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Topical Treatment for the Management of Atopic Dermatitis

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ABSTRACT

Atopic dermatitis affects up to 20% of children and continues to increase in prevalence. Effective disease control is aimed at decreasing symptoms and reducing the frequency of flares, which may be complicated by secondary bacterial infections. Although recent advances have produced a number of non-systemic treatment options, topical corticosteroids remain a fundamental component of treatment algorithms.

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INTRODUCTION

Atopic Dermatitis (AD) is a chronic, relapsing, pruritic inflammatory skin disease with an estimated prevalence of 15-20% in children.[1] The onset of AD occurs within the first year of life for approximately 60% of children, most commonly at 6 months of age.[2] While the presentation of AD can vary widely in morphology and distribution depending on age and chronicity, pediatric AD is typically characterized by facial, neck, and extensor involvement. Lesions may manifest as papular, vesicular, erythematous, or lichenified pruritic patches on a background of dry skin.[3]

The pathogenesis of AD involves a complex interplay of genetic, immunologic, and environmental factors that combine to produce a defective skin barrier and dysregulated immune system. A family history of atopic disease is strongly associated with the development of AD, with the odds of development being two-fold higher in children with one atopic parent, and three-to-five-fold higher in children with two atopic parents.[4] Among many heritable immune defects, mutations in the filaggrin gene have been prominently implicated. The gene encodes profilaggrin, which then degrades to filaggrin, a critical epidermal barrier protein.[5] Functional impairments in filaggrin lead to decreased epidermal hydration and disruption of barrier function. A null mutation in the filaggrin gene confers a three-fold increased risk for earlier-onset AD and is associated with more severe forms.[5,6] Genetic alterations producing a defective epidermal barrier contribute to epidermal water loss, a predisposition to infection by pathogenic microbes, and the penetration of environmental allergens.

Topical Corticosteroids

The topical management of AD is focused on symptomatic relief, increasing the duration of intervals between flares, and the management of acute flares. The regular application of emollients, preferably soon after bathing in order to improve hydration, is an integral component of topical regimens. Consistent use can ease the symptoms of AD, prevent flares, reduce the severity of disease, and possibly avoid the need for more aggressive pharmacological intervention. There is limited evidence regarding the benefit of adding oils, emollients, or other additives to bath water. Soaps that can damage and further irritate the skin should be avoided.[7]

Topical corticosteroids remain the first-line treatment for AD and continue to be used in conjunction with systemic therapies for severe cases. Topical agents provide a multi-pronged effect due to their anti-inflammatory, immunosuppressive, anti-proliferative, and vasoconstrictive properties. These qualities of corticosteroids are thought to arise through genomic mechanisms.[8] Lipophilic glucocorticoid molecules passively diffuse through cell membranes and bind to cytoplasmic glucocorticoid-specific receptors in keratinocytes and fibroblasts within the epidermis and dermis. A conformational change in the receptor-corticosteroid dimer complex allows entry into the nucleus to bind to specific glucocorticoid-response elements. This process induces the synthesis of anti-inflammatory proteins and regulatory proteins, thereby modulating the inflammatory response. Corticosteroids are also able to indirectly and directly regulate pro-inflammatory gene transcription factors, such as nuclear factor k B (NFkB), activator protein-1, and interferon regulatory factor-3.[9] The upregulation of phospholipase A2 inhibitory protein lipocortin-1 prevents the release of arachidonic acid, a precursor of inflammatory mediators such as prostaglandins and leukotrienes.

When selecting an appropriate potency and formulation of topical corticosteroid, it is important to consider the treatment area and length of treatment, while balancing the efficacy and

tolerability of the agent. Long-term or inappropriate use of topical corticosteroids has been associated with several cutaneous and systemic side effects. Cutaneous side effects include skin atrophy, purpura, telangiectasias, striae, and acneiform or rosacea-like eruptions.[7] Systemic effects, while rare, include hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, glucosuria, and growth retardation in children. In pediatric patients, their relatively large ratio of body surface area to mass results in a higher degree of absorption, augmenting the potential risk of HPA axis suppression.

