Tapinarof in the treatment of psoriasis: A review of the unique mechanism of action of a novel therapeutic aryl hydrocarbon receptor–modulating agent

Robert Bissonnette, MD,[a] Linda Stein Gold, MD,[b] David S. Rubenstein, MD, PhD,[c] Anna M. Tallman, PharmD,[c] and April Armstrong, MD[d]

Montréal, Canada; Detroit, Michigan; Morrisville, North Carolina; and Los Angeles, California

Tapinarof, a novel, first-in-class, small-molecule topical therapeutic aryl hydrocarbon receptor (AhR)–modulating agent, is in clinical development for the treatment of psoriasis and atopic dermatitis. The efficacy of tapinarof in psoriasis is attributed to its specific binding and activation of AhR, a ligand-dependent transcription factor, leading to the downregulation of proinflammatory cytokines, including interleukin 17, and regulation of skin barrier protein expression to promote skin barrier normalization. AhR signaling regulates gene expression in immune cells and skin cells and has critical roles in the regulation of skin homeostasis. Tapinarof-mediated AhR signaling underlies the mechanistic basis for the significant efficacy and acceptable tolerability observed in early-phase clinical trials of tapinarof cream in the treatment of psoriasis. (J Am Acad Dermatol 2021;84:1059-67.)

Key words: Antioxidant; aryl hydrocarbon receptor (AhR); cytokines; dermis; epidermis; homeostasis; immune; inflammation; ligand; psoriasis; small molecule; T cell; tapinarof; therapeutic aryl hydrocarbon receptor–modulating agent (TAMA); topical; transcription factor.

Plaque psoriasis is a common, chronic, immune-mediated disease characterized by scaly, erythematous, and pruritic well-demarcated lesions that can be painful and disfiguring.[1,2] The burden of psoriasis is reported to be similar to that of other chronic conditions, such as congestive cardiac failure and chronic lung disease, and includes significant physical, psychological, and socioeconomic burdens.[3-6] People with psoriasis are at increased risk of anxiety and depression,[7-9] and

From Innovaderm Research Inc, Montréal[a]; Henry Ford Health System, Detroit[b]; Dermavant Sciences, Inc, Morrisville[c]; and Keck School of Medicine of the University of Southern California, Los Angeles.[d]

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Correspondence to: Dr Robert Bissonnette, MD, Innovaderm Research, 3530 St-Laurent, Suite 300, Montréal, QC H2X 2V1. E-mail: rbissonnette@innovaderm.com.

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experience an increased incidence of several comorbidities.[3,10-12]

Although the introduction of biologics and systemic agents targeting key immune pathways, such as the interleukin (IL)-23/IL-17 axis, has significantly advanced treatment, particularly of more severe disease, conventional topical treatments are used by the vast majority of patients with psoriasis.[1,13,14] Topical agents forming the mainstay of psoriasis treatment include corticosteroids, vitamin D derivatives (calcipotriene, calcitriol), vitamin A derivatives (tazarotene), anthralin, and coal tar,[15] with topical corticosteroids and vitamin D derivatives being the most frequently prescribed.[16] Although efficacious, topical corticosteroids have restrictions regarding duration, location, and extent of use. The effectiveness of corticosteroids may also be limited by the potential for tachyphylaxis and recurrence of symptoms associated with reduced frequency or cessation of treatment.[16] Other topical agents, such as calcipotriene and tazarotene, have well-documented adverse events, such as skin irritation.[15,17] Considering the importance of topical agents in psoriasis, few options with novel mechanisms have been introduced in recent years, and the need for more effective and well-tolerated topical therapies remains (Table I[18-30]).

