

Basic Skin Care and Topical Therapies for Atopic Dermatitis: Beyond Essential Approaches

Running title: TOPICAL THERAPIES FOR ATOPIC DERMATITIS

Sala- Cunill A^{1*}, Lazaro M^{2*}, Herráez L³, Quiñones MD⁴, Moro-Moro M⁵, Sanchez I⁶

*Both authors contributed equally to the manuscript

On behalf of the Skin Allergy Committee of Spanish Society of Allergy and Clinical Immunology (SEAIC)

¹Allergy Section. Internal Medicine Department. Hospital Universitario Vall d'Hebron. Barcelona. Spain

²Allergy Department. Hospital Universitario de Salamanca. Alergoasma, Salamanca. Spain

³Allergy Department. Hospital Universitario 12 de Octubre. Madrid. Spain

⁴Allergy Section. Hospital Monte Naranco. Oviedo. Spain

⁵Allergy Department. Hospital Universitario Fundación Alcorcón, Alcorcón, Madrid, Spain

⁶Clínica Dermatología y Alergia. Badajoz. Spain

Corresponding author:

Lys Herráez

Hospital Universitario 12 de Octubre

Madrid, SPAIN

lysherraez@hotmail.com

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ABSTRACT

Atopic dermatitis (AD) is a recurrent and chronic skin disease characterised by dysfunction in the epithelial barrier, skin inflammation and immune dysregulation with changes in the skin microbiota and colonisation of *Staphylococcus aureus* being common. For this reason, the therapeutic approach to AD is complex and should be directed at restoring skin barrier function, reducing dehydration, maintaining acidic pH and avoiding superinfection and exposure to possible allergens. No curative treatment for AD currently exists. However, a series of measures are recommended to alleviate the disease and enable patients to improve their quality of life, including adequate skin hydration and restoration of the skin barrier with the use of emollients, antibacterial measures, specific approaches reducing pruritus and scratching, wet wrap applications, avoidance of typical AD triggers and topical anti-inflammatory drugs. Anti-inflammatory treatment will be, generally, recommended during the acute flares or more recently, for preventive management. Nevertheless, the selection of the pharmacologic agent, its potency, duration and the frequency of application must be in accordance with the severity of the disease, the distribution or the type of lesion. The purpose of this review is emphasising the importance of basic skin care as well as describing the current and novel topical therapies for atopic dermatitis.

Key words: eczema, topical treatment, atopic dermatitis, pruritus, emollients.

RESUMEN

La dermatitis atópica (DA) es una enfermedad cutánea crónica y recurrente que se caracteriza por la existencia de una disfunción de la barrera epitelial, un proceso inflamatorio cutáneo, una alteración del sistema inmune y posibles cambios en la microbiota cutánea, siendo frecuente una posible colonización por *Estafilococo Aureus*. Por ello, el abordaje terapéutico de la DA es complejo y debe de estar enfocado principalmente hacia la restauración de la barrera cutánea, la reducción de la deshidratación, el mantenimiento del PH ácido y la evitación de posibles sobreinfecciones y exposiciones a diferentes fuentes alérgicas. Actualmente no existe tratamientos curativos para la DA. Sin embargo, con el fin de aliviar la enfermedad y que mejore la calidad de vida de los pacientes, se recomiendan una serie de medidas que incluyen una adecuada hidratación y restauración de la barrera cutánea gracias a la aplicación de emolientes, medidas antibacterianas, reducción del picor y del rascado mediante determinados abordajes específicos, la aplicación de vendajes húmedos, la evitación de los desencadenantes de la DA y una terapia tópica antiinflamatoria adecuada. Los tratamientos anti-inflamatorios se recomiendan habitualmente durante las reagudizaciones y, más recientemente, como tratamiento preventivo. Sin embargo, dependiendo de la gravedad de la enfermedad, la distribución o el tipo de lesión, se seleccionará el agente farmacológico, su potencia, la duración y frecuencia necesaria de aplicación. El objetivo principal de esta revisión es resaltar la importancia del cuidado básico de la piel, además de describir los tratamientos tópicos, tanto actuales como emergentes, que existen para el abordaje de la dermatitis atópica.

Palabras clave: eczema, tratamiento tópico, dermatitis atópica, prurito, emolientes

1. Introduction

Atopic dermatitis (AD) is a recurrent and chronic skin disease initially characterised by dry and very itchy skin. Onset tends to be at an early age [1]. It is estimated that it may affect 20% of the infant population in industrialised cities [2], with a higher prevalence in these areas compared to rural ones. It negatively affects the quality of life of the patients and their relatives.

AD is characterised by dysfunction in the epithelial barrier, skin inflammation and immune dysregulation with changes in the skin microbiota and colonisation of *Staphylococcus aureus* being common. It could be the first step of the so-called atopic march, which is a well-described sequential appearance of AD, rhinitis and asthma in affected patients [3]. Its physiopathology is multifactorial and polygenic [4].