Caregiver concerns relating to the safety of topical corticosteroids are one of the primary barriers to treatment adherence, which can result in treatment failure in pediatric patients.[10] In order to minimize the risk of systemic and cutaneous side effects, the lowest potency corticosteroid that is effective is preferred for long-term treatment, large surface areas, or thin-skinned areas (eg, face, groin, axilla). Weaker concentrations of topical corticosteroids under occlusion may have fewer systemic effects than more concentrated versions while still maintaining comparable efficacy.[11] Educating patients and caregivers on the proper use of topical corticosteroids is integral to developing therapeutic plans, which should include discussions about patient preferences in vehicle preparations in order to optimize compliance and prevent treatment failure.

Vehicles

The selection of topical corticosteroid vehicle has an important impact on efficacy, tolerability, and patient compliance. Powders, oils, and liquids are used in different combinations to produce the major types of vehicles.

Ointments are semi-solid emulsions composed of water suspended in oil. Ointments provide a high degree of skin moisturization by decreasing transepidermal water loss. Due to their occlusive properties, ointments allow for greater penetration of medication and thus confer greater potency. However, the high viscosity of the vehicle leads to a greasy sensation that patients may find unpleasant. Ointments are therefore preferred for dry, hyperkeratotic lesions and should be avoided on hair-bearing areas. Infants and children often tolerate ointments well and derive significant benefit from the occlusive nature of these formulations.

Creams are emulsions of oil and water in roughly equal proportions. With lower viscosity than ointments, creams are easier to apply over large surface areas. In addition, creams are less occlusive and less potent than ointment formulations of the same medication.

Lotions are mixtures of water with powder and confer decreased potency relative to ointments and creams. The low viscosity and rapid evaporation of lotions allows for easy application to large surface areas and provides for higher cosmetic appeal. Lotions are particularly well-suited for intertriginous areas.

Solutions are mixtures of water with alcohol, glycols, or other non-aqueous liquids. Solutions quickly evaporate, making them most applicable for moist lesions and hair-bearing regions.

Gels are semi-solid emulsions that were classically formulated in an alcohol base. These gel formulations are non-greasy and self-drying, providing for high patient satisfaction. Gels should be used with caution in areas with open erosions or fissures, where the alcohol base can be irritating. Within the last 15 years, gels have been introduced with new water-based formulations. These gels are both hydrating and well tolerated and will not irritate open skin in the way that alcohol-based gels tended to irritate.

Foams are dispersions of gas bubbles in a liquid matrix. The vehicle spreads easily and absorbs rapidly into the skin. As such, foams are considered ideal vehicles for the scalp and other hair-bearing regions.

Desonide

Among lower potency corticosteroids, desonide is the most commonly prescribed agent in the United States.[12] Desonide is a Class VI, nonfluorinated, synthetic topical corticosteroid that has been implemented since 1972 for the treatment of mild-to-moderate steroid-responsive dermatoses.[13] This topical steroid is available in cream, lotion, foam, ointment, and hydrogel formulations.

Several large clinical trials have demonstrated a favorable safety and efficacy profile of topical desonide in the treatment of pediatric AD.[14-16] A pharmacovigilance program has provided post-marketing surveillance data on topical desonide from nearly a decade of collection.[17] A total of 62 adverse event reports were obtained, 37 of which were provided by consumers and not medically substantiated. The most common adverse events were local skin irritations.

Desonide 0.05% foam was approved in 2006 for the treatment of mild-to-moderate atopic dermatitis in patients 3 months of age and older.[18] Prepared in a petrolatum-based emulsion aerosol foam, desonide 0.05% foam may be more tolerable than ethanol-based preparations that often sting or burn, particularly in areas where skin is already irritated. The incorporation of petrolatum delivers an occlusive layer to the skin on application, which has been shown to reduce the evaporation of moisture, increase hydration of the stratum corneum, and thereby enhance delivery.[19] Moreover, the cosmetic benefit of a foam vehicle that allows for controlled and uniform applications—

TABLE 1.

