dealing with a patient with atopic dermatitis. A recent study showed that this disease significantly affects mental health, emotional balance, and social relationships.[43] Furthermore, it is recommended to use of quality-of-life scales that are based mainly on these aspects and that place less importance on physical symptoms. Not only is the quality of life of the patient affected, but also that of the family. Caring for a child with atopic dermatitis has been associated with sleep disturbances in the parents, and these are comparatively greater than in parents of asthmatic children. Such sleep disturbances also correlate with a greater degree of anxiety and depression (the latter only in mothers).[47]

Diagnosis

Atopic dermatitis is diagnosed by its clinical presentation, as no test exists with sufficient sensitivity or specificity. Despite being a widely studied disease there is no definitive consensus regarding its diagnosis. Several factors may hinder consensus, such as the clinical heterogeneity of the disease, its variability over time, the involvement of other specialties, such as allergology, pediatrics, and so on.

Various diagnostic criteria have been developed to solve this problem, especially those of Hanifin and Rajka[48] on the one hand, and those of the UK Working Party, on the other. In 1980, in a consensus working group that included American and European authors, Hanifin and Rajka[48] developed a series of clinical criteria for the diagnosis of atopic dermatitis. The criteria constitute a collection of signs and symptoms that are grouped into major and minor characteristics, at least 3 of which have to be present from each group (Table 1). Under normal circumstances these criteria are difficult to apply, and this becomes more complicated due to the particular characteristics of the disease which vary with age. The UK Working Party, in turn, developed simpler diagnostic criteria (Table 2), with the collaboration of dermatologists, pediatricians, and primary care physicians.[49-51] These diagnostic criteria have been compared and those of Hanifin and Rajka have greater sensitivity than those of the UK Working Party (96% vs 86%, respectively) but have a similar specificity (93% vs 95%, respectively).[52] This would seem to indicate that the criteria developed by Hanifin and Rajka are better, but in practice many authors question their applicability, especially in population studies, due to the time required to apply them, the need for laboratory tests (IgE, patch tests); they therefore would seem more appropriate in hospital settings. Patients with mild disease are the main problem when applying diagnostic criteria; the UK Working Party criteria present difficulties, particularlly if prevalence is low and another pruriginous disease is frequent in the population.[53]

Economic Impact

Atopic dermatitis places a great economic burden on both families and healthcare systems. Several studies have been conducted to quantify the exact economic cost of prescribed treatment, medical care, patient care measures, and hours dedicated to the disease. In a multicenter study conducted recently in Germany, the mean economic cost of an outbreak of atopic dermatitis was €123 per patient. Each patient generates an annual cost of €1425, ranging between €956 (mild symptoms) and €2068 (severe symptoms).[54] A study in preschool children conducted in the United Kingdom reported mean costs of 79.59 pounds sterling per child per year, most of which was for consultations assumed by the national health system (28.62 pounds/child/y) and prescriptions (22.03 pounds/child/y). Taken as a whole, 76% of the costs of prescriptions involved emollients and hygiene and bath products.[55] A multicenter study conducted in the USA compared the costs of each disease in the atopic triad, obtaining an average of $219 per patient per year for atopic dermatitis, $627 per patient per year for asthma, and $57 per patient per year for rhinoconjunctivitis.[56] That study emphasized that, in the case of asthma and dermatitis, costs are higher when applying treatments for the first time and decrease later, which seems to indicate that learning is relevant when managing these diseases and helps to reduce the associated costs.

