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Systematic Review of Management Approaches of Atopic Dermatitis

[1]Mohammad siraj ahmad alghamdi, [2]Sarah Fahad Altemani, [3]Naif saeed alzahrani,
[4]Afnan dheifallah Alotaibi, [5]Abdullah AEDH AlOtaibi,
[6]Ibrahim Ghazy Kiran Alreshidi, [7]Eyman Omar Halabi, [8]Rahmah Rubayyi AlJadani,
[9]Waad Ahmed shalabi, [10]Abdulaziz Aati alharbi, [11]Zena Maasarji,
[12] Ghadah Abdulrahman Bukhari

Abstract: **Atopic dermatitis (AD) also known as atopic eczema and it is a common persistent skin disease identified by serious pruritus. It generally appears in infancy or youth and might persist into adulthood. We aimed by this systematic review study to highlight the most effective management for atopic dermatitis through evaluating the literature in this topic, and also to emphasize the proper treatment in different populations. All data sources were identified through computer-assisted searches of electronic databases of medical references, accompanied by complementary manual searches of the literature. In collaboration with a research librarian, the MEDLINE database and the Cochrane Central Register of Controlled Trials were searched with the following key words: 'atopic dermatitis' and 'eczema' combined via the AND operator to the keyword 'treatment options' after all search terms had been exploded by the Medical Subjects Heading (MeSH) thesaurus. Returned results were restricted to clinical trials. Phototherapy with UVA1 is probably the most effective method for treating severe AD. An upkeep regimen of topical corticosteroids might lower regression rates in patients who have reoccurring moderate to extreme atopic dermatitis. Pimecrolimus and tacrolimus are calcineurin inhibitors that are advised as second-line treatment for individuals with moderate to serious atopic dermatitis and who are at risk of atrophy from topical corticosteroids.**

Keywords: **Atopic dermatitis (AD), Medical Subjects Heading (MeSH).**

1. INTRODUCTION

Atopic dermatitis (AD) also known as atopic eczema and it is a common persistent skin disease identified by serious pruritus. It generally appears in infancy or youth and might persist into adulthood. Introduced in the 1950s, topical corticosteroids have actually long been the requirement of care for the treatment of AD [(1)]. A genetic defect in the filaggrin protein is thought to cause atopic dermatitis by interrupting the epidermis. This disruption, in turn, results in contact between immune cells in the dermis and antigens from the external environment leading to intense itching, scratching, and inflammation [(2)]. Scratching can then cause more disturbance and inflammation of the epidermal skin barrier; this has been referred to as the itchscratch cycle [(3)].

The beginning of atopic dermatitis generally is prior to two years of age, with only 10 percent of cases detected after 5 years of age [(3)]. A 2003 survey of children in the United States approximated an overall prevalence of approximately 11 percent, and as high as 19 percent in some states [(4)]. A 2007 U.S. population-based study recommended an approximated 17.8 million persons are dealing with atopic dermatitis, and the majority of cases have actually not been diagnosed [(5)].

Atopic dermatitis can present in three medical phases. Acute atopic dermatitis provides with a vesicular, weeping, crusting eruption. Subacute atopic dermatitis presents with dry, scaly, erythematous papules and plaques [(6)]. Persistent atopic dermatitis demonstrates lichenification from duplicated scratching. A more subtle discussion of atopic dermatitis that typically happens in children is pityriasis alba, which is characterized by hypopigmented, inadequately demarcated plaques with fine scale. Atopic dermatitis has the tendency to involve the flexural surface areas of the body, lateral and

anterior neck, eyelids, forehead, face, wrists, dorsa of the feet, and hands. Since atopic dermatitis has lots of appearances, the differential diagnosis is broad (**Table 1**) [6].

Objective:

We aimed by this systematic review study to highlight the most effective management for atopic dermatitis through evaluating the literature in this topic, and also to emphasize the proper treatment in different populations.

