Pruritus associated with direct MAPK inhibitors: A systematic review and meta-analysis

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Background: Pruritus is a common, yet underreported cutaneous adverse event that can impair quality of life and compromise treatment adherence. Although direct MAPK inhibitors are increasingly used, the incidence of pruritus and pruritus-associated cutaneous adverse events and differences across the MAPK pathway have not been systematically evaluated. Thus, this systematic review and meta-analysis sought to identify and analyze the current literature on pruritus and pruritus-associated cutaneous adverse events in the setting of direct MAPK inhibitor treatment for non-melanoma cancers.

Methods: Following PRSIMA guidelines, PubMed, Embase, Scopus, Web of Science, and Ovid MEDLINE databases were systematically searched from 2000 to 2026 using combinations of terms related to MAPK, RAS, RAF, BRAF, MEK, ERK, cutaneous adverse events, and individual drug names. Reference lists of eligible studies were also screened. Randomized and nonrandomized trials, and observational studies on single agent MAPK inhibitor therapies for non-melanoma indications that specified “pruritus” as an adverse event were included. Studies lacking extractable pruritus data, nonhuman studies, and reviews were excluded. Two reviewers independently screened studies, extracted study data, and assessed risk of bias. Pooled event rates were estimated using random-effects meta-analysis.

Results: Twenty-five of 3,382 identified records met inclusion criteria, encompassing 1,617 participants (average age 46.8 years; range 2.1 – 75 years old). The pooled incidence of treatment-

related pruritus was 15.4% (95% CI, 12.3%–19.1%). Pruritus incidence differed significantly across inhibitor classes, with the highest pooled incidence observed among ERK inhibitors 22.8% (95% CI, 17.1%-29.9%) as compared to 14.1% (95% CI, 10.7%-18.3%) among RAF inhibitors, and 14.1% (95% CI, 11.5%-20.2%) among MEK inhibitors. However, meta-regression did not demonstrate a significant association between inhibitor class and pruritus incidence ($Q = 1.46$; $p = 0.48$). Among studies reporting severe adverse events, grade 3 or higher pruritus occurred in 1.1% (95% CI, 0.7%-1.9%) of patients receiving direct MAPK inhibitors. To contextualize the burden of isolated pruritus within the broader spectrum of cutaneous adverse events that are associated with pruritus, pooled incidences for rashes and dry skin were evaluated (Figure 1). Rash, inclusive of specified and unspecified types, was the most frequently reported cutaneous adverse event overall 46.9% (95% CI, 36.6%-57.5%). Sensitivity analyses demonstrated stable pooled estimates across included studies. Management strategies were reported inconsistently across studies with only 16 studies reporting dose modifications due to cutaneous adverse events and 10 studies reporting interventions. Common interventions included topical and oral corticosteroids, antihistamines, emollients, and pain medication. Across studies reporting treatment modification, most cases were managed conservatively without permanent treatment discontinuation. Limited standardized reporting precluded pooled analysis of treatment efficacy.

Conclusions: Direct MAPK inhibitors are associated with a substantial burden of treatment-related pruritus, affecting approximately one in five patients. The higher incidence observed with ERK inhibition suggests that dermatologic toxicities may vary according to the level of MAPK pathway inhibition. Our findings suggest substantial phenotypic variation in pruritus and pruritus-associated cutaneous adverse events exist across levels of MAPK pathway inhibition. Improved recognition and reporting of treatment-associated pruritus may facilitate earlier intervention and enhance supportive care for patients receiving targeted cancer therapies.

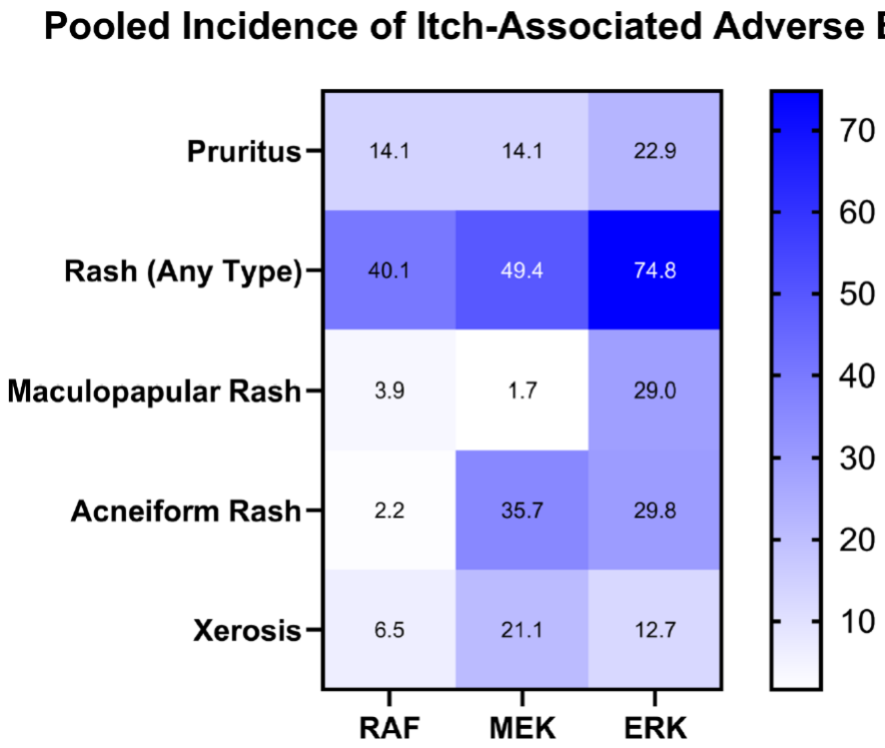


Figure 1. Heatmap Display of Pooled Incidence of Pruritus and Pruritus-Associated Adverse Events