Tapinarof is a novel, first-in-class, small-molecule topical therapeutic aryl hydrocarbon receptor (AhR)—modulating agent (TAMA) currently in late-stage clinical trials for the treatment of psoriasis and atopic dermatitis. Here, the unique mechanism of action of tapinarof cream for the treatment of psoriasis is reviewed in the context of the current understanding of AhR signaling in the skin and a growing body of clinical trials evidence on the efficacy and safety of tapinarof cream in psoriasis[29,30] and atopic dermatitis.[31-33]

CAPSULE SUMMARY

- Tapinarof is a topical therapeutic aryl hydrocarbon receptor—modulating agent that downregulates interleukin 17 and promotes skin barrier normalization, with antioxidant activity
- The efficacy and tolerability of tapinarof in psoriasis clinical trials is attributed to its unique mechanism of action, representing an important potential advance in the development of topical medicine

THE AhR RECEPTOR

AhR is a ligand-dependent transcription factor

AhR is a ligand-dependent transcription factor that regulates gene expression in a range of cells, including immune and epithelial cells. In healthy skin, AhR signaling plays an integral part in maintaining skin homeostasis by regulating the skin immune network, keratinocyte differentiation, skin barrier function and pigmentation, and responses to oxidative stress.[34,35]

AhR is crucial to maintaining homeostasis by mediating responses to xenobiotic and environmental challenges and is activated by a wide range of low-molecular-weight ligands found in endogenous, dietary, environmental, and microbial sources.[34,36,37] Endogenous AhR ligands include indigoids, heme metabolites, and arachidonic acid metabolites. Dietary AhR ligands include flavonoids, carotenoids, and metabolites of commensal gut bacteria,[37] and environmental ligands include polycyclic aromatic hydrocarbons and polychlorinated-biphenyls.[38]

An important characteristic of AhR is its differential activation by this wide range of ligands. Upon ligand binding in the cytoplasm, the activated AhR-ligand complex heterodimerizes with the AhR nuclear translocator (ARNT), resulting in transformation of the complex into a high-affinity DNA-binding transcription factor. The AhR-ligand/ARNT complex binds to specific DNA recognition sites, resulting in transcriptional control of AhR-responsive genes.[39,40] In addition to its direct effect on gene transcription, AhR can signal through other transcription factors, such as nuclear factor κB and nuclear factor erythroid 2-related factor 2 (Nrf2), to modulate gene expression.[39-41] Thus, depending on the specific ligand, binding to AhR can result in induction or repression of different genes, causing diverse biologic responses in numerous tissue types.[42]

How different ligands activate AhR to cause such diverse responses has been an area of research for numerous years. Although the diverse molecular mechanisms of AhR binding and downstream signaling remain to be fully elucidated, its therapeutic potential in skin disease has become a focus of attention, given growing evidence for the essential role of AhR signaling in regulating inflammatory responses and skin homeostasis.[42-44]

AhR signaling and psoriasis

AhR is widely expressed in immune cells, including antigen-presenting cells, T cells, fibroblasts, macrophages, mast cells, and other skin immune cells, with the expression of AhR being necessary for the functioning of antigen-presenting

Abbreviations used:

AhR:	aryl hydrocarbon receptor
ARNT:	AhR nuclear translocator
IL:	interleukin
Nrf2:	nuclear factor erythroid 2-related factor 2
ROS:	reactive oxygen species
TAMA:	therapeutic AhR modulating agent
Th:	T helper

cells, including Langerhans cells, and cytokine expression.[34] AhR signaling has been shown to regulate the terminal differentiation of $CD4^+$ T helper (Th) 17 and Th22 cells, as well as the expression of IL-17 and IL-22 cytokines.[43,45]

AhR is expressed in keratinocytes, and AhR signaling regulates keratinocyte terminal differentiation, promotes skin barrier integrity, and prevents transepidermal water loss.[46,47] To maintain skin barrier integrity, AhR activation and signaling have been shown to upregulate barrier protein gene expression, including filaggrin.[39] Additionally, AhR-mediated activation of transcription factors such as Nrf2 induce cytoprotective antioxidant responses that suppress oxidative stress and restore skin homeostasis.[35,39]

