

A SUPPLEMENT TO

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

ATOPIC DERMATITIS:
A REVIEW OF TOPICAL TREATMENT

ISSN: 1545 9616

February 2019 • Volume 18 • Issue 2 (SUPPLEMENT 2)

Funding Acknowledgment:

This research was supported by a grant from Almirall, LLC., Exton, PA 19341.

ATOPIC DERMATITIS: A REVIEW OF TOPICAL TREATMENT

INTRODUCTION

- s111 **The Importance of Vehicles in Management of Atopic Dermatitis**
Leon H. Kircik MD

ORIGINAL ARTICLES

- s112 **Topical Treatment for the Management of Atopic Dermatitis**
Peter W. Hashim MD MHS, Tinley Chen BA, Adelaide A. Hebert MD, Leon H. Kircik MD

The Importance of Vehicles in Management of Atopic Dermatitis

Leon H. Kircik MD

Icahn School of Medicine at Mount Sinai, New York, NY; Indiana University Medical Center, Indianapolis, IN; Physicians Skin Care, PLLC Louisville, KY; DermResearch, PLLC, Louisville, KY; Skin Sciences, PLLC, Louisville, KY



Leon H. Kircik MD

Atopic Dermatitis (AD) is estimated to affect 15-20% of children and remains a major health consideration for pediatricians and dermatologists.¹ Over the past three decades, studies have shown an increase in the prevalence of AD in industrialized nations, with lower numbers seen in developing countries.²

For most children, AD presents within the first year of life, and 80-90% of patients are diagnosed by age 5.³

The disease course is characterized by recurrent exacerbations and remissions. As patients age, flares tend to become less common, and only a minority of patients continue to experience the signs and symptoms of AD into adulthood. Asthma develops in roughly one third of patients, and seasonal allergies are present in roughly two-thirds.⁴

Emollients and topical corticosteroids remain the foundation of treatment for mild-to-moderate AD. Due to decreased expression of filaggrin and other dysfunctions of the epidermal barrier, AD patients are inherently xerotic and require frequent skin hydration. Topical steroids are used to improve symptoms, shorten the duration of acute flares, and prolong the duration between exacerbations. They deliver a multi-pronged effect due to anti-inflammatory, immunosuppressive, anti-proliferative, and vasoconstrictive properties. However, topical steroids are known to inhibit lipid synthesis and hence, worsen the impairment of epidermal barrier. Therefore, the vehicle formulation of topical steroids plays a significant role in efficacy, tolerability, and treatment compliance. Lotions, creams, and ointments each provide increasing levels of potency and hydration, but along with moisturization comes greasiness. Gels are rapidly self-drying, leading to a cooling effect when used on exudative inflammation.

Newer vehicles include foam and spray preparations. Foams leave minimal residue after application, and sprays are par-

ticularly well-suited for large body surface areas, where preparations can be rapidly and diffusely applied. The development of these vehicles represents a significant step forward for patients, as foams and sprays have demonstrated high levels of efficacy, cosmetic appeal, and patient compliance.

Low-potency steroids are preferred for chronic conditions like AD, especially in areas of the body with thinner skin and in pediatric patients. As such, low-potency steroids constitute the primary agent for children with AD. Non-steroid topicals—such as pimecrolimus, tacrolimus, and crisaborole—are useful adjuncts, although none are FDA-approved for patients under the age of 2. We have only very few topical steroids approved all the way down to 3 months of age.

Future treatment algorithms will undoubtedly be influenced by application of the biologic agent dupilumab in pediatric populations. Recent phase III clinical trials evaluating dupilumab in adolescents aged 12-17 years with moderate-to-severe AD demonstrated significant improvements in skin clearing, itching, and quality of life measures.⁵ Clinical trials are also underway for children aged 6 months–11 years. FDA approval in pediatric patients is likely to arrive within the next year, providing the first biologic agent for these patients.

The treatment horizon for pediatric AD is encouraging. Newer pharmaceuticals are now joined by novel formulations of established medications, which arms dermatologists with an increasing array of treatments to tackle this challenging condition.

Disclosure

Dr. Kircik has received compensation from JDD for his editorial support.

Dr. Kircik has been an investigator, consultant, advisory board member and a speaker for Stiefel, GSK, Aqua Pharmaceutical, and Almirall.

References

1. Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. 2006;368(9537):733-43.
2. Nutter S. Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab*. 2015;66 Suppl 1:8-16.
3. Kamei B, Pasowska R, Dolka E, et al. Prevalence of atopic dermatitis in infants during the first six months of life: authors' observations. *Postępy Dermatol Alergol*. 2013;30(5):277-81.
4. Somanunt S, Chinratanapisit S, Pacharn P, et al. The natural history of atopic dermatitis and its association with Atopic March. *Asian Pac J Allergy Immunol*. 2017;35(3):137-43.
5. Simpson EL, Paller AS, Siegfried EC, et al. Dupilumab Efficacy and Safety in Adolescents with Moderate-to-Severe Atopic Dermatitis: Results from a Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Phase 3 Study. The 27th European Academy of Dermatology and Venerology Congress, Paris, France, 15th September, 2018.