2. Physiopathological mechanisms of atopic dermatitis

The epidermis, especially the stratum corneum of the skin, is the body's first line of defence against the environment and minimises loss of water from the body and protects us against harmful environmental effects. Filaggrin is its main protein. It is synthesised as profilaggrin, whose gene is located in the 1q21 chromosome [5]. During the final phase of differentiation of the keratinocytes, filaggrin monomers are produced whose degradation generates a series of products that act as an osmotic barrier promoting water retention. These products, known as natural moisturising factors (NMFs) [6], contribute to the maintenance of the acidic pH of the skin that has an antimicrobial effect and contributes to the functionality of enzymes involved in the metabolism of ceramides and differentiation of the corneal layer [4]. The recently described filaggrin gene mutations [7, 8] are considered one of the main risk factors for the development of AD. Anyway, other mutations have been associated with the risk of atopic dermatitis, such a polymorphism in the receptor of vitamin D in a Turkish population [9].

Lipids are other important molecules in the function of the stratum corneum barrier and are responsible for the production of ceramides. An alteration in the arrangement of the latter determines, as occurs with filaggrin, the poor functioning of the skin barrier [10,11]. Other mutations have been associated with the risk of atopic dermatitis such as the receptor of Vitamin D

Both innate and adaptive immunity contribute to the physiopathology of AD. Regarding innate immunity, it has been observed in patients with AD that IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) are upregulated [12]. These epithelial cytokines are associated with the accumulation of type 2 innate lymphoid cells (ILC2). In addition, also a broad array of other innate immune cells including dendritic cells, mast cells, basophils and eosinophils have been described as participating in physiopathology of AD [13].

Adaptive immunity also participates in the physiopathology of AD. An initial Th2 polarisation and an increase in cytokines such as IL-4, IL-5 and IL-13 play an important role in AD. The paradigm of an exclusive Th2 polarisation has recently been revised since the participation of other Th17 and Th22 lymphocyte populations has been described in this disease [14, 15]. In addition to CD4+ lymphocytes,

CD8+ lymphocytes have been found in the skin of patients with AD that release IFN-gamma, IL-13 and IL-22 [16]. All of these cytokines impact in innate immunity by suppressing antimicrobial peptides and have a direct effect on skin barrier integrity by suppressing differentiation proteins such as involucrin, filaggrin and loricrin.

The alteration of the skin microbiota, based on the alteration of the balance between the number of commensal and pathogenic bacteria, could be critical in the development of AD. More than 90% of patients with AD are colonised by *S. aureus* in the skin compared to 5% of healthy patients. This bacterial colonisation appears to be caused by an alteration in the production of filaggrin, due to an increased pH in the stratum corneum and the reduction of antimicrobial peptides in the epidermis [17].

Therefore, the physiopathological mechanisms of AD are very complex and include genetic factors, an alteration in the structural barrier, an altered immune regulation and changes in the skin microbiota [18]. For this reason, the therapeutic approach to AD is complex and should be directed at restructuring the epithelial barrier, reducing dehydration, maintaining acidic pH and avoiding superinfection and exposure to possible allergens. Multidisciplinary management of the patient is necessary, in many cases the participation of psychologists, nursing personnel and dieticians in addition to physicians is required [19].

No curative treatment for AD currently exists. However, a series of measures are available and help to alleviate the disease and enable patients to improve their quality of life. This review is focused to basic skin care and the most important topical treatment in AD.

3. Basic and Topical Skin Care. Essential Approaches in AD

To provide the best basic care, it is essential to assess the condition of the skin and know all the vehicles of the emollient moisturising products to adapt the best treatment according to the stage of AD [20]. An emollient is a product that promotes the occlusion of the skin and prevent water loss and a moisturiser is a product that keeps it hydrated [21]. Many products (emollients, moisturiser or emollient moisturiser) exist in the marketplace with different forms of presentation such as creams, lotions or balms among others, whose consistency varies depending on its composition. Therefore, a prior assessment of the condition of the skin is important to choose the correct treatment, as it is shown in

Table 1.

Hygiene and skin hydration

Daily hygiene with warm water baths (30–33°) of maximum 5–10 minutes is recommended. In the baths, detergents and the use of a sponge should be avoided. The aim of the bath is to clean the skin, eliminate scabs, relax the patient, decrease pruritus and facilitate the application of drugs. The use of a shower gel in the form of oil with acidic pH, neutral or acidic detergents are most recommended, since they maintain the pH of the skin and produce less irritation of the corneal layer, retaining the fatty acids. It is important to dry off with a cotton towel, with soft dabs, avoiding scratching and proceeding to the immediate application of the emollient moisturising product, within 3 minutes. Emollients with barrier action rich in ceramides [22], substances that can improve the function of the

skin barrier, and new creams and soaps with acidic pH [23], might reduce the severity and flare of AD and avoid complications.

