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Targeting the Aryl Hydrocarbon Receptor to Address the Challenges of Atopic Dermatitis

Lawrence F. Eichenfield MD,[a,b] Jonathan I. Silverberg MD PhD MPH,[c] Adelaide A. Hebert MD,[d] Raj Chovatiya MD PhD,[e] Philip M. Brown MD JD,[f] Kimberly A. McHale PhD,[f] David S. Rubenstein MD PhD,[f] Anna M. Tallman PharmD[f]

[a]University of California San Diego School of Medicine, San Diego, CA
[b]Rady Children's Hospital, San Diego, CA
[c]School of Medicine and Health Sciences, The George Washington University, Washington, DC
[d]UTHealth McGovern Medical School and Children's Memorial Hermann Hospital, Houston, TX
[e]Northwestern University Feinberg School of Medicine, Chicago, IL
[f]Dermavant Sciences, Inc., Morrisville, NC

ABSTRACT

Background: Atopic dermatitis (AD) is a chronic relapsing–remitting disease with a multifactorial etiology involving epidermal barrier and immunologic dysfunction. Topical therapies form the mainstay of AD treatment, but options are limited by adverse effects and restrictions on application site, duration, and extent of use. Tapinarof (VTAMA®; Dermavant Sciences, Inc.) is a first-in-class, non-steroidal, topical aryl hydrocarbon receptor (AhR) agonist approved for the treatment of plaque psoriasis. AhR is a ligand-dependent transcription factor with wide-ranging roles, including regulation of homeostasis and immune response in skin cells. AhR expression and signaling are altered in many inflammatory skin diseases, and clinical trials with tapinarof have validated AhR as a therapeutic target capable of delivering significant efficacy. Tapinarof cream 1% once daily demonstrated efficacy versus vehicle in adults and adolescents with AD and is being investigated in the ADORING trials for the treatment of AD in adults and children down to 2 years of age.

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INTRODUCTION

The aryl hydrocarbon receptor (AhR) is a ligand-dependent transcription factor regulating gene expression in various cells, including immune and epithelial cells.[1] AhR is expressed ubiquitously throughout the body, has roles in many physiologic processes, and is activated by a wide range of ligands.[2-5] AhR also affects signaling through interaction with other proteins, such as the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2).[1]

Atopic dermatitis (AD) is an inflammatory skin disease associated with changes in AhR signaling, reduced Nrf2 activity, abnormal immune responses, impaired skin barrier function, and oxidative stress.[1,6-8] Increased T helper (Th)2 cell cytokine expression, particularly interleukin (IL)-4, IL-5, IL-13, and IL-31, has been implicated in AD pathogenesis.[9-11] Management of AD includes reducing symptoms and improving the quality of life for patients and caregivers.[12]

There is a need for efficacious and well-tolerated therapies that can be used by children and adults, without restrictions on the duration or extent of use, or sites of application.[13] Clinical trials with tapinarof (VTAMA®; Dermavant Sciences, Inc.) validate AhR as a therapeutic target in inflammatory skin diseases. Tapinarof is an AhR agonist that downregulates cytokines, promotes skin-barrier normalization, and reduces oxidative stress.[1,14,15] Tapinarof cream 1% once daily (QD) is approved for the treatment of adults with plaque psoriasis,[16] and is under investigation for the treatment of psoriasis in children down to 2 years of age and for the treatment of AD in adults and children down to 2 years of age, having demonstrated efficacy in adults and adolescents with moderate to severe AD in previous trials.[17,18]

This review discusses the rationale for targeting AhR in the treatment of AD based on the current understanding of the role of tapinarof in the treatment of inflammatory skin disease.

Rationale for Targeting AhR

Overview of AhR

AhR is a ligand-dependent transcription factor expressed in most cell types, including skin, immune, and epithelial cells,[3] and acts as a master regulator of homeostasis in healthy cells, mediating responses to low-molecular-weight ligands from endogenous,

dietary, xenobiotic, and environmental sources.[1,19-21] Depending on the ligand and cellular context, AhR signaling results in the induction or repression of different genes with diverse responses in a wide range of tissues.[1]

Ligand-dependent AhR activation induces cytoprotective responses in the skin by upregulating antioxidant pathways and skin-barrier protein and ceramide lipid production.[1,14,22] After AhR binds to a ligand in the cytoplasm, conformational changes result in nuclear translocation,[23,24] where the AhR–ligand complex heterodimerizes with AhR nuclear translocator (ARNT) and binds to specific DNA recognition sites to control transcription of AhR-responsive genes.[23,24]

