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Topical Retinoid-Associated Acne Flare in Acne Vulgaris: A Systematic Review of Incidence, Clinical Characteristics, and Outcomes

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 May 2026 and was last updated on 25 May 2026.

INTRODUCTION

Review question / Objective Review question/objective:
To systematically review the incidence, clinical features, and treatment outcomes of acne flare or early acne worsening associated with FDA-approved topical retinoids, including tretinoin, adapalene, tazarotene, and trifarotene, in patients with acne vulgaris.

PICOS framework:
Patients with acne vulgaris treated with topical retinoids will be included. The intervention/exposure will be topical tretinoin, adapalene, tazarotene, or trifarotene. Comparators may include vehicle/placebo, non-retinoid topical acne treatment, another topical retinoid formulation, concentration, or regimen, or baseline status before treatment. Outcomes will include acne flare, early acne worsening, lesion-count increase, acne severity worsening, treatment modification, discontinuation, and final treatment outcomes. Eligible studies will include randomized controlled trials, non-randomized clinical trials, and prospective or retrospective cohort studies.

Condition being studied Acne vulgaris is a common chronic inflammatory disorder of the pilosebaceous unit characterized by comedones, papules, pustules, nodules, and, in some cases, scarring. Topical retinoids are core treatments for acne vulgaris and are commonly used to normalize follicular keratinization, reduce comedone formation, and improve inflammatory and non-inflammatory lesions. However, early acne worsening or “acne flare” after treatment initiation has been described in clinical practice and may affect treatment adherence. This review will evaluate acne flare or early acne worsening associated with FDA-approved topical retinoids, including tretinoin, adapalene, tazarotene, and trifarotene.

METHODS

Participant or population Patients diagnosed with acne vulgaris who received treatment with at least

one FDA-approved topical retinoid, including tretinoin, adapalene, tazarotene, or trifarotene, will be included. Participants of any age, sex, ethnicity, acne severity, and acne distribution, including facial, truncal, or mixed acne, will be considered. Studies involving patients receiving systemic retinoids only, such as oral isotretinoin, will be excluded. Studies involving mixed dermatologic conditions will be included only if data for patients with acne vulgaris can be extracted separately.

Intervention The intervention/exposure of interest will be FDA-approved topical retinoids used for acne vulgaris, including tretinoin, adapalene, tazarotene, and trifarotene. Studies evaluating different formulations, concentrations, vehicles, application frequencies, or treatment regimens of these topical retinoids will be considered. Fixed-dose combination products containing one of these retinoids will be included only if relevant data on acne worsening or flare can be extracted for the retinoid-containing regimen.

Comparator Comparators may include vehicle/placebo, non-retinoid topical acne treatments, different topical retinoid types, formulations, concentrations, vehicles, application frequencies, or treatment regimens. Baseline status before treatment initiation will also be considered as a comparator for single-arm or non-comparative studies.

Study designs to be included This review will include primary clinical studies with denominator-based data, including randomized controlled trials, non-randomized clinical trials, prospective cohort studies, and retrospective cohort studies. Case reports, case series, case-control studies, reviews, systematic reviews, meta-analyses, editorials, commentaries, guidelines, conference abstracts without sufficient data, animal studies, and in vitro studies will be excluded.

Eligibility criteria Eligible studies must include patients with acne vulgaris treated with at least one topical retinoid of interest: tretinoin, adapalene, tazarotene, or trifarotene. Studies must report extractable data on acne flare, acne worsening, acne aggravation, acne exacerbation, early lesion-count increase, worsening acne severity score, treatment-emergent acne worsening, or treatment interruption/discontinuation due to acne worsening. Full-text, peer-reviewed articles published in English from inception to 31 May 2026 will be included. Studies reporting only local irritation or tolerability outcomes, such as erythema, dryness, peeling, scaling, burning, stinging, or pruritus, without acne lesion worsening will be excluded. Studies involving systemic retinoids only, non-acne indications, or non-extractable acne-specific data will also be excluded.

Information sources The literature search will be conducted using electronic databases, including Scopus, PubMed/MEDLINE, Cochrane Library, and the Directory of Open Access Journals (DOAJ), from inception to 31 May 2026. The Cochrane Library search will include the Cochrane Central Register of Controlled Trials (CENTRAL), when available. Reference lists of included studies and relevant review articles will also be manually screened to identify additional eligible studies. No formal grey literature search is planned.

Main outcome(s) The main outcome will be the incidence of topical retinoid-associated acne flare or early acne worsening in patients with acne vulgaris. Acne flare or early worsening will be defined as acne aggravation, acne exacerbation, patient-reported acne worsening, investigator-assessed worsening, treatment-emergent acne worsening, or an increase in inflammatory, non-inflammatory, nodular, or total acne lesion counts after treatment initiation. When available, early worsening will be assessed during the first 2–8 weeks of therapy. Effect measures will include the number and proportion of patients experiencing acne flare or worsening, changes in lesion counts from baseline, changes in acne severity scores, and comparative estimates between treatment and comparator groups when reported.

Quality assessment / Risk of bias analysis The risk of bias of included studies will be assessed according to study design. Randomized controlled trials will be evaluated using the Cochrane Risk of Bias 2 tool. Non-randomized clinical trials will be evaluated using the ROBINS-I tool. Prospective and retrospective cohort studies will be evaluated using the Newcastle–Ottawa Scale. Two reviewers will independently assess the risk of bias, and disagreements will be resolved through discussion or consultation with a third reviewer. The results will be summarized narratively and presented in tables or figures.

Strategy of data synthesis A narrative synthesis will be conducted to summarize the included studies. Study characteristics, retinoid type, formulation, concentration, treatment regimen, comparator, follow-up duration, definition of acne flare or worsening, timing of onset, severity, management, treatment modification or discontinuation, and final treatment outcomes will be extracted and presented in tables. The

incidence of acne flare or early acne worsening will be summarized as the number and proportion of affected patients among treated participants. Where sufficient clinically and methodologically homogeneous data are available, a meta-analysis may be performed using appropriate effect measures, such as proportions, risk ratios, odds ratios, or mean differences. Heterogeneity will be assessed using clinical judgment and, when meta-analysis is conducted, the I^2 statistic. If substantial heterogeneity or insufficient comparable data are present, findings will be synthesized narratively.

Subgroup analysis If sufficient data are available, subgroup analyses will be conducted according to topical retinoid type, including tretinoin, adapalene, tazarotene, and trifarotene; formulation or vehicle; concentration; application regimen; monotherapy versus fixed-dose combination therapy; acne severity at baseline; acne distribution, such as facial or truncal acne; age group; sex; and study design. Subgroup analyses may also compare early worsening reported as lesion-count increase, investigator-assessed worsening, patient-reported worsening, or treatment-emergent acne aggravation/exacerbation. Subgroup analyses will be performed only when data are sufficiently comparable across studies.

Sensitivity analysis Sensitivity analyses will be performed if sufficient data are available. Planned sensitivity analyses may include excluding studies at high risk of bias, excluding fixed-dose combination products, excluding studies with non-standard or unclear definitions of acne flare or worsening, excluding retrospective studies, and restricting the analysis to randomized controlled trials. Additional sensitivity analyses may be conducted by excluding studies with very short follow-up periods, small sample sizes, or incomplete outcome reporting. Sensitivity analyses will be used to assess the robustness of the findings and to explore whether conclusions are influenced by study design, methodological quality, or outcome definition.

Language restriction English.

Country(ies) involved Thailand.

Keywords acne vulgaris; topical retinoids; acne flare; acne worsening; tretinoin; adapalene; tazarotene; trifarotene; systematic review.

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