Antiseptics

In the event of a bacterial superinfection due to *S. aureus*, very common in these patients, topical treatment with mupirocin is recommended. Also 6% bleach baths (half a cup of bleach in 180 litres of water) twice per week has demonstrated in a randomised, placebo-controlled study they efficacy [24]. In this study, in addition to bleach baths 2 days per week, topical nasal mupirocin was applied, 5 days per month in the active group compared to baths with water and the application of intranasal petrolatum in the placebo group; a significant reduction ($p=0.004$) was observed in the severity of AD compared to the placebo group. Dermatophyte infections may also be common (the most common being *Malassezia sympodialis*), especially in seborrheic areas such as the scalp, face and neck. Treatment in these cases is topical ketoconazole as a cream (1 application every 12 hours until symptoms are resolved) and as a gel if the scalp is affected (1 application twice per week, leaving it to take effect for 3–5 minutes until the symptoms are resolved) [25]. If the condition is extensive, systemic treatment with ketoconazole may be considered. In the event of nail involvement, a study demonstrated the benefit of ciclopirox olamine, 1 application every 12–24 hours until attaining regeneration [26].

Preparations with tar

Although it has been used for many years, no randomised, placebo-controlled studies exist with tar preparations [27,28]. In any case, given they have fewer side effects than corticosteroids and currently new preparations have been developed that are better tolerated, with less odour and less staining, it can be effective to use creams or ointments with 0.5–5% coal tar (mineral tar) for the chronic phase or in very lichenified areas [29]. Its application in areas of acute inflammation is not recommended since it may irritate these areas further. In general, it is applied at night and taken off in the morning with bathing. It can also be used as a shower gel (adding it to water, with anti-itch effect) and as a 0.5–3% shampoo when AD affects the scalp, once or twice weekly [30]. Exposure to sun must be avoided for at least 24 hours following application of the treatment, since tar is photosensitive.

Wet compresses for exudative lesions

When the lesions are exudative, in order to dry them, the use of compresses or astringent baths with an aqueous solution of potassium permanganate 1: 10,000 (magistral formula) is recommended. The preparation of between 20 and 100 sachets of 0.1 grams, each diluted in a litre of water is recommended. It will be applied twice or 3 times daily by the application of wet compresses for 20 minutes, until the exudative lesion dries out. Solutions with zinc sulphate, copper or silica can also be applied once or twice per day with the same objective. During the exudative period, avoiding creams is recommended as they are not absorbed and can aggravate the lesions [25].

Wet wrap therapy

Wet wrap with physiological saline are useful in AD with chronic lesions and lesions that are refractory to other treatments. To increase the local action, they can be used with diluted topical corticosteroids or emollients, if there are no signs of infection [31, 32]. Wet wraps also serve to protect the skin against scratching and avoid excoriation. Application for extended periods can cause maceration and folliculitis. A greater tendency towards local infections is observed when used with topical corticosteroids than when they are used with emollient moisturisers only [33]. For their preparation, dressings are submerged in a container with warm water and afterwards are placed on the area of the skin with lesions, where the prescribed topical treatment has previously been applied. On this first moist layer, a second one is placed with a dry dressing.

Urea

It facilitates desquamation regulating the expression of certain genes related to keratinocyte differentiation, the synthesis of lipids and the production of antimicrobial peptides, which improves the barrier function and, probably, the antimicrobial defences, according to the results of some studies [34]. In addition, it is also anti-itch. Its potency is lower than the potency of salicylic acid. It is used in concentrations that vary between 3–30%. If the concentration is elevated, it may irritate some patients with AD. A recent, multicentre, randomised, double-blind study [35] with cream with 5% urea shows that in the treatment group, the symptom-free period was significantly extended compared to the group applied with the reference cream.

Anti-pruritus Creams

Polidocanol

It is a fatty alcohol ethoxylate with local anaesthetic properties that are included in the formulation of moisturising and emollient preparations to relieve the atopic skin pruritus.

Naltrexone as a cream

In a comparative study with placebo, the application of a cream with 1% naltrexone (a μ -opioid receptor antagonist) for 2 weeks, demonstrated better and faster itch control compared to the placebo, with significant differences ($p < 0.05$) [36]. It has also been used by oral route for cases of very intense pruritus.

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This agent inhibits capsaicin responses in sensory neurons and improves itch in psoriasis. This agent has completed a phase II clinical trial in DA (NCT01808157) but the results have not been published, yet. [37]

New topical treatments

Many new topical therapies are currently being developed. Following the most important treatments with randomized controlled trials (RCTs) are presented.

Cream with 5% *Vitreoscilla filiformis*

Vitreoscilla filiformis (Vf) extract, is a photosynthetic bacterium, with good tolerance and few adverse effects (mild burning sensation a few minutes following administration) [38]. A randomised, double-blind study that compared 5% Vf cream with the vehicle, twice per day for 4 weeks, with a cream with the vehicle only, demonstrated that the group of patients that had received the cream with Vf presented, in a statistically significant manner, an improvement in SCORAD, pruritus, sleep loss and in colonisation by *S. aureus*, compared to the control group [39]. A recent study that uses a mouse model shows that the application of Vf lysates activates immunomodulatory mechanisms that reduce inflammation. This finding implies a new knowledge about the existing relationship between bacteria and host immunity [40].