The contribution of aberrant immune responses to the pathogenesis of psoriasis is well established and supported by the demonstrated efficacy and approval of biologics that selectively target cytokines, such as tumor necrosis factor α, IL-23, and IL-17A.[14] The immune response in psoriasis is characterized by increased skin infiltration and activation of effector $CD4^+$ T cells, including the upregulation of Th17 and Th22 cells.[48,49] Crosstalk between immune cells and skin cells contributes to the formation and exacerbation of psoriatic plaques and, histologically, psoriasis is characterized by aberrant differentiation and hyperproliferation of keratinocytes in the upper layers of the epidermis.[2] Furthermore, in psoriasis, abnormal epidermal differentiation and impaired skin barrier function have been associated with downregulation of skin barrier protein expression, including filaggrin and loricrin.[50] Oxidative stress has also been implicated in the pathogenesis of psoriasis, through a pathogenic effect that results in cellular damage, inflammation, and impairment of skin barrier function.[51-53]

Current understanding of the expression and function of AhR in the skin supports further investigation into AhR signaling as a therapeutic target in psoriasis and other inflammatory skin diseases. Nonspecific modulation of AhR signaling possibly underlies the mechanism of action of coal tar, one of the oldest topical treatments in psoriasis, which contains a mixture of organic compounds, including polycyclic aryl hydrocarbons that may activate AhR to exert a therapeutic effect.[54,55]

A potential functional role of AhR in psoriasis has been shown in AhR-deficient mice that developed exacerbated psoriasiform skin inflammation with increased IL-17 and IL-22 expression in an imiquimod-induced psoriasis model. Additionally, treatment of wild-type mice with 6-formylindolo[3,2-b]carbazole, an endogenous AhR ligand found in skin, ameliorated psoriasiform skin inflammation and pathology in an imiquimod-induced psoriasis model.[56]

In patients with psoriasis, dysregulated AhR expression has been shown. Increased serum levels of AhR were identified in patients with psoriasis compared with healthy individuals.[57] Increased AhR expression in peripheral blood mononuclear cells of patients with psoriasis was associated with increased Th22 cells and IL-22 expression compared with healthy individuals.[58] Increased AhR expression has been identified in skin biopsy samples of patients with psoriasis,[59] and treatment of skin cells with AhR ligands in vitro resulted in the modulation of genes implicated in the pathogenesis of psoriasis, including IL-6, IL-8, and type I and II interferon pathway genes.[56,59]

Taken together, these findings suggest that AhR ligation may modulate downstream effector functions of AhR signaling to affect multiple mechanisms contributing to the development of psoriasis. The specific binding and activation of AhR by tapinarof leads to the modulation of a unique set of target genes that are dysregulated in psoriasis and includes IL-17, thus exerting therapeutic effects that are distinct from other AhR ligands.[60] This is significant because the activity of AhR is highly ligand dependent, and several naturally occurring and synthetic AhR ligands are known to exert differential biologic effects via the AhR transcription factor and downstream pathways.[34]

TAPINAROF AS A TREATMENT FOR PSORIASIS

Tapinarof discovery

The discovery of tapinarof (DMVT-505; previously known as WBI-1001 and GSK2894512) was a fortuitous outcome of investigations into the secondary metabolites of *Photorhabdus luminescens*, a bioluminescent, Gram-negative bacillus, which lives symbiotically within parasitic, soil-living entomopathogenic nematodes of the genus *Heterorhabditis*.[61,62] *P luminescens* is essential to the reproduction of the nematode because the worm carries the symbiont in its intestines and, upon

Table I. Tapinarof* and FDA-approved topical monotherapy for the treatment of plaque psoriasis†