Classical AhR signaling pathways were initially elucidated in determining the toxicologic effects of polycyclic aromatic hydrocarbons, which may explain the association between atmospheric pollution and AD and asthma.[25-28] In addition to regulating gene expression as a nuclear receptor, AhR interacts with other genes and proteins to modulate genomic and cytosolic pathways.[29]

The AhR is a Master Regulator of Epithelial Homeostasis

In vitro, ex vivo, and in vivo models point to a key role for AhR as a regulator of homeostasis in immune and epithelial cells, via multiple pathways, including alteration of the transcriptional program of regulatory T (T_{reg}) cells and epithelial cells.[30] AhR also signals through Nrf2 to induce cytoprotective antioxidant responses, and mediates antioxidative and cytoprotective signaling when activated by flavonoids and azoles.[1,31-33] Additionally, AhR regulates epithelial homeostasis, via immune-mediated skin responses and skin barrier effects.[1,34-36] AhR is widely expressed in skin cells, including keratinocytes, macrophages, dendritic cells, T-cell subtypes, T_{reg} cells, mast cells, neutrophils, and resident memory T cells (T_{RM}).[37,38] In immune cells, AhR signaling reduces the Th2 differentiation and cytokine expression implicated in AD, including IL-4, IL-5, and IL-13.[9,37,39] Furthermore, AhR signaling regulates the differentiation of $CD4^+$ Th cells that produce inflammatory cytokines[1,37] and decreases major histocompatibility complex class II expression and the production of Th2- (IL-4, IL-5, and IL-13), Th1 and Th17- cytokines (IL-21 and IL-22).[40,41]

AhR signaling also regulates keratinocyte differentiation, promotes skin-barrier integrity, and prevents transdermal water loss.[35,42] To normalize skin-barrier integrity, AhR signaling upregulates barrier components including proteins such as filaggrin, loricrin, hornerin, and involucrin, as well as ceramide lipids.[22,24] AhR-mediated activation of the Nrf2 transcription factor induces cytoprotective antioxidant responses that suppress oxidative stress, which further promotes skin homeostasis.[24,43]

AhR in Dermatologic Inflammatory Diseases

Alterations in AhR expression are known to occur in inflammatory skin diseases, including psoriasis and AD.[6,14] Targeting AhR in inflammatory skin diseases may therefore provide an innovative approach to alter multiple disease mechanisms via a single receptor, in contrast to therapeutic agents that inhibit specific cytokines or enzymes.[42,44,45] AD is multifactorial and heterogenous, thus modulation of multiple upstream mechanisms via AhR could be advantageous in restoring homeostasis to address underlying pathophysiologic processes (disease modification) in addition to improving symptoms.

Burden of AD and Limitations of Current Therapies

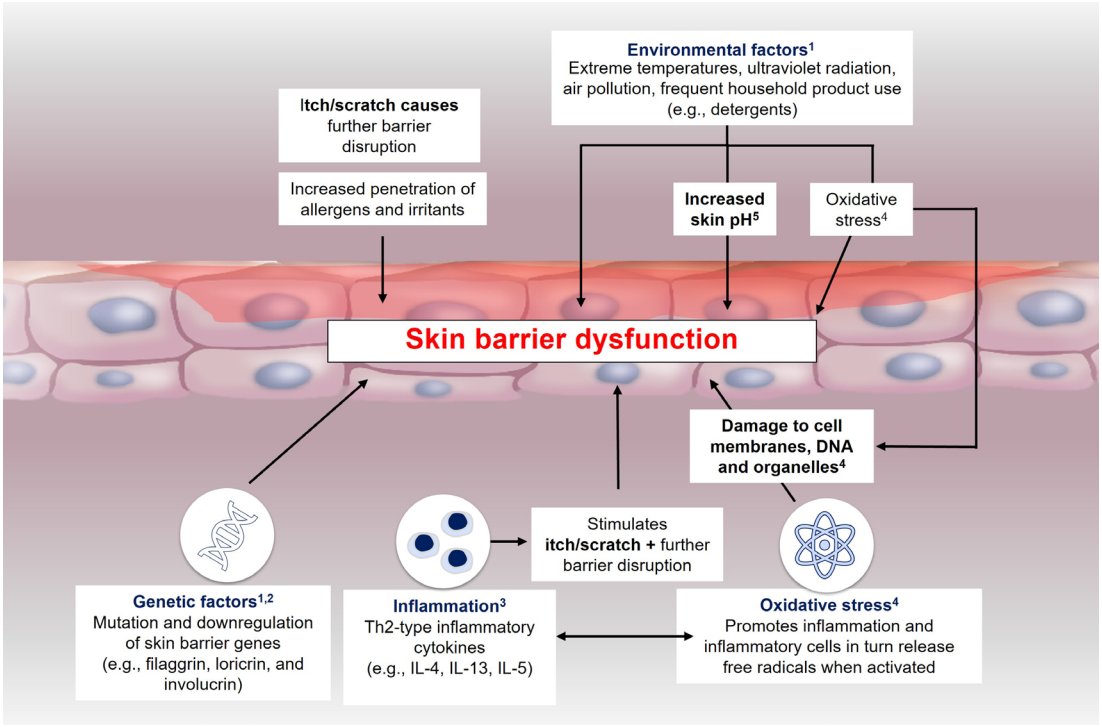
AD is a chronic relapsing-remitting disease affecting approximately 25% of children and 7–10% of adults worldwide. About 40% of adults and 33% of children with AD have moderate to severe disease.[46,47] Patients with AD are at high risk of developing other type 2 inflammatory diseases, food allergies, allergic rhinitis, and asthma. AD has an impact on sleep, and psychosocial functioning due to persistent pruritus and stigma associated with visibly affected skin.[12,18]