Table 1. Differential Diagnosis for Atopic Dermatitis *Information from reference (6).*

Candidiasis	**Nummular eczema**
Conditions that cause generalized	**pruritus Psoriasis**
Contact dermatitis	**Scabies**
Dermatitis herpetiformis	**Seborrheic dermatitis**
Impetigo	**Urticaria**
Lichen simplex chronicus	

2. METHODS

For this **systematic review** we have followed the guideline for reviews in conducting this study.

Search strategy:

All data sources were identified through computer-assisted searches of electronic databases of medical references, accompanied by complementary manual searches of the literature. In collaboration with a research librarian, the MEDLINE database and the Cochrane Central Register of Controlled Trials were searched with the following key words: 'atopic dermatitis' and 'eczema' combined via the AND operator to the keyword 'treatment options' after all search terms had been exploded by the Medical Subjects Heading (MeSH) thesaurus. Returned results were restricted to clinical trials. The two databases were searched for materials published through past decades to December 2016. The references of relevant articles were reviewed as part of a complementary manual search. The titles and abstracts of all reports generated by the search were reviewed by multiple reviewers. Only controlled clinical trials, review and systematic reviews discussing the treatment of AD in human subjects published in English language were included.

3. RESULTS

Phototherapy treatment of AD:

Treatment with ultraviolet (UV) phototherapy has actually been successfully used in the management of this disease and may represent among the most efficacious, well-tolerated treatments of AD. In 1978, Morison et al. [7] released one of the earliest reports of UV phototherapy for AD. This research study, prompted by the scientific observation that lots of atopic patients demonstrate appreciable improvement throughout the summer months, recorded the benefits of psoralen photochemotherapy with UVA for patients with AD.

- **UVA1 for the treatment of acute AD**:

Phototherapy with UVA1 (wavelength 340 - 400 nm) represents a fairly new treatment modality for AD. Krutmann et al. [8] demonstrated that highdose UVA1 treatment (130 J/cm2), as compared with conventional treatment with combined UVA and UVB (UVAB), achieves a more considerable improvement in the severity of signs as measured with a scoring system created by Costa et al. [9]. A later study by Krutmann et al. [10] registered 53 hospitalized patients with extreme, acute AD and randomized them into 3 treatment groups. One group was treated with high-dose UVA1 treatment, another group got just topical mid-potency corticosteroids, and a 3rd group was treated with UVAB. Phototherapy with UVA1 was revealed to be substantially superior to both options after 10 treatments. Von Kobyletzki et al. [11] investigated a unique UVA1 device created to decrease the huge heat load generated by conventional UVA1 machines. The so-called UVA1 cold-light was compared with traditional UVA1 and with UVAB in a research study including 120 patients with serious, intense AD. The cold-light UVA1 modality demonstrated superiority to both UVA1 and UVAB for lowering disease intensity as measured with the SCORAD [12] system immediately after treatment for 3 weeks and at 1-month

follow-up examinations. In all three research studies, the majority of the result of UVA1 phototherapy was observed early in the course of treatment.

UVA1 appears to be a better option for acute AD based on the readily available proof, no extrapolations can be made concerning its role in handling chronic AD. Numerous regulated scientific trials [13,14,15,16] have been conducted to identify the optimal wavelength of UV phototherapy for patients with chronic AD. In two different paired-comparison studies [13,14], Jekler and Larko ¨ investigated using UV radiation for dealing with persistent AD. Their very first research study [13] compared UVB to combined UVAB phototherapy. Thirty patients were treated with UVAB on one side of the body and with UVB on the contralateral side, with left-side and right-side projects figured out arbitrarily. Statistically substantial distinctions in favour of combined UVAB were demonstrated for 3 crucial specifications: pruritus score, total evaluation score [13]. No distinction was seen with respect to the level of dermatitis as calculated by body area. The second trial by Jekler and Larko ¨ [14] enrolled an overall of 43 patients into two treatment arms. One group of patients got low-dose UVB on one half of the body and combined UVAB on the contralateral side, while the second group was treated with UVA and combined UVAB in a comparable fashion. Statistically considerable lead to favour of UVAB were again demonstrated in both research study arms as determined by healing score, general evaluation score, and sum total rating.

