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Review

# Tapinarof as a new topical treatment in atopic dermatitis

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## SUMMARY

Atopic dermatitis (AD) is a chronic recurrent inflammatory skin disease with a complex and multifactorial etiology. Topical treatment remains the mainstay of therapy in AD and research in the pathogenesis of the disease led to the identification of aryl hydrocarbon receptor (AhR) as a target of a new topical treatment. AhR is an environment sensor highly expressed in the skin and a transcription factor with a key role in inflammatory and immune signaling networks. Tapinarof, an AhR agonist, is a new nonsteroidal topical agent applied to treat AD and psoriasis. Clinical trials have demonstrated its rapid and durable efficacy, favorable safety, and long-term tolerability, with minimal-to-no systemic absorption in adults and children. To confirm its long-term safety and efficacy across patient populations, ongoing and future trials and real-life studies will be essential.

**KEYWORDS:** atopic dermatitis, aryl hydrocarbon receptor, tapinarof, topical therapy

## INTRODUCTION

Atopic dermatitis (AD) is an intensely pruritic, chronic, relapsing, inflammatory skin disease. The incidence of AD has increased globally and now affects more than 200 million people worldwide [1-4]. It commonly starts in early childhood, with an estimated prevalence between 16% and 20%. However, it can affect adults in approximately 5-7% of the cases and impacts severely the quality of life of patients and their families.

In recent years, there have been significant advances in understanding the pathogenesis of moderate-to-severe AD. The pathogenesis of the disease is multifactorial and involves genetic predisposition, epigenetic, immunological dysregulation, environmental factors, skin barrier dysfunction, and microbiome dysbiosis [5-7]. Most patients with mild AD respond to optimized skin care and standard topical anti-inflammatory therapies [8-10]. However, currently, moderate-to-severe AD is still a huge psychological and economic burden on both patients and caregivers.

Although there is no conclusive treatment, affected children and their caregivers would benefit from the development of new and innovative, tailored therapies that could improve disease management and offer better outcomes. Therefore, presently, a variety of systemic treatments are available for patients with moderate-to-severe AD, including newer systemic therapies, such as Janus kinase (JAK) inhibitors, and more targeted antibodies that neutralize a specific

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cytokine or block its receptors, such as tralokinumab and dupilumab, respectively [11,12].

However, till now topical therapies [9,10,13,14] remain the mainstay of treatment for most patients with AD, regardless of disease severity: topical corticosteroids (TCSs) as initial options and topical calcineurin inhibitors (TCIs) and topical Janus kinase (JAK) inhibitors as second-line options.

TCSs are efficacious but may be associated with adverse events and different potencies may be required to treat AD in various body areas. Furthermore, their use is often restricted, particularly in sensitive skin areas (e.g., face, neck and genitalia) and in young children who are at increased risk of systemic absorption [13,14].

TCIs may be used to treat sensitive skin areas but are often associated with local tolerability issues such as irritation, burning, stinging, and erythema at the site of application, and are recommended for short-term and non-continuous use [10].

Topical phosphodiesterase-4 (PDE-4) inhibitors [15] may be used twice daily but can lead to burning, stinging, and application site pain. PDE-4 inhibitors are not available in Europe, due to market access limitations.

Therefore, considering the burden and heterogeneity of AD, a non-steroidal topical and effective treatment is needed for all patients, including very young children.

Tapinarof, an aryl hydrocarbon receptor (AhR), is a new topical agent that targets cutaneous diseases. It was developed to address the need for a novel, nonsteroidal, topical therapy with rapid, robust durable efficacy and favorable long-term tolerability, without restrictions on the duration of treatment or sites of application.

## ARYL HYDROCARBON RECEPTOR

To maintain skin homeostasis, skin cells express environmental sensors such as the aryl hydrocarbon receptor (AhR) [16,17]. AhR is typically located in the cytoplasm and moves to the nucleus upon activation by an agonist. There, it partners with either the aryl hydrocarbon receptor nuclear translocator (ARNT) or hypoxia-inducible factor 1b (HIF-1b). This complex then interacts with xenobiotic response elements (XREs) to control the expression of key genes.