There is no curative therapy for AD and treatment aims to reduce inflammation, relieve core symptoms such as pruritus, and reduce the frequency and severity of flares to improve quality of life.[18] Topical agents form the mainstay of treatment in patients with mild to moderate AD, with initial options including topical corticosteroids (TCSs) or topical phosphodiesterase-4 inhibitors; and topical calcineurin inhibitors or Janus kinase (JAK) inhibitors as second-line options.[48] With increasing severity, more potent TCSs may be used, however, concerns exist regarding application location, extent of body surface area treated, and long-term use, especially for mid- and high-potency TCSs.[49,50] Adverse events with TCSs, some of which are irreversible, include acne, rosacea, perioral dermatitis, facial erythema, hirsutism, skin thinning and atrophy, striae, telangiectasia, ecchymosis, dyschromia, and withdrawal phenomena.[49] Consequently, the use of TCSs is often limited or restricted, especially in sensitive skin regions (eg, face and skin flexures/intertriginous areas) and in infants and younger children who are at increased risk of systemic absorption and potential adverse events. Therefore, a need remains for efficacious non-steroidal topical therapies that can be used without these restrictions in patients down to 2 years of age.

Etiology of AD

The etiology of AD is multifactorial, involving epidermal barrier and immunologic dysfunction, genetics, and environmental factors (Figure 1).[51] A healthy epidermal barrier protects against water loss, pathogens, and inflammatory stimuli. In AD, changes

FIGURE 1. The pathogenesis of atopic dermatitis.



IL, interleukin; Th, T helper.
1. Ständer S. *N Engl J Med.* 2021;384:1136–43; 2. Furue M. *Int J Mol Sci.* 2020;21:5382; 3. Nakajima S, et al. *Cytokine.* 2021;148:155664; 4. Ji H, Li XK. *Oxid Med Cell Longev.* 2016;2016:2721469; 5. Hendricks AJ, et al. *Br J Dermatol.* 2020;183:16–23.

in skin-barrier integrity are associated with inflammation and immune-cell infiltration, alongside alterations in the expression of epithelial barrier proteins, such as filaggrin.

More than 30 risk loci for AD have been identified, including genes involved in epidermal differentiation, innate immunity, and T-cell function.[39,52] The strongest genetic risk for AD involves the filaggrin gene,[53,54] which plays a role in skin-barrier integrity.[52] Th2 cytokine genes, such as those encoding IL-4 and IL-13, are also associated with AD.[52]