Cream with phosphodiesterase-4 inhibitors (PDE-4)

There are 11 families of PDE enzymes, everyone with different selectivity. Phosphodiesterase-4 (PDE-4) inactivates cAMP (cyclic adenosine monophosphate) increasing the production of proinflammatory prostaglandins and cytokines. It is expressed in immune system cells, as well as in keratinocytes and fibroblasts, presenting greater activity in patients with AD [37]. In two conducted double-blind, placebo-controlled studies [41], ciprofylline and CP80,633 significantly reduced the severity of patients with AD compared with a cream with the vehicle only and a petroleum jelly cream, respectively, although in another study a lower efficacy was observed for ciprofylline compared to the treatment with hydrocortisone 17-butyrate. This novel therapy offers an alternative to topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) in the treatment of DA. **Crisaborole (AN2728)** is a PDE-4 inhibitor currently approved. The topical form applied in a 2% ointment (twice daily) and recently, in an advanced research phase, is showing encouraging results in children and adult patients with AD [42,43]. A long-term safety study with crisaborole 2% ointment has demonstrated efficacy, safety and well tolerance in mild to moderate DA [44]. **RVT 501 and MM36** are, also, other type of PDE-4 inhibitors that have been demonstrated efficacy in patients with DA in different RCTs [45].

Janus kinase inhibitors

Janus Kinase (JAK) and STAT (signal transducer and activator of transcription) form a signal transduction pathway. Interleukins involved in DA, such as IL-4, IL-13 and IL-31, use this pathway and they amplify the Th2 cell response and also downregulate structural epidermal proteins, e.g. filaggrin, loricrin or involucrin, diminishing the skin barrier function. Tofacitinib, is a small molecule that inhibits JAK1 and JAK3 and in theory, reduces these interleukins and, therefore, reduces inflammation [46]. Recently a phase IIa clinical trial has been published and it has demonstrated that topical 2% Tofacitinib ointment is relatively safe and superior to vehicle in the treatment of AD, however further studies should be required [47]. Others JAK inhibitors exist, but in oral formulation, such as Baricitinib (phase II clinical trial completed) and Upadacitinib (phase II recruiting) with promising results (Baricitinib is a small molecule inhibiting both JAK 1 and JAK2 [48]).

CRTH2 antagonism-Q301

Chemoattractant receptor-homologous molecule (CRTH2) is a transmembrane prostaglandin D2 receptor expressed on Th2 lymphocytes. Its stimulation leads to activation of Th2 cells and chemotaxis. This new topical cream (Q301) is thought to antagonize the CRTH2 receptor and decrease the Th2 response in AD. A phase II RCT comparing Q301 versus vehicle in patients with moderate to severe AD was recently completed (NCT02426359) but the results have not already been published [37]. In addition, two phase II clinical trials with CRTH2mAb have been completed with promising results (Fevipirant and Timapirant) [47].

Cream with Vitamin B12

Vitamin B12 inhibits the production of inflammatory cytokines produced by T lymphocytes, because it is an effective scavenger of Nitric Oxide and therefore represents a potentially effective treatment for AD [49]. In a phase III, multicentre, randomised, placebo-controlled clinical trial, topical vitamin B12, applied twice per day for 8 weeks on the affected areas, demonstrated to be effective in reducing the extension and severity of AD ($p < 0.001$), with no adverse effects and with good tolerance [50]. Recently, these results have also been obtained in a one hemi-body randomized, controlled, single-blind, intra-patient left-to right study with topical vitamin B12 barrier-cream (MB12) vs glycerol-petrolatum-based emollient cream (GPC). The group treated with MB12 improved significantly ($p < 0.001$) the symptoms in SCORAD as well as the itching, suggesting that MB12 could represent a new option in the treatment of DA [50].

5. Anti-inflammatory topical therapy for AD

The two most important classes of drugs with anti-inflammatory properties for the topical treatment of AD include the topical corticosteroids (TCSs) and the topical calcineurin inhibitors (TCIs).