AhR is a versatile environmental sensor that acts as a ligand-dependent transcription factor, responding to a wide range of small molecules originating from the environment, our diets, host microbiomes, and internal metabolic processes. In the skin, where it is highly expressed, AhR regulates inflammatory and immune pathways, leading to different modulatory effects on APCs, DCs, TRM cells, and regulation of cytokine expression of TH2, TH17 cells, TH22 cells, macrophages, neutrophils, and mast cells [18-20]. Its multiple actions can be schematically resumed as follows:

(A) modulation of the response to many microbial pathogens [21];
(B) control of the epidermal homeostasis, skin barrier structure and function [22] and
(C) antioxidant activity [22];
(D) role in the development of pruritus in AD [23]. Indeed, the ARNT gene is a target gene of AhR. It encodes the neurotrophic factor artemin, which is involved in pruritus. The expression pattern of artemin upon AhR activation depends on the AhR ligand. For example, several epidemiological studies have demonstrated that exposure of skin to air pollutants acts as a risk factor for the development or exacerbation of AD. Indeed, air pollutants can lead to prolonged activation of AhR and cause pruritus.

In recent decades, increasing evidence highlights AhR's role as a critical regulator of host-environment interaction. In particular, it can modulate skin immunity and barrier function exacerbating or mitigating inflammation of the skin, through a complex mechanism based on the way of activation (Tab. I). AhR activation depends on a specific ligand, which can include a wide range of synthetic and environmental chemicals such as dietary components, microbiota-derived factors, and endogenous tryptophan metabolites, as well as on the interaction with specific co-modulators of gene transcription and/or other transcription factors.

AhR, plays a key role in these signaling networks and, for this reason, it has been demonstrated to have therapeutic value [18,20] (Fig. 1).

## TAPINAROF'S MECHANISM OF ACTION

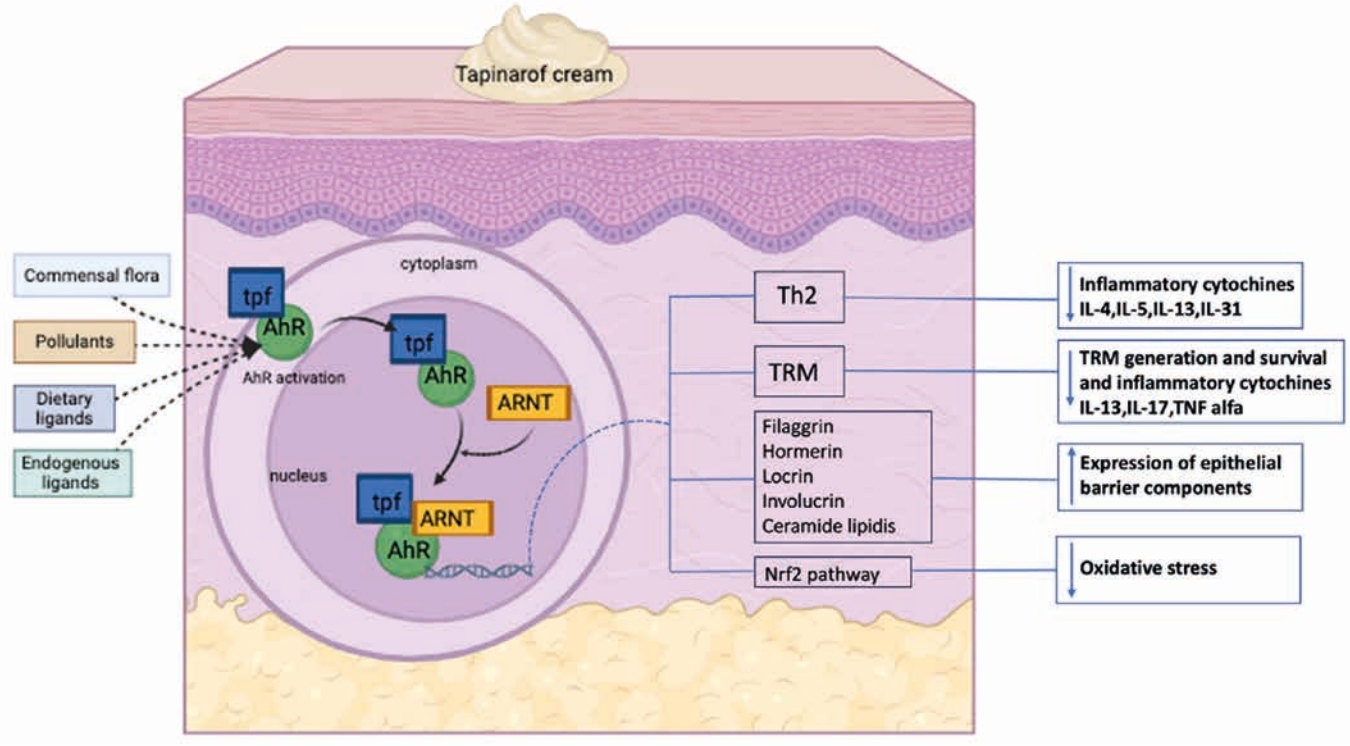
Tapinarof was first isolated from metabolites of *Photorhabdus luminescens*, a species of obligate symbiotic bioluminescent bacteria that live within the gut of insect-specific pathogenic nematodes. Tapinarof cream 1%, marketed as VTAMA (Dermavant Sciences Inc.), is a first-in-class, nonsteroidal topical AhR agonist with a pharmacokinetic profile that acts locally at sites of disease, avoiding systemic safety concerns, drug interactions or off-target effects [24].