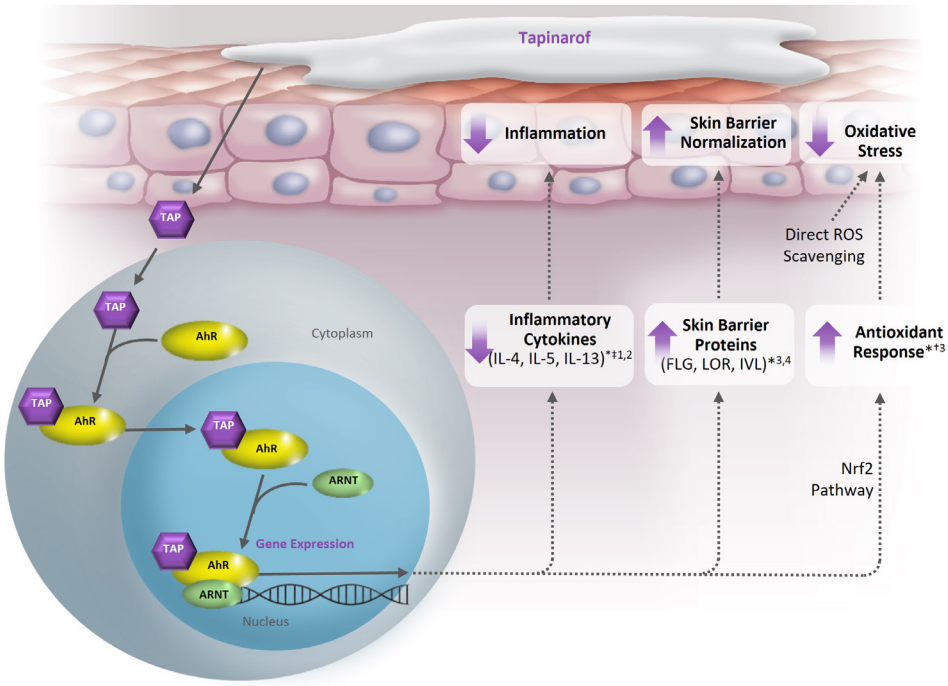
Oxidative stress is also implicated in AD, resulting in increased dermal inflammation and skin-barrier dysfunction.[55] Environmental factors implicated in the etiology of AD include pollutants, irritants, and microbial dysbiosis.[56] Pollutants, including polyaromatic hydrocarbons, induce oxidative stress, skin-barrier dysfunction, and immune dysregulation, and are linked to the development and exacerbation of AD and asthma.[22-25,57,58]

Th2 cytokines, such as IL-4, IL-5, and IL-13, are associated with AD pathogenesis.[59] Increased expression of IL-4 induces immunoglobulin E production, inflammation, and pruritus in vivo[59,60] and suppresses expression of the terminal keratinocyte differentiation proteins, filaggrin, loricrin, and involucrin.[60] IL-5 contributes to eosinophilia, which is characteristic of lesions in AD.[59,61] IL-13 is an inflammatory mediator of pruritus, skin-barrier dysfunction, and inflammation in AD.[62]

Tapinarof in the Treatment of Psoriasis and AD

Tapinarof is a first-in-class, non-steroidal, topical AhR agonist approved by the US Food and Drug Administration for the treatment of plaque psoriasis in adults,[16] and under investigation for the treatment of psoriasis in children down to 2 years of age, and for AD in adults and children down to 2 years of age. Tapinarof cream 1% QD demonstrated significant efficacy versus vehicle and was well tolerated in adults with mild to severe plaque psoriasis in two identical, 12-week, pivotal phase 3 trials.[63] Efficacy improved beyond 12-weeks in the long-term extension trial, with a high rate of complete disease clearance (Physician Global Assessment [PGA]=0; 40.9% [n=312]), an approximately 4-month remittive effect defined as off-treatment maintenance of a PGA score of 0 (clear) or 1 (almost clear), and durability of response when on therapy for up to 52 weeks.[64] The efficacy of tapinarof is attributed to its specific binding and activation of AhR, resulting in downregulation of pro-inflammatory cytokines, normalization of skin-barrier function, and antioxidant effects.[14] The remittive effect off therapy in psoriasis may be attributed in part to an observed reduction in the activity and persistence of pathogenic resident memory T cells (T_{RM}).[65,66]

FIGURE 2. Proposed mechanism of action of tapinarof in atopic dermatitis.



*Demonstrated in vitro. †Demonstrated ex vivo. ‡Demonstrated in mouse models.
AhR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; FLG, filaggrin; IL, interleukin; IVL, involucrin; LOR, loricrin; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TAP, tapinarof.

Adapted from Bissonnette R, et al. *J Am Acad Dermatol.* 2021;84(4):1059-67.
1. Dermavant Data on File [DMVT-505 Th2 Polarization; Apr 2015]; 2. Dermavant Data on File [DMVT-505 AD Mouse Model; Oct 2016]; 3. Smith SH, et al. *J Inv Dermatol.* 2017;137:2110–2119; 4. Kim BE, et al. *Allergy Asthma Immunol Res.* 2018;10:207–215.