Active principle, vehicle, concentration, and dosing frequency	FDA plaque psoriasis indication and initial, approval year	Efficacy outcomes and duration of response/follow-up: active versus vehicle	Duration of use	Common adverse events (≥1%)
Corticosteroids				
Clobetasol propionate				
0.05% spray twice daily[18]	• Plaque psoriasis • Moderate to severe, affecting ≤20% BSA • Age ≥18 years • 1985	• Week 2, IGA of 0/1: 47%-55% vs. 0%-2% • PASI: NA • Follow-up: NA	• ≤4 weeks; >2 weeks is limited to localized moderate/severe lesions that insufficiently improve	• Application site: burning (40%), pruritus (3%), dryness (2%), irritation (1%), pain (1%), pigmentation changes (1%) • URTI (8%) • Nasopharyngitis (5%) • Streptococcal pharyngitis (1%)
0.025% cream twice daily[19]	• Plaque psoriasis • Moderate to severe • Age ≥18 years • 1985	• Week 2, IGA of 0/1 + ≥2 GI: 30% vs 9%-10% • PASI: NA • Follow-up: NA	• ≤2 weeks	• Application site discoloration (2%)
Halobetasol propionate				
0.05% lotion twice daily[20]	• Plaque psoriasis • Age ≥18 years • 1990	• Week 2, IGA of 0/1 + ≥2 GI: 45% vs 6%-7% • PASI: NA • Follow-up: NA	• ≤2 weeks	• Application-site atrophy (1%) • Telangiectasia (1%) • Headache (1%)
0.01% lotion once daily[21]	• Plaque psoriasis • Age ≥18 years • 1990	• Week 8, IGA of 0/1 + ≥2 GI: 37%-38% vs 8%-12% • PASI: NA • Follow-up: ≤12 weeks (4 weeks after stopping therapy) superior to vehicle	• ≤8 weeks	• URTI (2%) • Application site dermatitis (1%) • Hyperglycemia (1%)
Desoximetasone				
0.25% spray twice daily[22]	• Plaque psoriasis • Age ≥18 years • 1977	• Week 4, PGA of 0/1: 31%-53% vs 5%-18% • PASI: NA • Follow-up: NA	• ≤4 weeks	• Application site: dryness (2.7%), irritation (2.7%), pruritus (2%)
Betamethasone dipropionate				
0.05% spray twice daily[23]	• Plaque psoriasis • Mild to moderate • Age ≥18 years • 1975	• Week 2, IGA of 0/1 + ≥2 GI: 19%-22% vs 2%-7% • PASI: NA • Follow-up: NA	• ≤4 weeks	• Application site: pruritus (6%), burning/stinging (4.5%), pain (2.3%), atrophy (1.1%)
Vitamin D analogs				
Calcitriol				
3 μg/g ointment twice daily[24]	• Plaque psoriasis • Mild to moderate • Age ≥18 years • 1978	• Week 8, IGA of 0/1 + ≥2 GI: 21%-23% vs 7%-14% • PASI: NA • Follow-up: NA	• ≤52 weeks	• Hypercalcemia (24%) • Laboratory test result abnormality (8%) • Hypercalciuria (3%) • Skin discomfort (3%) • Pruritus (1%-3%) • Urine abnormality (4%) • Psoriasis (4%)

Continued

Table I. Cont'd

Active principle, vehicle, concentration, and dosing frequency	FDA plaque psoriasis indication and initial, approval year	Efficacy outcomes and duration of response/follow-up: active versus vehicle	Duration of use	Common adverse events (≥1%)
Calcipotriene				
0.005% foam twice daily[25]	• Plaque psoriasis • Age ≥18 years • 1993	• Week 8, ISGA of 0/1 + ≥2 GI: 14%-27% vs 7%-16% • PASI: NA • Follow-up: NA	• ≤8 weeks	• Application site: pain (3%), erythema (2%)
0.005% cream twice daily[26]	• Plaque psoriasis • Age ≥18 years • 1997	• Week 8: 50% at least marked improvement; 4% complete clearing; vehicle, NA • PASI: NA • Follow-up: NA	• ≤8 weeks	• Skin irritation (10%-15%) • Rash, pruritus, dermatitis, and worsening of psoriasis (1%-10%)
Retinoids				
Tazarotene				
0.1% or 0.05% cream once daily[27]	• Plaque psoriasis • Affecting ≤20% BSA • Age ≥12 years • 1997	• Week 12, overall lesional assessment of none, minimal, or mild: 39%-51% vs 24%-26% • PASI: NA • Superiority over vehicle as early as week 1 or 2 for 0.1% or 0.05% cream once daily, respectively • Follow-up: ≤24 weeks (12 weeks after stopping therapy) superior to vehicle	• ≤12 weeks	• Pruritus, erythema, and burning (10%-23%)
Therapeutic aryl hydrocarbon receptor—modulating agents				
Provisional data from 1 phase 2b trial[28-30]				
Tapinarof*				
1% cream once daily	• Plaque psoriasis • Mild to severe • Age ≥18 years • TBD—pending phase 3 data	• Week 12, PGA of 0/1 + ≥2 GI: 56% vs 5% ($P < .05$) • Week 12, PASI75: 56% vs 5% ($P < .001$) • Week 12, PASI90 = 40% vs 0% ($P = .001$) • PGA and PASI75 responses were observed as early as week 2 and were significantly superior to vehicle by week 8 • Follow-up: 16 weeks (4 weeks after stopping therapy) superior to vehicle for all endpoints	• Restrictions not anticipated‡	• Contact dermatitis (11%) • Folliculitis (5%) • Application site dermatitis (5%) • Miliaria (5%) • Urticaria (5%) • Nasopharyngitis (3%) • Headache (3%)