5.1 Topical Corticosteroids

TCSs are the first-line pharmacological treatment for AD. They possess anti-inflammatory and immunosuppressant effects in addition to an antiproliferative and vasoconstrictive action [51]. The mechanism of the anti-inflammatory activity of TCSs is not fully known; they suppress various components of the inflammatory pathway, including the release of inflammatory cytokines, and they act on various cells of the immune system, from T lymphocytes, monocytes and macrophages to dendritic cells and their precursors [52]. They disseminate through cell membranes and interact with the cell receptors of dermal cells. The potency of TCSs is determined by the vasoconstriction [53] generated, measuring the degree and the duration of skin clearing following its application. As a national reference guide, 4 groups have been classified based on their potency: very high (class IV), high (class III), moderate (class II) and low (I), as shown in Table 2. Prescribers should know the existence of other guides, such as European [54] or US-American [55], with different TCSs potency classification and drug formulations. The efficacy of treatment with TCSs depends on factors such as

potency, which responds to specific modifications of the TCS molecule, in addition to the concentration of the active ingredient. For example, 1% hydrocortisone acetate is a low potency TCS whereas 0.1% hydrocortisone butyrate is a potent TCS. The pharmaceutical form of the drug facilitates its penetration and therefore influences its efficacy. Correct application, sufficient dose, the use or non-use of occlusive dressing, the prior condition of the skin and the anatomical area of application, determine the absorption of TCSs and should be considered to minimize TCSs related side effects [55].

Selection of the TCS for AD

The appropriate choice of a TCS for the treatment of AD can be complex since the number of clinical studies that compare two or more preparations are limited. Before prescribing this treatment, factors that influence its effectiveness and the risk of side effects must be considered. It is recommended applying low to intermediate potency TCSs on the face and genital areas although other higher potency TCSs can be applied on the rest of the corporal surface [56]. As a general recommendation in children, low potency TCSs are applied on any area [57]. The areas with lichenification require the application of more potent TCSs for a longer period. The vehicle in which a TCS is available may modify its potency and it must be considered according the anatomical area of application, the age of the patient and the severity of AD. Ointments provide a more uniform coverage and penetration than creams which, nevertheless, are applied more easily in numerous areas, including flexural and genital areas. Foams, lotions and gels are easier to apply in hair-bearing areas and are preferred in oily areas [58]. The preferences of the patient for one or other formulation must be considered to facilitate treatment compliance.

Frequency of application

According to current guidelines, twice-daily application of corticosteroids is generally recommended for the treatment of AD; however, evidence suggests that once-daily application of some corticosteroids may be sufficient [59]. Some TCSs such as fluticasone propionate and methylprednisolone aceponate have demonstrated their efficacy with one daily application [60,61]. Despite this, application of the TCSs twice daily may be chosen initially and the frequency of application can be reduced once improvement is achieved.

Treatment duration

TCSs are applied for 3 to 5 days until AD control is obtained and up to 2 weeks in moderate and severe AD [62]. The key symptom to evaluate treatment response is the improvement of pruritus which would indicate reduction in the frequency of treatment application [63]. Various therapeutic options may be considered since prescription habits are multiple and variable. Generally, for most of the topical TCs regardless of the potency, applied one or two times per day for two to four weeks [56] is recommended. (Table 3)

How to apply TCSs

TCSs must be applied on hydrated skin. They can be used together with emollient moisturisers, but their application on inflamed areas of the skin is recommended for approximately 15 minutes before an emollient moisturiser is used, if the TCS is an ointment whereas if it is a cream it could be applied after the emollient [63]. The use of an appropriate amount of TCS helps to reduce the

occurrence of side effects. A standardized finger-tip unit [64] has been devised to measure the amount of ointment necessary to cover specific anatomic areas adequately. Considered a valid method for the safe application of TCSs, one unit corresponds to the amount of ointment applied from the distal skin crease to the tip of the palmar aspect of the index finger, as shown in figure 1. One fingertip unit is approximately equivalent to 0.49 g of ointment and is required for adequate coverage of specific skin area equivalent to both palms in adults (2% of body surface area).

Wet Wrap Therapy

The use of topical corticosteroids as wet wrap would be a therapeutic option in recalcitrant cases [65]. Wet wrap act as an occlusive barrier that facilitates the penetration of the TCS in the skin, increasing the amount of medication released to the affected areas [66]. In general, double layer wrap (one layer impregnated with steroids diluted to 10% with emollients covered by another dry layer) is applied directly to the involved skin. They are recommended once daily for an average of 7 days (2–14 days) in children with refractory or severe AD [65]. The use of wet-wrap dressings with diluted topical corticosteroids has been found to be more efficacious, as a short-term intervention treatment in children with severe and/or refractory AD, than wet-wrap dressings with emollients only [66,67]. In a recent study by Leloup et al [68], significant improvement in SCORAD was demonstrated in children with the use of wet wrap by applying fluticasone propionate diluted to 25–50% with an emollient, for more than 6 hours per night until the erythema and pruritus disappear and, subsequently, maintaining the application twice or three times per week. Its efficacy in adult patients has also been demonstrated [69]. The correct explanation of the wet wrap technique and its application by nursing staff skilled in this type of therapy is of utmost importance [68].

Proactive treatment

Some studies suggest the beneficial effect of the preventative application of a potent TCS intermittently (twice weekly) and for an extended period, to avoid flare of AD. The application of either fluticasone propionate twice weekly (0.05% cream or 0.005% ointment) [70] or methylprednisolone (0,1% cream) [56] together with daily emollient products, significantly reduces the risk of relapse of AD in children and adult patients.

