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27874 Correlation of itch response to roflumilast cream with disease severity and patient-reported outcomes in patients with chronic plaque psoriasis

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Trifarotene transcriptomics analysis and acne-related gene expression

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Trifarotene cream, 0.005% is an FDA approved topical retinoid indicated for treatment of facial and truncal acne and has received positive outcome through the European Decentralized Procedure. Trifarotene is the first novel topical retinoid molecule approved for acne treatment in 20 years, and the only approved retinoid that specifically acts through retinoic acid receptor gamma. This study investigated new potential pathways through which trifarotene exerts its efficacy in acne by analyzing the changes in gene expression in the skin of acne patients. Subjects with moderate inflammatory acne of the back were treated with trifarotene 0.005% or vehicle cream on dedicated back areas for 27 days, and 4 biopsies were collected on each subject (non-involved skin, acne papule, trifarotene, and vehicle-treated site). Large-scale gene expression profiling of the biopsies was performed using Affymetrix technology, and treatment specific gene expression profiles were generated using statistical modeling. This analysis highlighted a specific gene expression profile, comprising of 67 genes uniquely driven by Trifarotene treatment with most of these genes known to affect immune responses as well as extracellular matrix reorganization. Interestingly, those genes were downregulated as compared with the papule signature suggesting that trifarotene reverses some inflammatory processes of the papule. Altogether, these results show that trifarotene has a unique action in acne treatment by acting on epidermal differentiation and proliferation (Aubert et al., 2018) as well as on innate and adaptive immune cells in acne pathogenesis.

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Correlation of itch response to roflumilast cream with disease severity and patient-reported outcomes in patients with chronic plaque psoriasis

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Roflumilast cream is a nonsteroidal, selective phosphodiesterase-4 inhibitor in development for plaque psoriasis (PsO). A Phase 2b, double-blinded trial randomized adults with PsO (2-20% body surface area) to once daily roflumilast 0.3%, roflumilast 0.15%, or vehicle for 12 weeks (NCT03638258). Throughout the trial, itch and its impact were evaluated via patient reported outcomes (PROs): Worst Itch Numeric Rating Scale (WI−NRS), Itch related Sleep Loss (IRSL), and Dermatology Life Quality Index (DLQI). This posthoc analysis reports correlation of WI−NRS with other PROs and with disease severity. Overall, 331 patients were randomized (109 to roflumilast 0.3%, 113 to 0.15%, and 109 to vehicle). At baseline, the mean WI−NRS score was 5.87. Throughout the trial, both roflumilast doses showed similar improvements in WI−NRS starting at Week 2 and were significantly superior to vehicle ($P \leq .002$). At baseline, Pearson correlation coefficients (PCCs) for WI−NRS and Psoriasis Area and Severity Index (PASI) were 0.189, 0.282, 0.205 for roflumilast 0.3%, roflumilast 0.15%, and vehicle, respectively ($P \leq .033$ for all correlations); for WI−NRS and IRSL: 0.548, 0.646, 0.652 ($P < .001$); for WI−NRS and DLQI: 0.445, 0.617, 0.422 ($P < .001$). At Week 8, PCCs for WI−NRS and PASI were 0.420, 0.409, 0.365 ($P < .001$); for WI−NRS and IRSL: 0.673, 0.725, 0.696 ($P < .001$); for WI−NRS and DLQI: 0.607, 0.823, 0.529. Treatment with roflumilast resulted in rapid and robust improvement in the severity of itch associated with PsO. Itch response to roflumilast was independent of disease severity and positively correlated with patient-reported sleep loss and quality of life improvement.

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The PASI-HD improved precision in measuring disease severity in subjects with mild to moderate plaque psoriasis treated with roflumilast cream, a phosphodiesterase-4 inhibitor

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Psoriasis Area and Severity Index (PASI), a gold standard measure in psoriasis clinical trials, lacks sensitivity in affected areas <10%; it does not distinguish disease regardless of severity in cases of low Body Surface Area (BSA). PASI-HD was developed to obtain higher discrimination in low BSA using the actual percentage of involvement of each anatomical area. PASI and PASI-HD were assessed in a randomized, vehicle-controlled, phase 2b, 12-week study of once-daily roflumilast cream. Patients with chronic plaque psoriasis were randomized to roflumilast 0.3% (n = 109), roflumilast 0.15% (n = 113), or vehicle (n = 109). In anatomical areas with involvement <10%, PASI area score was scored 1. PASI-HD was assigned a value of 1% to 9% and transformed to score of 0.1 to 0.9. Mean PASI and PASI-HD were highly correlated and showed larger magnitude improvement throughout the study in both roflumilast treatment groups relative to vehicle.(1) PASI-HD precision was demonstrated in a post hoc analysis assessing PASI and PASI-HD scores by percent area involvement and severity scores. PASI/PASI-HD (median) for roflumilast 0.15%, 0.3%, and vehicle at baseline by percentage area involvement were 12.8/9.7, 13.6/10.8, 11.9/ 9.0, respectively, and at week 8 were 9.0/2.6, 7.0/3.0, 10.0/7.6. Similar trends of lower median PASI-HD as compared with PASI were observed for each clinical manifestations (erythema, induration, desquamation) regardless of severity. The higher level of discrimination with PASI-HD allows more accurate evaluation of treatment efficacy in patients with smaller areas of involvement, while preserving anatomy and severity measures.

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Differences in pediatric vs adult clinical trial designs for atopic dermatitis

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Despite an increasing burden of atopic dermatitis (AD) in all ages, the distribution of participant age and trial characteristics remains unelucidated. The aim of this study was to compare trial characteristics between pediatric and adult AD trials. We collected data from ClinicalTrials.gov on AD therapeutic trials completed between 2003-2019 and further stratified trials by pediatrics (mean or median age <18 years of the experimental group participants) or adults. Trials without results on ClinicalTrials.gov were searched on PubMed. Exclusion criteria include non-pharmacologic trials or those without published data on ClinicalTrials.gov or PubMed as of April 30, 2020. Of 210 trials, 50 (24%) were pediatric trials [mean age: 8.2 ± 4.3 years (SD)] and 160 (76%) were adult trials [mean age 35.2 ± 5.7 years (SD)]. Pediatric and adult trials were equally likely randomized controlled trials; however, pediatric trials were more likely open label trials ($P < .001$) and have no comparator ($P < .001$). Adult trials were more likely industry funded (95% vs 80%, $P = .001$). Any evaluation of drug safety was more likely present in adult trials (83% vs 60%, $P = .001$). In trials examining AD severity as an outcome, Eczema Area and Severity Index (EASI) predominated in adult trials (51% vs 29%, $P < .05$) and SCORing Atopic Dermatitis (SCORAD) in pediatric trials (25% vs 10%, $P < .05$). The results suggest differences in trial design between pediatric and adult AD trials and also show the lack of trial standardization in trial design.

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