Clinical Trials on Desonide Foam						
Study Identifier	Study Objective(s)	Study Design and Type of Control	Dosage Regimen	Number of Subjects	Diagnosis of Patients	Duration of Treatment
DES.C.201	Safety of desonide foam 0.05%, including its effects on the hypothalamic pituitary adrenal axis	Open-label, non-controlled	Desonide foam twice daily	81	Patients with atopic dermatitis	4 weeks
DES.C.202	Safety and efficacy; verification of sample size for Phase 3	Randomized, double-blind, vehicle controlled	Desonide foam or vehicle foam twice daily	106	Patients with atopic dermatitis	4 weeks
DES.C.301	Safety and efficacy; superiority to vehicle foam	Randomized, double-blind, vehicle controlled	Desonide foam or vehicle foam twice daily	581	Patients with atopic dermatitis	4 weeks

while minimizing greasy sensations and appearance—may increase patient compliance with therapeutic regimens.

Desonide foam was evaluated in three clinical trials of patients with atopic dermatitis (Table 1).[20] The efficacy of desonide foam applied twice daily for four weeks was evaluated in a phase III, double-blind, randomized, multicenter trial in patients aged 3 months to 17 years. Clinical success was defined as meeting all of the following criteria: Investigator's Static Global Assessment (ISGA) score of clear or almost clear, a minimum two-grade improvement in the ISGA scores from baseline, and absent or minimal erythema and induration/papulation. Of the 387 subjects treated with desonide, 39% achieved clinical success versus 9% in the vehicle group (P<0.0001). Individual primary endpoint results indicated that 41% of subjects achieved an ISGA of clear or almost clear (versus 9% on vehicle), 68% of subjects achieved absent or minimal erythema (versus 36% on vehicle), and 69% of subjects achieved absent or minimal induration/papulation (versus 38% on vehicle; P<0.0001).[18, 20]

The safety profile of desonide foam is consistent with that of preceding formulations. Combined safety data from phase II and III studies (768 subjects in total, 540 receiving desonide) revealed that 6% of subjects receiving desonide experienced adverse events, as compared to 14% of subjects receiving vehicle foam (P=0.0002).[18, 20, 21] The majority of these adverse events were local skin irritations that were transient in nature, mild-to-moderate in severity, and independent of age, race, or gender. As HPA axis suppression is an adverse event of special concern in pediatric patients, the effect of desonide 0.05% foam on the HPA axis was evaluated in a 4-week phase II, multicenter, open-label study of adolescent and pediatric participants with mild-to-moderate AD. Of 75 participants, three subjects (4%) experienced mild, transient HPA axis suppression as determined by postcosyntropin stimulation serum cortisol levels. There was no increase in the risk of HPA axis suppression for infants and younger children compared with adolescents.[20]

Shortly after the approval of desonide foam, a hydrogel formulation was also approved in 2006. Several trials have since demonstrated the safety and efficacy of desonide hydrogel in atopic dermatitis (Table 2).[15, 22-24]

In particular, desonide hydrogel has been shown to be equally

TABLE 2.

Clinical Trials on Desonide Hydrogel						
Study Identifier	Study Objective(s)	Study Design and Type of Control	Dosage Regimen	Number of Subjects	Diagnosis of Patients	Duration of Treatment
Kircik (2014)	Efficacy of desonide hydrogel in improving pruritus	Open-label, non-controlled	Desonide hydrogel twice daily	20	Patients with atopic dermatitis	1 week
Trookman et al. (2011)	Comparison of desonide hydrogel to desonide ointment	Randomized, investigator-blind, parallel-group	Desonide hydrogel or ointment twice daily	44	Patients with atopic dermatitis	4 weeks
Eichenfield et al. (2007)	Effects on the hypothalamic pituitary adrenal axis	Open-label, non-controlled	Desonide hydrogel twice daily	40	Pediatric patients with atopic dermatitis	4 weeks
Hebert et al. (2007)	Safety and efficacy; superiority to vehicle	Randomized, double-blind, vehicle controlled	Desonide hydrogel or vehicle twice daily	425	Pediatric patients with atopic dermatitis	4 weeks