Treatment

Topical

In the treatment of atopic dermatitis, topical corticosteroids are considered the gold standard for assessment of other treatments.[57] A study analyzed more than 80 randomized controlled clinical trials in which atopic dermatitis was

Table 1. Diagnostic criteria of Hanifin and Rajka[45]

A. Major
Pruritus
Typical morphology and distribution:
Flexural lichenification (adults)
Facial, flexural, and extensor involvement (children)
Chronic or recurrent symptoms
Family or personal history of atopy
B. Minor
Xerosis
Ichthyosis
Palmar hyperlinearity
Keratosis pilaris
Immediate (type I) skin response
Elevated serum IgE levels
Early age of onset
Increase in cutaneous infections and impaired cellular immunity
Nonspecific dermatitis of the hands and feet
Nipple eczema
Cheilitis
Recurrent conjunctivitis
Dennie-Morgan infraorbital fold
Keratoconus
Anterior subcapsular cataract
Orbital darkening
Facial pallor or erythema
Pityriasis alba
Anterior neck folds
Pruritus when sweating
Intolerance to wool and lipid solvents
Perifollicular accentuation
Food intolerance
Course influenced by emotional and environmental factors
White dermographism or delayed blanching

Table 2. Diagnostic criteria of the UK Working Party[49-51]

Necessary
Intense pruritus in the last 12 months
At least 3 of the following
Onset before 2 years old (not applicable children under 4 years)
History of flexural dermatitis
History of dry skin
Flexural dermatitis visible on examination or in photographs
Personal history of atopy (or atopic first-degree family member if less than 4 years)

treated with topical corticosteroids with good overall outcome.[58] The potency and formulation employed depends on the area to be treated and the chronicity of the lesions, with areas that have undergone lichenification requiring stronger formulations. One application per day is sufficient, as treatment twice a day confers no advantage while increasing the likelihood of adverse reactions.[18] It has been found that the application of glucocorticoids to healthy skin twice a week can reduce the frequency of flares compared to the use of emollients alone, and thus this maintenance treatment is indicated in rapidly recurrent or severe cases.[59,60] Furthermore, its use been shown to reduce colonization of the skin by *Staphylococcus aureus*.[61] The adverse reactions are well known and frequently overestimated by patients and their family members, even though the new formulations have a demonstrated lower risk of causing cutaneous atrophy than the older ones, and that several studies have found a far lower incidence of local and systemic complications.[18]

The application of topical antibiotics in combination with corticosteroid therapy has advantages compared to topical corticosteroids.[17] Fusidic acid appears to be the topical antibacterial treatment of choice, due to its low minimum inhibitory concentration and its good penetration.[62]

Topical calcineurin inhibitors have proven to be effective in the treatment of atopic dermatitis. Topical tacrolimus seems to have an efficacy similar to high-potency corticosteroids, whereas pimecrolimus is substantially weaker.[63] Controlled pediatric studies have confirmed the superior efficacy of topical tacrolimus compared to pimecrolimus and hydrocortisone. There appear to be no significant differences between the response of children to concentrations of 0.03% and 0.1%.[64] Neither tacrolimus nor pimecrolimus cause cutaneous atrophy, but they can cause other adverse reactions such as local itching-burning sensation when being applied, which is an added discomfort for the skin of children with atopic dermatitis. No differences were found in the frequency of adverse reactions

in children between tacrolimus concentrations of 0.03% and 0.1%, nor when comparing tacrolimus with pimecrolimus.[64] The use of tacrolimus is contraindicated in patients with Netherton syndrome, due to the possibility of systemic absorption. Recently, the US Federal Drug Administration issued a warning regarding the use of both drugs, in relation to a possible lack of long-term safety and a possible association with certain tumors, especially lymphomas. A recent cohort study failed to demonstrate that the use of these products increases the risk of lymphomas.[65] On the other hand, cost-utility studies of calcineurin inhibitors vs topical corticosteroids support the use of the former as second-line drugs.[66] Similar to the situation regarding corticosteroids, several studies support the use of topical tacrolimus and pimecrolimus as maintenance treatment once the flare has improved, thereby achieving longer clinical remission and reducing the total dose of total topical corticosteroids.[67,68]

The use of emollients is widely recognized as a basic measure in the treatment and prevention of flares of atopic dermatitis. It has been shown that their use in combination with topical corticosteroids accelerates healing and decreases the total dose of corticosteroids required to resolve the flare.[69]

Systemic

Short-course systemic corticosteroids are recommended to control acute flares of eczema, taking into account that new flares are frequent after stopping treatment. Their long-term use in children is not recommended.[17]

Little evidence exists to support using oral antihistamines in atopic dermatitis.[57] When antihistamines are administered for their sedative effect rather than their antipruritic effect, sleep may be improved. In addition, children who have other atopic conditions, such as rhinitis or dermatographic urticaria, can benefit from these drugs.