BSA, Body surface area; *FDA*, US Food and Drug Administration; *GI*, grade improvement; *IGA*, Investigator's Global Assessment; *ISGA*, Investigator's Static Global Assessment; *NA*, not available; *PASI*, Psoriasis Area and Severity Index; *PASI75*, ≤75% improvement in Psoriasis Area and Severity Index; *PASI90*, ≤90% improvement in Psoriasis Area and Severity Index; *PGA*, Physician Global Assessment; *TBD*, to be decided; *URTI*, upper respiratory tract infection.

*Tapinarof is an investigational drug; data are from a phase 2b randomized controlled trial.[18,19,72] Two phase 3 trials, PSOARING 1 (NCT03956355) and PSOARING 2 (NCT03983980) completed in 2020 and have been preliminarily reported.[73]

†Table presents registration trial data extracted from FDA labels; comparisons between agents are not recommended in the absence of head-to-head trial data.

‡Restrictions regarding duration of use with tapinarof are not anticipated; more information will be available following completion of a phase 3 long-term extension trial, PSOARING 3 (NCT04053387).

entering a host insect, releases the bacilli, which help preserve insect tissue in optimal conditions for nematode growth.[62,63]

In 1959, Dutky first noted that insects infected by the nematode did not putrefy once dead, in contrast to the rapid decay seen in the absence of the nematode.[64] It was therefore postulated that *P luminescens* was producing metabolites with antimicrobial and other properties responsible for the observed biologic effect. One such metabolite was purified and identified as 3,5-dihydroxy-4-isopropylstilbene, a small molecule with a low molecular weight (254 g/mol).[62,65] Pharmaceutical development of 3,5-dihydroxy-4-isopropylstilbene (tapinarof) identified the compound as having anti-inflammatory properties.[66] The mechanism of action of tapinarof was elucidated by profiling against more than 800 potential cellular targets, including a diverse array of kinases and other intracellular enzymes, nuclear receptors, transcription factors, and mediators of epigenetic signaling, where the most potent interactions were observed with AhR.[44] Tapinarof was found to bind directly to AhR, resulting in downregulation of inflammatory cytokines, regulation of skin barrier protein expression, and antioxidant activity.[44,60]

Tapinarof-modulated AhR signaling in immunomodulation

One of the proposed mechanisms for the observed clinical effect of tapinarof in patients with psoriasis is via the suppression of key Th17/Th22 cytokines, IL-17, and IL-22. In a T-cell polarization assay, tapinarof markedly inhibited T-cell expansion and Th17-cell differentiation and reduced the production of IL-17,[44] while also reducing IL-17A and IL-17F levels in a $CD4^+$ T-cell assay.[44] In a mouse model of psoriasis, tapinarof treatment downregulated inflammatory cytokine expression in skin tissue, including *IL17A*, *IL17F*, *IL19*, *IL22*, *IL23A*, and *IL1B* gene expression.[44] The downregulation of cytokines by tapinarof was not observed in AhR-deficient mice, supporting the conclusion that tapinarof has an anti-inflammatory role mediated via AhR signaling in vivo.[44]