efficacious and preferred by patients relative to desonide ointment.[24] In a randomized controlled trial of 44 subjects with atopic dermatitis (ages 12 and older), subjects were treated with either desonide ointment or hydrogel twice daily for 4 weeks. The two formulations provided similar improvements in eczema signs and symptoms, but desonide hydrogel was rated by patients as significantly better than desonide ointment (P<0.05) in both absorption (at week 4) and (lack of) greasiness (at week 2). Other studies have demonstrated that desonide hydrogel can provide rapid alleviation of pruritus within 1 week and, importantly, does not suppress the HPA axis in pediatric patients.[22, 23]

Secondary Bacterial Infections

Secondary bacterial infections are common complications of AD. Frequently caused by Staphylococcus aureus and Streptococcus pyogenes, such infections present with weeping, crusted, or pustulated lesions. Up to 80 to 100% of AD patients are colonized by S. aureus, compared to 5-30% of the general population.[25, 26] Importantly, the density of S. aureus bacteria on the skin has been correlated with the clinical severity of AD.[27]

Several factors predispose AD patients to secondary bacterial infections. Due to mutations in filaggrin, patients with AD suffer from an inherent epidermal barrier dysfunction.[28]The atopic immune response, including the overexpression of interleukin (IL)-4 and IL-13, may lead to further inhibition of filaggrin gene expression.[29] In addition, the altered expression and secretion of antimicrobial peptides, which normally serve as endogenous antibiotics, contributes to innate susceptibility.[30, 31]

Topical antibiotics are integral to the treatment of bacterial infections in AD. Mupirocin 2% ointment is widely used, although concern exists over rising rates of resistance among S. aureus strains.[32, 33] Methicillin-resistant Staphylococcus aureus (MRSA) represents a particularly troubling issue in the AD population, where rates of colonization are substantially higher than in the general population.[34]Those with moderate-to-severe AD are especially at risk for MRSA colonization, which has in turn been linked to MRSA skin and soft tissue infections.[35, 36]

Retapamulin is a semisynthetic member of the pleuromutilin family of antimicrobials. Pleuromutilins were initially discovered in 1950s, with the first compounds—tiamulin and valnemulin—being approved for veterinary use. Pleuromutilin agents block protein synthesis in bacteria by binding to domain V of 23S rRNA and interfering with substrate binding.[37]

This mechanism of action is distinct from other antimicrobials, thereby reducing the likelihood of cross-resistance.[38]

The growing rates of anti-microbial resistance in bacteria, most notably MRSA, represent an important clinical consideration in selecting treatments. Retapamulin may provide an alternative not preferred treatment option for MRSA, especially where concern exists over mupirocin-resistance. In a study from six US dermatology centers, the susceptibility of S. aureus strains to different antimicrobials was tested.[39] Among 218 isolates of S. aureus, 10.6% were mupirocin-resistant compared to only 0.5% that were retapamulin-resistant. Similar results were seen in a large analysis of 403 MRSA isolates, which found that 9% of strains were mupirocin-resistant versus only 0.25% that were retapamulin-resistant.[40]

CONCLUSION

Treatment regimens continue to evolve as clinicians and scientists gain greater insight into the pathophysiology of AD. Early intervention with emollients and topical steroids remain principle components to therapy, and the arrival of topical calcineurin inhibitors and phosphodiesterase-4 inhibitors has now provided an even wider range of options. Continued pediatric research into biologic agents, such as interleukin-4 and -13 inhibitors, as well as Janus kinase inhibitors, are likely to yield safe and effective systemic therapies in the near future. Importantly, the comorbidities of AD, such as infection, allergy, and psychosocial impairment, are increasingly being recognized and addressed in a multidisciplinary approach.

In patients with poor control of AD, secondary bacterial infections are common complications, and the appropriate selection of antibiotic therapy can be challenging when faced with bacterial resistance. Although mupirocin remains a preferred first-line agent, growing concerns over MRSA resistance make retapamulin a treatment alternative in such pathogenic environments.

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