Topical corticosteroids in AD and pregnancy

Only the application of low or intermediate potency TCSs is recommended. An association between the application of high potency TCS and a reduction of foetal growth has been observed [71].

Adverse effects

TCSs have been used in clinical practice since 1962, although there is not much data on their adverse effects apart from those observed during a few weeks of treatment. However, it has been accepted that when they are applied long-term, but at the recommended doses, and with low or intermediate potency preparations [56], they are safe topical drugs with rare side effects. Although changes in the concentration of serum cortisol and, even hypothalamic pituitary axis (HPA)

suppression following long-term treatment with TCSs have been reported in some studies [72,73] the application of TCSs at any potency for short periods does not produce a clinically or statistically significant suppression of adrenal function [74, 75]. Other adverse effects that may appear with the use of TCSs include the occurrence of irritation at the application site, hypertrichosis, stretch marks, telangiectasia malaris, acne, folliculitis, bacterial infection, skin atrophy, contact dermatitis and glaucoma. Use of high potency corticosteroids, chronic use, applications to highly permeable and/or large areas, occlusion, poor skin integrity, systemic diseases and younger or older age, are factors to predispose cutaneous and systemic side effects. The risk of TCSs side effects is a common concern for parents or caregivers of children with AD and may generate a negative influence on the treatment adherence. Scientific information about the existence of approximately 25% of patients who avoid the treatment for this reason [58, 67] are provided.

Side effects of Wet Wrap Therapy

When they are applied for a period of 2 to 14 days in children, a temporary systemic bioactivity of the TCSs has been observed. This risk decreases if the amount of TCS is reduced, applying it once daily or at a greater dilution [68]. Side effects such as folliculitis, refractory lesions in the exposed areas, impetigo and herpes infections may also appear, although these are considered uncommon [67].

Contact Sensitization

It should be considered whenever there is worsening or failing to respond of skin lesions with TCSs application. Epicutaneous test should be considered to determine hypersensitivity to TCS itself or to some component of the vehicle. The prevalence was found to be higher with non-halogenated than with halogenated-corticosteroids and was considered the most prevalent contact allergen of the year in 2005 [76].

5.2 Topical calcineurin inhibitors

Tacrolimus (produced by *Streptomyces tsukubaensis*) and pimecrolimus (produced by *Streptomyces hygroscopicus*) belong to a new class of topical immunomodulators/immunosuppressants known as calcineurin inhibitors [52]. Both drugs bind and inhibit the action of this protein that is implicated in the activation of T cells, inhibiting the production of cytokines that participate in the inflammation of AD. Their efficacy has been demonstrated in comparison with the placebo in clinical trials for short and long-term use [77-79]. They are indicated as second-line treatment of AD that is not controlled with TCSs, when there is a significant risk of adverse effects due to their application or when they are contraindicated [54]. Topical tacrolimus is available as a 0.03% and 0.1% ointment and topical pimecrolimus as a 1% cream. 0.1% tacrolimus is approved for the treatment of adult patients, whereas 1% pimecrolimus and 0.03% tacrolimus are approved in the treatment of children aged over 2 years [80] and in adults [81]. Application in children under the age of 2 years is not recommended, although the safety and tolerance of 1% pimecrolimus in children from 3–23 month has been reviewed for 2 years and no cases of malignancy or signs of immunosuppression have been encountered [82]. The anti-inflammatory potency of the 0.1% tacrolimus ointment is similar to TCSs with intermediate potency [83] whereas the latter are clearly more active than 0,03% tacrolimus ointment [84]. In two systematic

reviews on the potency of topical tacrolimus [84,85] it is concluded that 0.03% and 0.1% tacrolimus is superior to 1% hydrocortisone acetate or 1% pimecrolimus, similar to information contributed by a previous review [86].

Indications and application methods

Tacrolimus. In children, start with a 0.03% application, twice daily, for a maximum of 3 weeks. Subsequently, the application frequency must be reduced to once daily until visible lesions were cleared. In adult patients, 0.1% tacrolimus must be used (according to the summary of product characteristics) from the start of the AD flares until clearance of the lesion [87,88]. The application of emollients must be postponed at least half an hour, so that it does not interfere with the absorption of the drug. As a proactive treatment, the application of tacrolimus ointment is effective and safe up to 1 year to reduce the number of flares and improve the quality of life of children and adult patients [89]. A maintenance regimen can be used with tacrolimus 2 consecutive days weekly to prevent flares [90,91]. However, TCSs (fluticasone propionate) may be more effective in the prevention of AD flares compared to tacrolimus. More research into this area is warranted before recommendation can be offered regarding the best therapeutic option. [92].

1% pimecrolimus. In patients with mild to moderate AD, used twice daily, it reduces itching and erythema (48 hours after starting treatment). If it is applied following the first signs of recurrence, it can reduce flares and the amount of TCSs used [93]. The long-term application of 1% pimecrolimus also has a preventative effect on flares and maintains AD improvement attained initially; patients present only minimal residual lesions, in a period of 2 years [25,80].