Topical Treatment for the Management of Atopic Dermatitis

Peter W. Hashim MD MHS,^a Tinley Chen BA,^a Adelaide A. Hebert MD,^b Leon H. Kircik MD^{a-c}

^aThe Icahn School of Medicine at Mount Sinai, Department of Dermatology, New York, New York

^bIndiana University School of Medicine, Indianapolis, IN

^cUTHealth McGovern Medical School-Houston, Houston, TX

^dPhysicians Skin Care PLLC, Louisville, KY

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.

J Drugs Dermatol. 2019;18(2 Suppl):s112-116.

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 κ B (NF κ B), 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.

REFERENCES

- Nutten S. Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab*. 2015;66 Suppl 1:8-16.
- Kay J, Gawkrödger DJ, Mortimer MJ, Jaron AG. The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol*. 1994;30(1):35-9.
- Thomsen SF. Atopic dermatitis: natural history, diagnosis, and treatment. *ISRN Allergy*. 2014;2014:354250.
- Kuster W, Petersen M, Christophers E, Goos M, Sterry W. A family study of atopic dermatitis. Clinical and genetic characteristics of 188 patients and 2,151 family members. *Arch Dermatol Res*. 1990;282(2):98-102.
- Brown SJ, McLean WH. One remarkable molecule: filaggrin. *J Invest Dermatol*. 2012;132(3 Pt 2):751-62.
- Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. *N Engl J Med*. 2011;365(14):1315-27.
- Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014;71(1):116-32.
- Stahn C, Buttgerit F. Genomic and nongenomic effects of glucocorticoids. *Nat Clin Pract Rheumatol*. 2008;4(10):525-33.
- De Bosscher K, Vanden Berghe W, Haegeman G. The interplay between the glucocorticoid receptor and nuclear factor-kappaB or activator protein-1: molecular mechanisms for gene repression. *Endocr Rev*. 2003;24(4):488-522.
- Sokolova A, Smith SD. Factors contributing to poor treatment outcomes in childhood atopic dermatitis. *Australas J Dermatol*. 2015;56(4):252-7.
- Wolkerstorfer A, Visser RL, De Waard van der Spek FB, Mulder PG, Oranje AP. Efficacy and safety of wet-wrap dressings in children with severe atopic dermatitis: influence of corticosteroid dilution. *Br J Dermatol*.

