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The preponderance of evidence supports an aryl hydrocarbon receptor-dependent mechanism of action of tapinarof

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The preponderance of evidence supports an aryl hydrocarbon receptor-dependent mechanism of action of tapinarof

To the Editor: We thank Haarmann-Stemmann et al[1] for their interest in our article on the mechanism of action of tapinarof, a novel, first-class, small-molecule topical therapeutic aryl hydrocarbon receptor (AhR)-modulating agent in development for the treatment of psoriasis and atopic dermatitis.

While we attribute a major part of tapinarof's clinical effect in psoriasis to its specific binding and activation of AhR, we did not intend to rule out the possibility of additional beneficial effects unexplained by AhR signaling. In fact, in our original article, we note that tapinarof, as a stilbene molecule, has intrinsic antioxidant and reactive oxygen species-scavenging activities, thus also acts in an AhR-independent manner. We also concur with Haarmann-Stemmann et al[1] that cell-specific and other factors are likely to play important roles in the clinical effect of tapinarof.

However, we assert that the preponderance of good quality evidence supports an AhR-dependent mechanism of action of tapinarof, explaining a major part of its highly significant efficacy recently reported in 2 large phase 3 trials.[2] In particular, evidence that knocking out AhR expression in mouse models abrogates the beneficial effects of tapinarof on psoriasiform inflammation strongly supports an AhR-dependent mechanism.[3]

Although absence of evidence does not equate to evidence of absence, to the best of our knowledge the authors' assertion that tapinarof clears psoriasis by altering the skin microbiome is not supported by the same level of rigorous empirical evidence. These additional pathways may explain the modest efficacy of unstandardized applications such as coal tar, making it tempting to speculate that these pathways may also be involved with tapinarof. However, evidence on their contribution to the clinical efficacy of the active principle in tapinarof cream 1%, which is a well-characterized, naturally identified, small-molecule pharmacologic product, is insufficient.

Moreover, in a maximal-use pharmacokinetic study, using tapinarof cream 1% once daily was shown to result in negligible systemic exposure, even under conditions that maximize the potential for drug absorption.[4] Thus, while we cannot rule out that the active principle may have beneficial skin microbiome effects, negligible systemic exposure with topical tapinarof cream 1% is unlikely to have significant effects outside of the skin.[4]

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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 from 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. Drs Rubenstein and Tallman are both employees of Dermavant Sciences, Inc with stock options. Dr Armstrong has served as a research investigator and/or scientific advisor for AbbVie, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Novartis, Ortho Dermatologics, Sun, Dermavant Sciences, Inc, Dermira, Sanofi, Regeneron, Pfizer, and Modmed.

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