There is poor scientific evidence available regarding the combined application of TCSs and TCIs. Herbert et al. [94] studied the use of 0.25% desoximetasone and 0.1% tacrolimus, twice daily, compared to tacrolimus and placebo, twice daily, in more than 80 adults with AD. The combined therapy was statistically more effective and presented similar side effects to the other groups. In addition, the pruritus and burning sensation associated with the application of tacrolimus were logically lower in the group with the combined therapy. The TCIs applied by wet wrap dressings could represent an alternative to the application of TCSs, as long as the data on their systemic absorption confirm that they do not reach immunosuppressive levels [95].

Side effects

Both tacrolimus and pimecrolimus present a good safety profile [86]. The most common side effect is a burning sensation following their application. In this respect, a comparative study in children with 0.03% tacrolimus and 1% pimecrolimus [96] showed better local tolerance to 1% pimecrolimus. Unlike TCSs, they do not produce skin atrophy, which should be considered when the skin surface to treat is particularly delicate, such as the face or flexural areas. During treatment with TCIs, generalised viral infections have been observed such as *eczema herpeticum* or *eczema molluscatum* although an increase in their frequency has not been demonstrated or only temporarily, in different clinical trials [97,98]. In 2005, the FDA issued a warning regarding the potential relationship between these pharmacological agents and malignancies (especially

lymphoma and skin cancer) based on the results of animal studies, case reports, and the knowledge of their mechanism of action [99,100]. Long-term data is needed on the possible carcinogenicity, although currently there is no proof of a causal relationship [83,101]. Some authors consider that this recommendation and the minimum age for their application in children should be reviewed [101].

6. Phototherapy

Phototherapy consists of exposure to light by the application of ultraviolet (UV) rays. It is a second-line treatment for severe AD in adolescents and adults [102]. The beneficial action of phototherapy is due to its anti-inflammatory effects and immunomodulating properties. In the treatment of AD, various modalities may be used that include narrow-band UVB (NB-UVB), UVA 1, psoralens plus UVA (PUVA), wide-band UVA, wide-band UVB, and these last two combined [103,104]. The result of various systematic reviews [105-106] supports the use of the UVA 1 phototherapy (340–400 nm) and NB-UVB (311 nm) in moderate to severe AD. Whereas NB-UVB radiation is the preferred phototherapy modality for the treatment of patients with refractory AD, UVA 1 radiation, which is less available, may be more effective for the treatment of severe acute flare-ups in patients with AD [107,108]. The treatment regimen in this case would be to administer a short cycle of medium dose UVA 1 until improvement, followed by NB-UVB. In general, it is applied 3 times per week for at least 2 months (an average of 20–30 sessions) [104,106]. There is little evidence for the use of PUVA in patients with AD and its application is considered when NB-UVB phototherapy has not been effective [108]. Phototherapy in children with severe AD is moderately effective and, in general, well-tolerated. The risk of long-term side effects is unknown; therefore, it should be limited to the most severe cases that are refractory to other treatments [109-111]. Its application in pregnant women is not recommended as there is no evidence in this population group. Side effects may appear in the short (acute pruritus and burns) and long term (premature skin ageing and increased risk of skin cancer). Appropriate equipment and trained personnel are needed for its administration, which can limit its use in some cases [112].

Conclusions

Treatment of AD can become a great challenge even for the most expert physician. The essential skin care in AD should be based on those topical therapies to impact AD physiopathology, diminish inflammation, improve pruritus, as well as avoid the infections and side local effects. Not only we might focus on the management of acute AD flares, but we need to establish an adequate long-term maintenance regimen and prophylactic approach. Although there are multiple and optimal topical therapeutic options trying to control AD, other innovative therapies are being investigated looking for the goal to reduce the severity of this disease, decrease its activity and improve the quality of life of patients with AD.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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TABLES AND FIGURES

Table 1. Treatment of AD according to the skin condition

<p>Acute phase (erythema, oedema, vesiculation and exudation)</p> <ul style="list-style-type: none"> • If exudative lesions are present: astringent compresses or baths with an aqueous solution of potassium permanganate at 1:10,000 or a solution of zinc, copper and silica. • Hydration in the form of lotion. • If topical corticosteroids are needed, apply ones of low potency and as a lotion.
<p>Subacute phase (erythema and minimal vesiculation)</p> <ul style="list-style-type: none"> • Hydration in the form of creams or lotions. • If topical corticosteroids are needed, apply ones of medium potency and as a cream. • Topical immunomodulators as a cream.
<p>Chronic phase (lichenification, intense xerosis and scales)</p> <ul style="list-style-type: none"> • Hydration in the form of creams or ointments • Prepare wet wraps with physiological saline and add corticosteroids to increase the anti-inflammatory effect. In lichenified areas, increase occlusive dressings • If topical corticosteroids are needed apply as an ointment or balm • Topical immunomodulators as a cream or ointment • Add urea as a keratolytic agent in very lichenified areas or areas with scales • Preparations with tar in very dry or lichenified areas may also be added