Tapinarof cream 1% QD resulted in minimal-to-no systemic exposure in the phase 3 plaque psoriasis pivotal trials[67] and in patients with plaque psoriasis covering up to 46% of their body surface area (BSA).[68] This pharmacokinetic profile underlies the low potential for systemic adverse effects and drug interactions with topical tapinarof, no QT interval effects, and no requirement for dose modifications based on renal/hepatic dysfunction.[16]

Tapinarof activates AhR, resulting in downregulation of Th2 cytokines implicated in the pathogenesis of AD (Figure 2).[14,15] AhR activation by tapinarof restores the epidermal barrier by increasing the expression of the skin-barrier proteins filaggrin, loricrin, hornerin, and involucrin, as well as ceramide lipid components.[14,15,42] Tapinarof increases antioxidant responses through the Nrf2 pathway and by direct oxygen scavenging.[14] In addition to activation of Nrf2 through AhR, tapinarof directly binds to and activates Nrf2.[14]

Tapinarof cream 1% QD demonstrated significant efficacy and tolerability in adults and adolescents with AD in early clinical trials.[17,18] In a phase 2 clinical trial evaluating tapinarof cream 1% QD in adults and adolescents with moderate to severe AD, efficacy was maintained 4 weeks after completing the 12-week treatment period.[18] This remittive effect off therapy is in alignment with findings in adult patients with plaque psoriasis treated with tapinarof[64] and is being further investigated in the ADORING phase 3 trial program. Moreover, consistent with the pharmacokinetic profile in psoriasis, tapinarof cream 1% QD demonstrated minimal-to-no systemic exposure in adolescents and children down to 2 years of age with extensive AD, with up to 90% BSA affected.[69]

The ADORING phase 3 program is a year-long evaluation of the efficacy and safety of tapinarof cream 1% QD for the treatment of AD in adults and children down to 2 years of age. The program comprises two 8-week, vehicle-controlled pivotal trials (ADORING 1 [NCT05014568] and 2 [NCT05032859]) and a 48-week open-label long-term extension trial (ADORING 3 [NCT05142774]). In the pivotal trials, patients with AD received tapinarof or vehicle QD. The primary endpoint of a Validated Investigator Global Assessment for Atopic Dermatitis™ (vIGA-AD™) of 0 (clear) or 1 (almost clear) and ≥2-grade improvement from baseline at week 8, was highly statistically significant in the tapinarof cream 1% QD group versus vehicle at Week 8 in both ADORING 1 and 2: 45.4% vs 13.9% and 46.4% vs 18.0% (both $P<0.0001$), respectively.[70]

Eligible patients were permitted to enroll in ADORING 3 for a further 48 weeks of treatment based on their vIGA-AD™ score, whereby patients with a vIGA-AD™ score of 0 (clear) discontinue treatment and are monitored for remittive effect (maintaining a vIGA-AD™ score of 0 or 1 when off treatment).

CONCLUSION

AhR signaling has an important role in the regulation of skin health. Clinical trials with tapinarof, an AhR agonist, validate AhR as a therapeutic target for the treatment of inflammatory skin diseases. The targeting of transcription factors such as AhR represents a novel approach to AD therapy, distinct from treatments that target specific cytokines and enzymes.

Tapinarof cream acts locally at sites of application, with minimal-to-no systemic exposure. Tapinarof demonstrated efficacy and favorable tolerability in adults and adolescents with AD and is being evaluated in the ADORING trials in adults and children down to 2 years of age.

DISCLOSURES

L.F.E. has served as a consultant, advisor, or investigator for AbbVie, Almirall, Amgen, Arcutis, Arena, Aslan, Dermavant Sciences, Inc., Eli Lilly, Forté, Galderma, Incyte, Janssen, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi Genzyme, and UCB Pharma. J.I.S. has received honoraria or grants, and/or has served as a consultant, advisory board member, or speaker for Afyx, Aobiome, Arena, Asana, BioMX, Bluefin Biomedicine, Bodewell, Boehringer Ingelheim, Celgene, Dermavant Sciences Inc., Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, LEO Pharma, Luna, Menlo, Novartis, Pfizer, RAPT, Regeneron, and Sanofi Genzyme. A.A.H. has received research support paid to the medical school from AbbVie, Arcutis, Dermavant Sciences Inc., and Pfizer; honoraria received from GSK, Sanofi Regeneron, and Ortho Dermatologics (as part of a Data Safety Monitoring Board); honoraria received from Dermavant Sciences, Inc., Incyte, LEO Pharma, Pfizer, Arcutis, Sun Pharma, Galderma, Novan, and Verrica. R.C. has served as an advisor, consultant, speaker, and/or investigator for AbbVie, Apogee, Arcutis, Argenx, ASLAN, Beiersdorf, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Dermavant Sciences, Inc., Eli Lilly and Company, Galderma, Genentech, Incyte, LEO Pharma, L'Oréal, Novan Inc., Pfizer Inc., Regeneron, Sanofi, and UCB Pharma. P.M.B., K.A.M., D.S.R., and A.M.T. are employees of Dermavant Sciences, Inc., with stock options.

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AUTHOR CORRESPONDENCE

Lawrence F. Eichenfield MD
E-mail:..... leichenfield@rchsd.org