- 2000;143(5):999-1004.
12. Kircik L, Del Rosso J. A novel hydrogel vehicle formulated for the treatment of atopic dermatitis. *J Drugs Dermatol*. 2007;6(7):718-22.
 13. Kahanek N, Gelbard C, Hebert A. Desonide: a review of formulations, efficacy and safety. *Expert Opin Investig Drugs*. 2008;17(7):1097-104.
 14. Freeman S, Howard A, Foley P, Rosen R, Wood G, See JA, et al. Efficacy, cutaneous tolerance and cosmetic acceptability of desonide 0.05% lotion (Desowen) versus vehicle in the short-term treatment of facial atopic or seborrheic dermatitis. *Australas J Dermatol*. 2002;43(3):186-9.
 15. Hebert AA, Cook-Bolden FE, Basu S, Calvarese B, Trancik RJ, Desonide Hydrogel Study G. safety and efficacy of desonide hydrogel 0.05% in pediatric subjects with atopic dermatitis. *J Drugs Dermatol*. 2007;6(2):175-81.
 16. Jorizzo J, Levy M, Lucky A, Shavin J, Goldberg G, Dunlap F, et al. Multicenter trial for long-term safety and efficacy comparison of 0.05% desonide and 1% hydrocortisone ointments in the treatment of atopic dermatitis in pediatric patients. *J Am Acad Dermatol*. 1995;33(1):74-7.
 17. Wong VK, Fuchs B, Lebwohl M. Overview on desonide 0.05%: a clinical safety profile. *J Drugs Dermatol*. 2004;3(4):393-7.
 18. Verdeso (desonide) Foam [package insert]. Research Triangle Park NSL, Inc; 2013. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021978s0101bl.pdf (accessed April 30, 2018).
 19. Abram AZ, inventor; Stiefel West Coast LLC, assignee. Mousse composition. US patent 7,029,659 B2. April 18, 2006.
 20. U.S. Food and Drug Administration CfDEaRMRMRDF. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021978s000_MedR.pdf (accessed April 30, 2018).
 21. Hebert AA, Desonide Foam Phase IIICSG. Desonide foam 0.05%: safety in children as young as 3 months. *J Am Acad Dermatol*. 2008;59(2):334-40.
 22. Eichenfield LF, Basu S, Calvarese B, Trancik RJ. Effect of desonide hydrogel 0.05% on the hypothalamic-pituitary-adrenal axis in pediatric subjects with moderate to severe atopic dermatitis. *Pediatr Dermatol*. 2007;24(3):289-95.
 23. Kircik L. The effect of desonide hydrogel on pruritus associated with atopic dermatitis. *J Drugs Dermatol*. 2014;13(6):725-8.
 24. Trookman NS, Rizer RL. Randomized controlled trial of Desonide Hydrogel 0.05% versus Desonide Ointment 0.05% in the treatment of mild-to-moderate atopic dermatitis. *J Clin Aesthet Dermatol*. 2011;4(11):34-8.
 25. Leyden JJ, Marples RR, Kligman AM. Staphylococcus aureus in the lesions of atopic dermatitis. *Br J Dermatol*. 1974;90(5):525-30.
 26. Hauser C, Wuethrich B, Matter L, Wilhelm JA, Sonnabend W, Schopfer K. Staphylococcus aureus skin colonization in atopic dermatitis patients. *Dermatologica*. 1985;170(1):35-9.
 27. Williams RE, Gibson AG, Aitchison TC, Lever R, Mackie RM. Assessment of a contact-plate sampling technique and subsequent quantitative bacterial studies in atopic dermatitis. *Br J Dermatol*. 1990;123(4):493-501.
 28. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet*. 2006;38(4):441-6.
 29. Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, DeBenedetto A, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol*. 2009;124(3 Suppl 2):R7-R12.
 30. Howell MD, Wollenberg A, Gallo RL, Flaig M, Streib JE, Wong C, et al. Cathelicidin deficiency predisposes to eczema herpeticum. *J Allergy Clin Immunol*. 2006;117(4):836-41.
 31. Mallbris L, Carlen L, Wei T, Heilborn J, Nilsson MF, Granath F, et al. Injury downregulates the expression of the human cathelicidin protein hCAP18/LL37 in atopic dermatitis. *Exp Dermatol*. 2010;19(5):442-9.
 32. Upton A, Lang S, Heffernan H. Mupirocin and Staphylococcus aureus: a recent paradigm of emerging antibiotic resistance. *J Antimicrob Chemother*. 2003;51(3):613-7.
 33. Jones JC, Rogers TJ, Brookmeyer P, Dunne WM, Jr., Storch GA, Cooper-smith CM, et al. Mupirocin resistance in patients colonized with methicillin-resistant Staphylococcus aureus in a surgical intensive care unit. *Clin Infect Dis*. 2007;45(5):541-7.
 34. Warner JA, McGirt LY, Beck LA. Biomarkers of Th2 polarity are predictive of staphylococcal colonization in subjects with atopic dermatitis. *Br J Dermatol*. 2009;160(1):183-5.
 35. Jagadeesan S, Kurien G, Divakaran MV, Sadanandan SM, Sobhanakumari K, Sarin A. Methicillin-resistant Staphylococcus aureus colonization and disease severity in atopic dermatitis: a cross-sectional study from South India. *Indian J Dermatol Venereol Leprol*. 2014;80(3):229-34.
 36. Lo WT, Wang SR, Tseng MH, Huang CF, Chen SJ, Wang CC. Comparative molecular analysis of methicillin-resistant Staphylococcus aureus isolates from children with atopic dermatitis and healthy subjects in Taiwan. *Br J Dermatol*. 2010;162(5):1110-6.
 37. Schlunzen F, Pyetan E, Fucini P, Yonath A, Harms JM. Inhibition of peptide bond formation by pleuromutilins: the structure of the 50S ribosomal subunit from Deinococcus radiodurans in complex with tiamulin. *Mol Microbiol*. 2004;54(5):1287-94.
 38. Brooks G, Burgess W, Colthurst D, Hinks JD, Hunt E, Pearson MJ, et al. Pleuromutilins. Part 1. The identification of novel mutilin 14-carbamates. *Bioorg Med Chem*. 2001;9(5):1221-31.
 39. Biedenbach DJ, Bouchillon SK, Johnson SA, Hoban DJ, Hackel M. Susceptibility of Staphylococcus aureus to topical agents in the United States: a sentinel study. *Clin Ther*. 2014;36(6):953-60.
 40. Harrington AT, Black JA, Clarridge JE, 3rd. In vitro activity of retapamulin and antimicrobial susceptibility patterns in a longitudinal collection of methicillin-resistant Staphylococcus aureus isolates from a veterans affairs medical center. *Antimicrob Agents Chemother*. 2015;60(3):1298-303.

AUTHOR CORRESPONDENCE

Leon H. Kircik MD

Email:..... wedoderm@yahoo.com