Tapinarof-modulated AhR signaling in regulating keratinocyte function

The regulation of skin barrier protein expression and normalization of skin cell differentiation via modulation of the AhR signaling pathway both provide a mechanistic rationale for the therapeutic effects of tapinarof observed in clinical trials of psoriasis and atopic dermatitis.[29,32] Tapinarof has been shown to induce the expression of skin barrier genes related to keratinocyte differentiation[44] that are downregulated in psoriasis, including filaggrin and loricrin.[67] The role of tapinarof in restoring epidermal function to promote normalization of skin barrier mechanisms is also supported by the finding that AhR-deficient keratinocytes are hyperresponsive to proinflammatory cytokines, exhibit increased production of inflammatory mediators, and develop psoriatic pathology.[68,69]

Tapinarof-modulated AhR signaling in reduction of oxidative stress

In patients with psoriasis, increased circulating reactive oxygen species (ROS) and decreased antioxidant levels are associated with increased disease severity.[70] Tapinarof is a stilbene molecule containing 2 phenol groups that directly scavenge ROS, including superoxide anions and hydroxyl radicals, showing intrinsic antioxidant activity.[44] Tapinarof also induces the AhR-Nrf2 transcription factor pathway, leading to expression of antioxidant enzyme genes, such as nicotinamide adenine dinucleotide phosphate quinone oxidoreductase 1, and heme oxygenase-1, to reduce ROS.[35,44] AhR-mediated antioxidant activity and subsequent ROS reduction has been shown to reduce inflammatory responses, including decreasing keratinocyte IL-8 expression.[71] Thus, the combined antioxidant response through the Nrf2 pathway and direct ROS scavenging by tapinarof may together reduce epidermal oxidative stress known to cause significant cellular damage to skin in the pathogenesis of psoriasis.

Tapinarof in psoriasis clinical trials

Initial clinical proof-of-concept studies were conducted using a different formulation of tapinarof cream, WBI-1001. A phase 2 study showed that WBI-1001 1% concentration cream applied twice daily for 12 weeks significantly improved Physician Global Assessment scores compared with vehicle in patients with mild to moderate plaque psoriasis. Adverse drug reactions, mostly at application sites, were more frequent with active treatment than with vehicle, but all were mild or moderate in intensity.[66] WBI-1001 was later reformulated to enhance the drug product's stability and delivery, resulting in the current formulation of tapinarof cream in clinical development, which was evaluated in a phase 2b dose-ranging study in patients with mild to severe plaque psoriasis. In this study, patients were randomized to tapinarof cream 0.5% or 1% once daily or twice daily, or vehicle once daily or twice daily for 12 weeks with a 4-week treatment-free follow-up.

