Tapinarof-associated folliculitis is generally mild, self-limiting, and rarely interferes with therapy.

To the Editor: We thank Konstantinou et al1 for their interest in our article on the mechanism of action of tapinarof. We appreciate the opportunity to clarify and share information on folliculitis observed in tapinarof clinical trials, as this is completely different from dioxin-induced chloracne or hidradenitis suppurativa.

Konstantinou et al1 draw associations between tapinarof and dioxin-like compounds based on their aryl hydrocarbon receptor (AhR)-binding activity. However, since AhR is a ligand-dependent transcription factor, any downstream effects are highly dependent on the molecule to which it binds. Therefore, the mechanisms underlying the efficacy and safety of tapinarof in psoriasis are distinct from dioxins and other AhR-binding ligands.

Tapinarof is a naturally identified topical therapeutic AhR modulating agent, thus different from pathologic AhR modulating agents, such as the manmade toxin, dioxin. Tapinarof and dioxins bind at distinctly different sites on the AhR complex, modulate different genes and pathways, and cause vastly different downstream effects.2,3 Moreover, tapinarof has limited systemic exposure as demonstrated by maximal use pharmacokinetic studies.4

Information on folliculitis has been obtained from more than 2200 patients in 18 tapinarof clinical trials. Across all trials, the incidence, morphology, and severity of folliculitis have remained consistent. In the most recent, pivotal, phase 3 psoriasis trials in 1025 patients,3 the adverse event associated with tapinarof was folliculitis, which was mostly mild, resulted in a low incidence of study discontinuation (1.8%), was localized to the hair follicle, and was not associated with a higher frequency in areas prone to acne. Therefore, localized folliculitis in these studies was not analogous to hidradenitis suppurativa5 or the lesions seen in chloracne, which involve the sebaceous glands. Sebaceous gland atrophy has never been observed with tapinarof in any preclinical in vivo studies, regardless of the route of delivery, including chronic exposure.

In summary, evidence with tapinarof is not supportive of the associations proposed by Konstantinou et al,1 and the clinical data demonstrates that tapinarof-associated folliculitis is generally mild, self-limiting, and rarely interferes with therapy.
REFERENCES


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