Tapinarof medication is a pioneering small molecule that works as an AHR-modulating agent, and exhibits the unique ability to bind to and activate AhR specifically [25-27].

Recent studies have suggested that AhR signaling contributes

**TABLE I.** Roles of aryl hydrocarbon receptor (AhR) when activated by specific ligands, including tapinarof (modified by Kim et al., 2022) [20].

| |
|---|
| Aryl hydrocarbon receptor activation |
| Modulation of the response to microbial pathogens |
| Modulation of the skin immunity and inflammation |
| Regulation of epidermal homeostasis |
| Regulation of pruritus |
| Regulation of skin barrier structure and function |
| Antioxidant activity |




Tpf: Tapinarof; AhR: aryl hydrocarbon receptor; ARNT: aryl hydrocarbon receptor nuclear translocator; Th2: T helper 2 cells; TRM: tissue-resident memory T cells; Nrf2: nuclear factor erythroid 2-related factor 2.

**FIGURE 1.** Effects of tapinarof and other ligands on AhR activation (modified by Cannon et al., 2021; Gold et al., 2025; Silverberg et al., 2024) [19,27,32].

to AD pathogenesis and AHR modulation can lead to potential therapeutic effects [26,27]. As an AhR agonist, tapinarof has a profile that fundamentally differs from available AD treatments. Based on evidence from in vitro and animal studies, AhR activation by tapinarof induces gene expression that leads to decreased skin inflammation (by downregulation of Th17 cytokines implicated in plaque psoriasis, including IL-17A and IL-17F, and Th2 cytokines implicated in AD, including IL-4, IL-5, and IL-13), and to restore the integrity of the skin barrier, through upregulation of skin barrier components, including filaggrin, loricrin, hornerin, involucrin and ceramide lipids [26]. Moreover, it reduces oxidative stress by increasing antioxidant response through the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, as well as direct suppression of reactive oxygen species. Tapinarof may also reduce the activity and persistence of pathogenic TRM cells [26].

Therefore, tapinarof, acting as an immune-modulator, anti-oxidative and anti-inflammatory treatment, represents a novel therapeutic approach to AD, with the potential to address several gaps in the current treatment options (Fig. 1).

## CLINICAL EFFICACY AND SAFETY OF TAPINAROF IN AD

Tapinarof cream 1% received its first approval on 23 May 2022 in the USA for the topical treatment of plaque psoriasis in adults, after its efficacy was confirmed in a clinical trial [24]. Tapinarof cream 1% is also being investigated for the treatment of AD in various trials in Europe, US, Japan, and China [28-32] (Tab. II).

All multicenter trials (ADORING phase 1, 2 and 3), identically designed as randomized, double-blind, and vehicle-controlled, evaluated the efficacy and safety of tapinarof cream 1% *vs.* vehicle cream in adults and children younger than 2 years of age with moderate-to-severe AD. After a 30-day screening period, eligible patients were randomly assigned 2:1 to tapinarof or vehicle cream. In all ADORING reports, tapinarof cream 1%, administered once daily, demonstrated significant efficacy compared to vehicle and was well tolerated in adults and children.

In two phase 3 trials, 813 patients were randomized to tapinarof or vehicle once daily for 8 weeks [30,31]. Significant results were seen in both studies concerning the primary efficacy endpoint, consisting

**TABLE I.** Baseline patient demographics, clinical characteristics and safety results (modified by Silverberg et al., 2024; Gold et al., 2025) [31,32].