Cyclosporine A has been shown to rapidly control symptoms, but new flares occur very quickly after stopping administration.[70] Continuous treatment with oral cyclosporine A provides satisfactory control of symptoms.[71] Continuous therapy with this drug (1 year) in children was compared to multiple short courses of 12 weeks with at least 7 days between courses. In general, continuous treatment was more effective, but in some cases good control of the disease was achieved with far lower cumulative doses, and so this option deserves further study.[72] A recent metaanalysis confirmed the efficacy of this drug, with clinical improvement estimated to occur in 55% of cases on average (although larger long-term studies were unavailable).[73] Other immunosuppressants, such as azathioprine, have been used to treat severe dermatitis. In a randomized clinical trial, this agent reduced disease activity by 26% in 12 weeks at a dosage of 2.5 mg/kg. However, adverse reactions have been observed, such as leukopenia and gastrointestinal disturbances, some of which were severe.[74] Fewer patients have received mycophenolate mofetil, but 2 studies have shown some promising results (improvements in 55% and 68% of cases, respectively), although the number of cases was small.[75,76]

Light therapy can be effective in managing atopic dermatitis and is frequently used in adults, although its use in children under 12 years old can only be recommended in exceptional cases.[17]

Interferon-γ seemed to be effective in some studies which included adults and children, reducing dermatitis activity by between 30% and 50%. No benefit has been found in the use of intravenous immunoglobulins.[77]

Dietary restrictions have proven effective in the case of children with egg-specific IgE, but not for other foods which have the same effect.[57] It seems reasonable to establish diets that avoid food proven to cause an allergic response using the radioallergosorbent test, although the most relevant test would be the challenge test, which in many cases cannot be performed.[17] The use of probiotics in treating and preventing atopic dermatitis initially raised hopes; however, several studies that included children found that the administration of *Lactobacillus* does not offer advantages in the treatment of eczema flares[78] or in preventing atopic dermatitis from developing.[79] In fact, a greater frequency of sensitization to various allergens was verified by the skin-prick test in children who received *Lactobacillus acidophilus* in the first 6 months of life.[79]

Biologic treatment has recently appeared in the field of dermatology and has shown some potential. Infliximab was tested in 9 adults with severe atopic dermatitis and initially a good response was achieved, although this was only maintained in the long-term in 2 patients.[80] Etanercept was used in 2 children with atopic dermatitis, without improvement and with associated complications.[81] Better results, at least initially, have been obtained with efalizumab in atopic dermatitis. A pilot study of 10 adult patients with atopic dermatitis treated with efalizumab for 12 weeks reported clear improvement in 6 patients (more than 50% on the Eczema Area and Severity Index).[82] Another study of a child with severe atopic dermatitis treated with efalizumab reported improvement; there had been little improvement previously despite having received cyclosporine and etanercept.[83] Omalizumab is an anti-IgE humanized monoclonal antibody used in treating persistent asthma in patients older than 12 years with reduced pulmonary function. Several series have obtained good responses with this agent in patients with atopic dermatitis refractory to other treatment.[84,85] Three cases have also been reported where no improvement was obtained.[86] Some authors suggest that IgE concentrations above a certain level would lead to less effect, and thus this drug could find a role in cases

where serum IgE serum concentrations are no higher than 7000 IU/mL.[87]

Psychological care is recommended to help deal with the emotional needs of patients with atopic dermatitis, and should be based on providing education and information on the clinical and preventable aspects of the disease. One study found that this type of intervention reduced anxiety scores.[88] However, a recent study conducted in Spain did not find overall differences in anxiety levels between intervention and nonintervention, although there were differences in the 9- to 15-year-old subgroup.[89]

Conflicts of Interest

The authors declare no conflicts of interest.

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