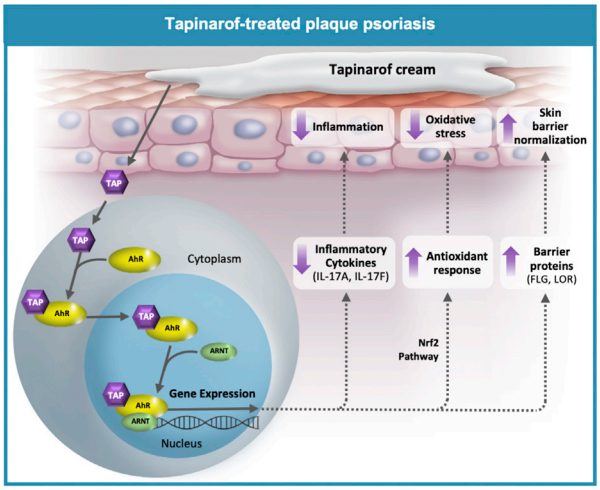

Fig 1. Potential mechanisms of action of tapinarof in the treatment of psoriasis. Tapinarof activation of the aryl hydrocarbon receptor modulates gene expression that leads to significant reduction of T helper type 17 cytokines implicated in plaque psoriasis, including IL-17A and IL-17F (demonstrated in vitro, ex vivo, and in mouse models); increase in antioxidant response through the Nrf2 pathway, as well as direct ROS scavenging by tapinarof (demonstrated in vitro and ex vivo); and regulation of skin barrier protein expression, including filaggrin and loricrin (demonstrated in vitro). *AbR*, Aryl hydrocarbon receptor; *ARNT*, aryl hydrocarbon receptor nuclear translocator; *FLG*, filaggrin; *IL*, interleukin; *LOR*, loricrin; *Nrf2*, nuclear factor erythroid 2-related factor 2; *ROS*, reactive oxygen species; *TAP*, tapinarof.

The primary endpoint was Physician Global Assessment score of 0 or 1 and a 2-grade or greater improvement at week 12. The proportion of patients achieving the primary endpoint was significantly higher in all tapinarof cream groups than in vehicle groups (65% [1% twice daily], 56% [1% once daily], 46% [0.5% twice daily], and 36% [0.5% once daily] vs 11% [vehicle twice daily] and 5% [vehicle once daily]), and was maintained for 4 weeks after the end of treatment through week 16 in all tapinarof groups except for the 0.5% twice daily group. Clinically meaningful improvements in psoriasis outcomes were observed at as early as 2 weeks of treatment with tapinarof cream, and significant improvements were maintained for 4 weeks after treatment discontinuation. Tapinarof was generally well tolerated, and most treatment-emergent adverse events were mild or moderate in severity.[29] The safety and efficacy of tapinarof 1% cream once daily has been evaluated in a pivotal phase 3 psoriasis clinical program that completed in 2020 and awaits full publication, comprising 2 randomized controlled trials in adults with plaque psoriasis (NCT02564042 and NCT03983980).[73]

Evidence thus far shows that tapinarof-mediated AhR activation has the potential to exert multiple mechanistic effects in psoriasis, from immune modulation to the regulation of skin barrier function, which is supported by the potential of AhR to control gene transcription directly or indirectly through other transcription factors and its wide expression in different cell types and tissues (Fig 1). In psoriasis, the totality of in vitro, ex vivo, and in vivo data support an anti-inflammatory mechanism in which tapinarof/AhR/ARNT complexes directly bind to the *IL17A* promotor and suppress *IL17A* transcription. Additionally, the observation that methylation of the *IL17A* promoter is increased in response to tapinarof provides further support for an anti-inflammatory effect mediated by decreased expression of IL-17A upon treatment (Dermavant Sciences, Inc, unpublished data, 2017 - written communication); the latter epigenetic modification of the *IL17A* promoter may explain, in part, the durability of therapeutic effect in the phase 2b clinical trial, where significant improvements were maintained for 4 weeks after discontinuation of tapinarof in patients with psoriasis.[29]

Further studies will contribute to a more precise mechanistic understanding of how AhR activation by tapinarof leads to downstream effector functions and is an opportunity for future study with tapinarof cream to further support the translation of its mechanistic effects to clinical outcomes in patients with psoriasis.

CONCLUSIONS

The efficacy of tapinarof in psoriasis is attributed to its activation of AhR, a ligand-dependent transcription factor, which modulates gene expression of IL-17 and skin barrier proteins to exert an anti-inflammatory effect and promote skin barrier normalization, respectively, in addition to its antioxidant activity.[44,60] Tapinarof binds to a specific site on AhR, leading to unique biologic outcomes that manifest clinically as significant therapeutic efficacy for a topical agent in the treatment of inflammatory skin diseases.[72] Tapinarof has been effective and generally well tolerated in clinical trials to date, and the positive phase 2 findings have led to progression to a pivotal phase 3 clinical trial program. Further data from those clinical trials will provide a greater understanding of the benefits and safety and tolerability profile of tapinarof in the management of psoriasis.

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