| | ADORING 1 | | ADORING 2 | |
|---|---|---|---|---|
| **Characteristics** | **Tapinarof 1% QD (n = 270)** | **Vehicle QD (n = 137)** | **Tapinarof 1% QD (n = 271)** | **Vehicle QD (n = 133)** |
| Age, years, mean (SD) | 15.6 (16.6) | 15.6 (16.5) | 16.4 (16.2) | 16.8 (16.1) |
| Age group, n (%) | | | | |
| 2-6 Years | 76 (28.1) | 39 (28.5) | 65 (24.0) | 30 (22.6) |
| 7-11 Years | 75 (27.8) | 37 (27.0) | 64 (23.6) | 32 (24.1) |
| 12-17 Years | 67 (24.8) | 34 (24.8) | 89 (32.8) | 44 (33.1) |
| ≥ 18 Years | 52 (19.3) | 27 (19.7) | 53 (19.6) | 27 (20.3) |
| Male, n (%) | 130 (48.1) | 66 (48.2) | 117 (43.2) | 57 (42.9) |
| vIGA-AD™ score, n (%) | | | | |
| 3 (Moderate) | 244 (90.4) | 122 (89.1) | 228 (84.1) | 113 (83.5) |
| 4 (Severe) | 26 (9.6) | 15 (10.9) | 43 (15.9) | 22 (16.5) |
| EASI score, mean (SD) | 12.2 (5.0) | 12.9 (5.6) | 13.5 (5.6) | 13.1 (4.7) |
| BSA affected, mean (SD) | 16.5 (8.7) | 17.7 (9.5) | 17.1 (8.7) | 15.8 (7.9) |
| PP-NRS total score, mean (SD) | | | | |
| All | 6.8 (2.3) | 6.5 (2.4) | 6.7 (2.4) | 6.9 (2.1) |
| ≥ 12 Years | 6.5 (2.4) | 6.3 (2.3) | 6.3 (2.4) | 6.5 (2.2) |
| < 12 Years | 7.0 (2.3) | 6.6 (2.5) | 7.1 (2.3) | 7.4 (1.8) |
| Averse events | | | | |
| Any adverse event | 123 (45.6) | 35 (25.5) | 100 (36.9) | 28 (21.1) |
| Serious adverse event* | 3 (1.1) | 0 | 2 (0.7) | 0 |
| Treatment-related adverse events | | | | |
| Any | 34 (12.6) | 9 (6.6) | 32 (11.8) | 9 (6.8) |
| Serious | 0 | 0 | 0 | 0 |
| Adverse events of special interest§ | | | | |
| Contact dermatitis | 4 (1.5) | 3 (2.2) | 3 (1.1) | 2 (1.5) |
| Grade 3 | 0 | 0 | 0 | 0 |
| Led to trial discontinuation | 2 (0.7) | 2 (1.5) | 0 | 1 (0.8) |
| Follicular event | 27 (10.0) | 1 (0.7) | 24 (8.9) | 2 (1.5) |
| Grade 3 | 0 | 0 | 0 | 0 |
| Led to trial discontinuation | 1 (0.4) | 0 | 0 | 0 |
| Headache | 19 (7.0) | 3 (2.2) | 4 (1.5) | 0 |
| Grade 3 | 1 (0.4) | 0 | 0 | 0 |
| Led to trial discontinuation | 1 (0.4) | 1 (0.7) | 0 | 0 |
| Any TEAE (≥ 5%) | | | | |
| Folliculitis | 22 (8.1) | 1 (0.7) | 22 (8.1) | 2 (1.5) |
| Headache | 19 (7.0) | 3 (2.2) | 4 (1.5) | 0 |

*(continues)*

**TABLE II** *(follows).* Baseline patient demographics, clinical characteristics and safety results (modified by Silverberg et al., 2024; Gold et al., 2025) [31,32].

| Characteristics | ADORING 1 | | ADORING 2 | |
|---|---|---|---|---|
| | Tapinarof 1% QD (n = 270) | Vehicle QD (n = 137) | Tapinarof 1% QD (n = 271) | Vehicle QD (n = 133) |
| Nasopharyngitis | 13 (4.8) | 7 (5.1) | 4 (1.5) | 1 (0.8) |
| Local tolerability scores, mean (SD) | | | | |
| Patient- or parent/caregiver-assessed burning/stinging | 1.3 (1.4) | 1.1 (1.3) | 1.0 (1.3) | 1.1 (1.3) |
| Patient- or parent/caregiver-assessed itching | 1.9 (1.5) | 1.7 (1.5) | 1.6 (1.6) | 1.5 (1.5) |
| Investigator-assessed irritation (dryness, erythema, and peeling) | 0.5 (0.9) | 0.6 (1.0) | 0.3 (0.8) | 0.3 (0.9) |
| Location of AD, n (%) | | | | |
| Head and neck region | 190 (70.4) | 101 (73.7) | 200 (73.8) | 105 (77.8) |
| Face | 109 (40.4) | 48 (35.0) | 93 (34.3) | 59 (44.4) |
| Neck | 120 (44.4) | 63 (46.0) | 112 (41.3) | 58 (43.6) |