Topical Corticosteroids & topical calcineurin inhibitors (TCIs) for treatment of AD:

There is currently no cure for AD, so disease management is concentrated on trigger avoidance and relief of signs. First-line upkeep treatment consists of nonpharmacological treatment with different emollients and skin barrier repair work representatives, which have actually been shown to enhance skin look and dryness and/or to minimize the need for pharmacological treatment [17,18]. When flares occur, anti-inflammatory agents are utilized to manage the inflammatory aspects of the disease. For several years, the main medicinal alternative was topical corticosteroids; however, in December 2000, tacrolimus ointment 0.03 % (for patients ≥ 2 years of age) and 0.1 % (for patients > 15 years of age) were approved as second-line short-term or intermittent chronic therapy for patients ≥ 2 years of age with moderate-to-severe AD [19]. In December 2001, pimecrolimus cream 1 % was authorized for the very same sign in patients ≥ 2 years of age with mild-to-moderate AD (20). Due in part to concerns about corticosteroid use, TCIs rapidly became a popular treatment alternative. Prior to the approval of tacrolimus (1997-2000), topical corticosteroids were prescribed during 34 % of all AD-related visits in the US; between 2001 and 2004, that portion was up to 25 %, and TCIs were recommended throughout 23 % of gos to [21].

Topical corticosteroids are first-line treatment for atopic dermatitis flare-ups [22,23]. The strengths range from group I, which is most powerful (e.g., clobetasol [Temovate], through group VII, which is least potent (e.g., hydrocortisone 1%). In general, the effectiveness ought to be tailored to the severity of the disease. For individuals with lichenified plaques consistent with chronic eczema (e.g., lichen simplex chronicus), higher-potency corticosteroids for longer time periods often are needed, and occlusive treatment can be handy [22,23].

One RCT has broken new ground by trying to examine the effectiveness of topical corticosteroids in avoiding relapse instead of the normal trend of simply aiming to demonstrate short-term efficacy. The research study's methodological deficiencies and missing out on data gone over in other places [24] made it hard to say whether prevention of relapse was due to application of steroids to previously healed sites or due to application to 'new' locations, in which case, the study has actually ended up being a straightforward vehicle-controlled contrast. The study did however recommend a benefit of using periodic topical corticosteroid to prevent relapse. Generalizing from the 37.5% subsample of initial research study participants is likewise troublesome. This is one of the very first studies to look at long-lasting outcomes of this persistent disease in a practical way. When utilized in short bursts over a long period [24].

Mechanism of Action of topical calcineurin inhibitors (TCIs)

Tacrolimus and pimecrolimus are macrolactams with immunosuppressive characteristics. Both TCIs are believed to apply their immunosuppressive results by hindering the activation of T lymphocytes, thereby decreasing the release of the numerous proinflammatory cytokines talked about previously (**Figure 1**) [25]. Unlike topical corticosteroids, TCIs do not have an impact on Langerhans' cells and do not reduce the varieties of Th cells in healthy skin [25]. Transepidermal penetration of both TCIs is lower (70- to 100-fold) than that of topical corticosteroids, with the transepidermal flux of pimecrolimus in cream being roughly fivefold lower than the flux of tacrolimus in lotion [25]. Due to these qualities,

tacrolimus and pimecrolimus have been investigated for a variety of other inflammatory skin diseases [26] and oral and intravenous tacrolimus is indicated for graft-versus-host prophylaxis [27].

