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Folliculitis with tapinarof, when it occurs, is generally mild, self-limiting, and rarely interferes with therapy

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

To the Editor: We thank Konstantinou et al[1] 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 al[1] 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 suppurativa[5] 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.

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Conflicts of interest

Dr Bissonnette is a consultant with honoraria for Bausch Health Companies Inc and Boston Pharmaceuticals; an investigator with grants/research funding for AbbVie Inc and Escalier Biosciences, Inc; an advisor with honoraria and an investigator with grants/research funding for BMS, Boehringer Ingelheim, Eli Lilly and Company, and Pfizer Inc; a consultant with honoraria and an investigator with grants/research funding for Janssen-Ortho Inc, Sienna Biopharmaceuticals, Inc, and Valeant Pharmaceuticals North America LLC; and an advisor, a consultant with honoraria, and an investigator with grants/research funding for Dermavant Sciences, Inc.

Dr Gold is an investigator, consultant, and speaker with honorarium for Leo Pharma; an investigator with honorarium for Incyte; a consultant and speaker with honorarium for Mayne Pharma and Taro Pharmaceutical Industries; an investigator and consultant for Ortho Dermatologics and Sun; and a consultant with honorarium and an investigator for Dermavant Sciences, Inc.

Dr Rubenstein is an employee of Dermavant Sciences, Inc with stock options.

Dr Tallman is an employee of Dermavant Sciences, Inc with stock options.

Dr Armstrong has served as a research investigator or scientific advisor to AbbVie, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Novartis, Ortho Dermatologics, Sun,

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