* No serious adverse events were considered by the investigators to be related to tapinarof 1% cream.
§ No adverse events of special interest were graded 4 or 5 (considered either life-threatening or related to death).
Grade 3 = Severe or medically significant but not immediately life-threatening.

in obtaining the Validated Investigator Global Assessment for Atopic Dermatitis score of 0 or 1 and a ≥ 2-grade improvement from baseline at Week 8: 45.4% for tapinarof *vs*. 13.9% for vehicle in a trial and 46.4% *vs*. 18.0% in the other. At Week 8 significantly superior EASI75 responses ($P < 0.0001$ for both studies) were also observed with tapinarof *vs*. vehicle: 55.8% *vs*. 22.9% and 59.1% *vs*. 21.2%. Rapid improvements in patient-reported pruritus were also significant in the case of tapinarof *vs*. vehicle.

Mostly mild or moderate common adverse events (≥ 5%) such as folliculitis, headache, and nasopharyngitis were observed, and fewer discontinuations due to adverse events in the tapinarof groups than in case of vehicle were reported.

To assess the long-term efficacy, a 48-week open-label extension study, ADORING 3 (NCT05142774), was performed. This study confirmed the durability (lack of tachyphylaxis), and potential to achieve complete clearance, with disease control maintained while off therapy.

Trials also demonstrated a favorable safety and tolerability profile of tapinarof, acting locally at application sites with minimal-to-no systemic absorption even in case of maximal use in adults and children with extensive AD, as well as a low potential for off-target effects and drug-drug interactions [30-32].

## CONCLUSIONS

Tapinarof's recent approval by the U.S. Food and Drug Administration, on December 16, 2024 for the treatment of AD in adults and children from 2 years of age considerably expands the available therapeutic options for AD management.

Tapinarof has been shown to promote barrier repair through upregulation of skin barrier components, including different proteins and ceramide lipids, to reduce inflammatory cytokines, including IL-31, which is a mediator of itch in AD and to reduce oxidative stress in AD [26,27].

Tapinarof cream 1% demonstrated a safety profile in all clinical trials on AD and plaque psoriasis [19,21-23]. It was well tolerated locally from the first application in different populations of patients with AD, including adults and children less than 2 years of age. No-to-minimal adverse events like burning/stinging and itching, also when applied to sensitive skin, such as the face and neck, were reported by the majority of patients or parents/caregivers and investigators.

While 8-week trials were of relatively short duration, the subsequent long-term extension trial, ADORING 3, assessed the efficacy, safety, and tolerability of tapinarof cream in AD across the spectrum of severity, including patients with mild to more severe AD for up to 48 weeks [30-32]. The efficacy was assessed and documented across different ages with an age range of 2 to 81 years (80% of pediatric patients in ADORING 1 and 2) [31].

Tapinarof is formulated as a cosmetically elegant cream without added fragrance and is free of petrolatum, para-aminobenzoic acid, phthalates, and parabens [32]. The vehicle is specifically designed to reduce skin irritation and optimize the delivery to the treated skin.

While current evidence is very encouraging, ongoing and future trials will be essential to confirm its long-term safety and efficacy across patient populations different for age and disease severity [33].

The clinical effectiveness of tapinarof cream, demonstrated in inflammatory skin diseases (psoriasis and AD) together with the

ubiquitous expression of AhR and its ability to be activated by a wide range of ligands, suggest that targeting AhR may have potential applications in a broad spectrum of other inflammatory disorders such as skin, gut, lung, ocular, and CNS diseases.

The development of AhR-targeted therapies in these diseases may require the use of new chemical entities with distinct formulations and routes of administration, which will need to be appropriately evaluated for bioavailability, efficacy, and safety.

The number of novel agents for the treatment of AD is expected to increase as the pathophysiology of this condition becomes clearer. Elucidating the endotypes of AD associated with various phenotypes is a major challenge for the future and will help in the development of new targeted and personalized therapies.

## Ethical considerations

Not applicable.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## Conflict of interest statement

The authors declare no conflict of interest.

## Authors' contributions

EG: conceptualized the manuscript, wrote the first draft and finalized it. BLC: contributed to write and finalize the draft. All authors revised the manuscript and approved the final version.

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