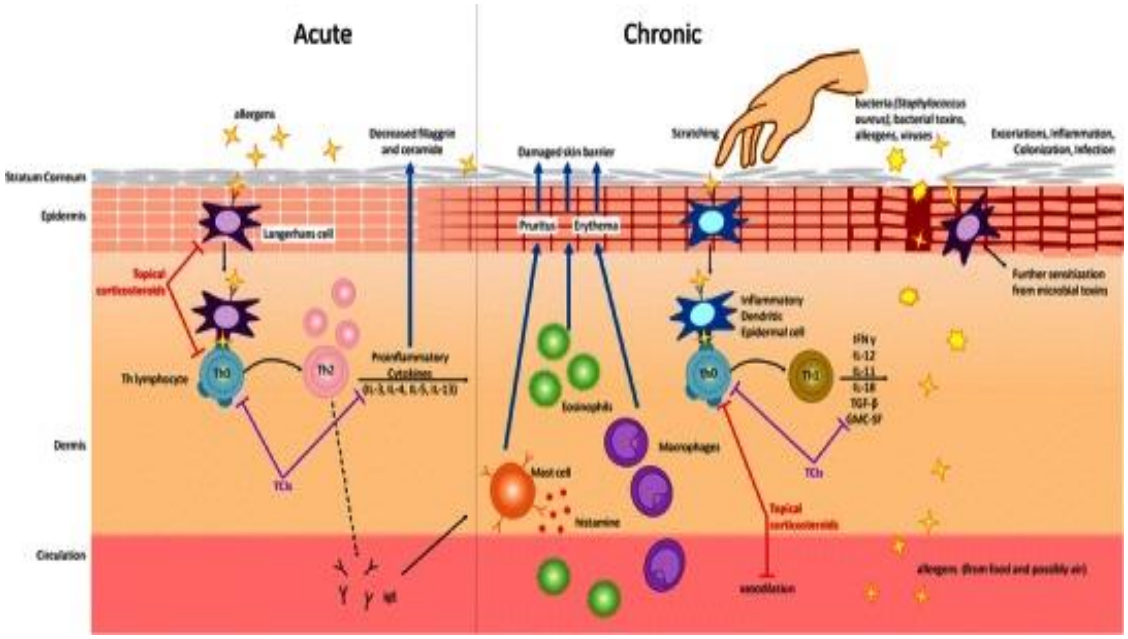

Figure 1: The mechanism of atopic dermatitis and sites of action of topical calcineurin inhibitors and topical corticosteroids. *GMC-SF* granulocyte-macrophage colony-stimulating factor, *IFNγ* interferon γ, *IL* interleukin, *IgE* immunoglobulin E, *TCI* topical calcineurin inhibitor, *TGF-β* tumor growth factor- β, *Th* helper T lymphocyte [25]

Adverse effects of Topical corticosteroids:

RCTs are not the best studies to assess adverse results. A more comprehensive search for other monitoring and case-control information is required, which is beyond the scope of this review. Those RCTs that have actually specifically collected information on skin thinning and suppression of the pituitary-- adrenal axis have actually cannot find any evidence of harm, though these research studies are very short-term. The research study on avoidance of regression [28] likewise found no proof of skin thinning after 4 months, intermittent use of a potent topical corticosteroid. Four other RCT studies of topical corticosteroid use in healthy volunteers reviewed elsewhere [29] show skin thinning at 6 weeks, which reversed within 4 weeks of stopping. While there are certainly periodic scary stories of individuals establishing Cushing's syndrome, irreversible skin thinning and striae after long-lasting use of potent topical corticosteroids in large areas, there is no proof to suggest that they are an issue for normal clinical usage characterised by bursts of 1 - 2 weeks' treatment followed by 'vacation' periods with emollients just. Nonetheless, steroid 'phobia' is now strongly established in the UK among both doctors and patients [30].

4. CONCLUSION

Phototherapy with UVA1 is probably the most effective method for treating severe AD. An upkeep regimen of topical corticosteroids might lower regression rates in patients who have reoccurring moderate to extreme atopic dermatitis. Pimecrolimus and tacrolimus are calcineurin inhibitors that are advised as second-line treatment for individuals with moderate to serious atopic dermatitis and who are at risk of atrophy from topical corticosteroids.

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