Table 2. Classification of the corticosteroids according to their potency and the vehicle available (modified from Martindale [18])

<p>Very high potency (IV)</p> <ul style="list-style-type: none"> - 0.05% clobetasol propionate (cream, ointment, lotion) - 0.3% diflucortolone valerate (ointment, balm) - 0.2% fluocinolone acetonide (cream, solution) - 0.1% halobetasol (cream)
<p>High potency (III)</p> <ul style="list-style-type: none"> - 0.025% beclomethasone dipropionate (cream, ointment, balm, emulsion) - 0.05% betamethasone dipropionate (cream, ointment) - 0.5–0.1% betamethasone valerate (cream, ointment, solution, gel) - 0.025% budesonide (cream, ointment) - 0.25% desoximetasone (cream, ointment) - 0.1% diflucortolone valerate (cream, ointment, balm) - 0.025% fluocinolone acetonide (cream, solution, gel) - 0.005 and 0.05% fluticasone propionate (cream) - 0.1% hydrocortisone butyrate (cream) - 0.1% methylprednisolone aceponate (cream, ointment, balm, emulsion, lotion) - 0.1% triamcinolone acetonide (cream)
<p>Moderate potency (II)</p> <ul style="list-style-type: none"> - 0.05% clobetasone butyrate (cream)

<ul style="list-style-type: none"> - 0.01% fluocinolone acetonide (cream) - 0.25% fluocortolone hexanoate (cream) - 0.127% hydrocortisone aceponate (cream, ointment) - 0.1% hydrocortisone buteprate (cream, ointment) - 0.1% mometasone furoate (cream, ointment, balm, solution) - 0.25% prednicarbate (cream, ointment, balm, solution)
<p>Low potency (I)</p> <ul style="list-style-type: none"> - 0.75% fluocortin (cream, ointment) - 0.1–2.5% hydrocortisone acetate (cream, ointment, lotion)

Table 3. Recommendations and key points in the use of topical corticosteroids in AD

<ul style="list-style-type: none"> • TCSs are the main anti-inflammatory drugs in the acute phase of AD; they have a significant effect on the improvement of skin lesions compared to the placebo. • The possible adverse effects in general are mild and temporary. • The recommended TCSs are those that present a better risk-benefit ratio, applying them correctly (finger-tip unit) and assessing the potency of each one of them based on the severity and the area to treat. • Application of a low potency TCS on the face and neck. An intermediate potency TCS can be applied for short periods (3–5 days) in severe flares. • Application of an intermediate or even a high potency TCS for short periods (7–14 days) in delicate body areas such as the axilla region or the inguinal fold. • In severe or refractory AD, the efficacy of the TCSs may increase by Wet Wrap procedure with diluted TCSs, once per day for approximately 7 days; this is a relatively safe treatment in both children and adults. • Avoid use in children under 6 months of age.
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- In pregnant women, use low potency TCSs.
- They should be applied once daily, except in more severe cases when they can be applied twice per day.
- “Proactive” treatment (twice weekly application) can improve the long-term follow-up and reduce flares.

Figure 1. Correct method of applying the corticosteroid (Finger-tip unit)



Table 4. Recommendations for calcineurin inhibitors in the treatment of AD (modified by Ring J et al.43)

- They are effective compared with the placebo in the short and long-term treatment of AD.
- They are specifically indicated in sensitive skin areas (face, folds, anogenital region).
- 0.03% tacrolimus and 1% pimecrolimus are applied as second-line treatment in children aged over 2 years and adults with mild-moderate AD. 0.1% tacrolimus is only indicated in adults with moderate or severe AD.
- Tacrolimus has been effective as a proactive treatment (applied two consecutive days weekly).
- Effective sun protection is recommended during treatment period.

Table 5. Recommendations for therapeutic regimens according to the severity of AD

<p>Mild forms</p> <ul style="list-style-type: none"> • Topical corticosteroids of low-medium potency (use the appropriate vehicle according to the condition of the skin and the area to treat). • 1% topical pimecrolimus in children ≥ 2 years and adults.
<p>Moderate forms</p> <ul style="list-style-type: none"> • Topical corticosteroids of low-medium potency (use the appropriate vehicle according to the condition of the skin and the area to treat). • 1% topical pimecrolimus in children ≥ 2 years and adults. • 0.03% topical tacrolimus in children ≥ 2 years and adults. • Oral antihistamines. • Topical or oral antibiotics. • Phototherapy.
<p>Severe forms</p> <ul style="list-style-type: none"> • Topical corticosteroids of medium-high potency (use the appropriate vehicle according to the condition of the skin and the area to treat) and in areas that are very lichenified use high-very high potency. • 0.03% topical tacrolimus in children ≥ 2 years and 0.1% topical tacrolimus in adults. • Oral antihistamines. • Topical or oral antibiotics. • Phototherapy/ Systemic treatment.