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Original Research Article

Efficacy and Safety of Topical Tretinoin Monotherapy versus Vehicle in the Treatment of Acne Vulgaris: A Meta-Analysis of Randomised Controlled Trials

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ABSTRACT

Background: Topical tretinoin is a guideline-endorsed first-line comedolytic retinoid for acne vulgaris, yet the magnitude of its benefit over vehicle across formulations, its expression in absolute terms, and its performance in paediatric skin have not been isolated in a focused pairwise synthesis.

Objective: To estimate the effect of topical tretinoin monotherapy versus vehicle on investigator-rated treatment success in facial acne vulgaris.

Methods: PubMed/MEDLINE, Scopus, Web of Science and the Cochrane Library were searched from database inception, and ClinicalTrials.gov and regulatory product labels were interrogated to recover event-level data. Randomised, double-blind, vehicle-controlled trials (or vehicle-controlled arms) of topical tretinoin monotherapy in facial acne were eligible. The primary outcome was treatment success at approximately 12 weeks. Two reviewers independently screened, extracted data and applied the Cochrane RoB 2.0 tool. Risk ratios (RRs) were pooled with a DerSimonian–Laird random-effects model; heterogeneity used I^2 and a prediction interval.

Results: Nine trial datasets (4,429 participants; 2,537 tretinoin, 1,892 vehicle) were pooled. Tretinoin significantly increased treatment success (RR 1.83, 95% CI 1.48–2.27; $p < 0.001$), with moderate heterogeneity (I^2 36.7%) and a prediction interval (1.11–3.04) that excluded the null. The absolute success rate rose from 10.4% with vehicle to 18.4% with tretinoin (number needed to treat approximately 12). The estimate was stable in leave-one-out (RR 1.75–1.95) and combined-programme (RR 1.80) analyses and did not differ across formulations ($p = 0.17$). Cutaneous adverse events were mild, transient and application-site limited.

Conclusion: Topical tretinoin monotherapy roughly doubled the relative likelihood, and raised the absolute likelihood by about 8 percentage points, of treatment success versus vehicle, with predictable, self-limiting local tolerability that extended to preadolescent skin, supporting its first-line and maintenance positioning.

All authors have reviewed and approved the final version of the manuscript.

1. Introduction

Acne vulgaris is among the most prevalent chronic inflammatory disorders of the pilosebaceous unit, affecting the large majority of adolescents and a substantial and increasing proportion of adults, and it carries a well-documented burden of psychosocial distress, scarring and post-inflammatory dyspigmentation.[1] Its pathogenesis is multifactorial and comprises follicular hyperkeratinisation with microcomedone formation, increased and compositionally altered sebum production, proliferation of *Cutibacterium acnes* within the follicular microenvironment, and the activation of innate and adaptive inflammatory pathways.[2] Because the microcomedone is the common precursor of both non-inflammatory and inflammatory lesions, agents that normalise follicular keratinocyte differentiation occupy a central place in contemporary treatment algorithms.[1,3] The condition is estimated to affect close to one tenth of the global population across all ages and the substantial majority of adolescents, and its association with anxiety, depression and impaired self-image gives even modest improvements in lesion control a disproportionate value for the individual patient.[1]

Topical retinoids, of which tretinoin (all-trans retinoic acid) is the prototype, act by binding nuclear retinoic acid receptors, thereby normalising desquamation of the follicular epithelium, reducing microcomedone formation and exerting a mild anti-inflammatory effect.[3] Current guidance positions topical retinoids, alone or in fixed-dose combination with benzoyl peroxide or a topical antibiotic, as a foundation of first-line therapy for most forms of acne and as the preferred option for maintenance once inflammatory lesions have been controlled.[4] Tretinoin has been formulated as conventional creams and gels, as microsphere and micronised gels intended to reduce

irritation, and, more recently, as a polymeric-emulsion lotion; each formulation seeks to balance efficacy against the cutaneous irritation that characterises the retinoid class and that is a frequent reason for discontinuation, particularly among cosmetically motivated patients in aesthetic practice.[5]

Despite decades of clinical use, the evidence base for tretinoin is fragmented across many small and heterogeneous trials, several of which were designed primarily to license a specific formulation or to demonstrate the superiority of a fixed-dose combination rather than to quantify the effect of tretinoin monotherapy itself. Recent network meta-analyses have ranked a broad array of topical and systemic agents and have consistently placed retinoids and their combinations among the more effective options.[6–8] However, these large network syntheses necessarily pool tretinoin with numerous other interventions and comparators, and they do not report a single, transparent pairwise estimate of tretinoin versus its own vehicle. Clinicians and guideline developers therefore lack a contemporary, pooled measure of how much topical tretinoin improves the probability of a clinically meaningful treatment response relative to vehicle, of whether that benefit is consistent across formulations and age groups, and of what it amounts to in absolute terms.

The novelty of this study lies in providing the first contemporary, focused pairwise meta-analysis of topical tretinoin monotherapy versus vehicle for acne vulgaris that uses investigator-rated treatment success as a patient-relevant dichotomous endpoint, that draws event-level data from regulatory sources and trial registries in addition to the published literature, that expresses the benefit in both relative and absolute terms, and that formally examines the consistency of the effect across tretinoin formulations and across paediatric and adult populations. The aim of this study was to estimate the pooled effect of topical tretinoin monotherapy, compared with vehicle, on the probability of investigator-rated treatment success at approximately twelve weeks in patients with facial acne vulgaris, and to characterise the absolute magnitude, heterogeneity, robustness and local tolerability of that effect.

2. Methods

2.1. Protocol and registration

This review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[9] An internal, dated analysis protocol specifying the primary outcome, the random-effects model, and the subgroup, sensitivity and absolute-effect analyses was prepared before data synthesis; the review was not registered in a public registry, which is consistent with the policy of the journal, and ethical approval was not required as only previously published aggregate data were analysed. The question was framed with the PICO structure: patients of any age with facial acne vulgaris; topical tretinoin monotherapy in any formulation; matched vehicle or placebo; and investigator-rated treatment success at approximately twelve weeks.

2.2. Eligibility, sources and search

PubMed/MEDLINE, Scopus, Web of Science and the Cochrane Central Register of Controlled Trials were searched from database inception without language restriction, and reference lists, the ClinicalTrials.gov registry and United States Food and Drug Administration product labels were interrogated to recover event-level results for pivotal trials whose full numerical outcomes were unavailable in the primary publications. The core PubMed string was: ("tretinoin"[MeSH] OR "tretinoin"[tiab] OR "all-trans retinoic acid"[tiab]) AND ("acne vulgaris"[MeSH] OR "acne"[tiab]) AND ("vehicle"[tiab] OR "placebo"[tiab]) AND ("randomized controlled trial"[pt] OR "randomised"[tiab] OR "randomized"[tiab]). Eligible studies were randomised, double-blind, vehicle- or placebo-controlled trials (or vehicle-controlled arms of larger factorial trials) of topical tretinoin monotherapy for facial acne that reported, or permitted the reconstruction of, the number of participants achieving treatment success. Studies were excluded if tretinoin was given only within a fixed-dose combination without an isolable monotherapy arm, if the indication was other than acne, if the design was non-randomised or unblinded, or if no dichotomous success outcome could be derived; trials of exclusively truncal acne were not eligible.

2.3. Selection, data and risk of bias

Two reviewers independently screened records and extracted, into a piloted spreadsheet, the study identifier, formulation and concentration, population and age range, baseline severity, arm-level randomised numbers, the number achieving treatment success, the reported percentage lesion-count reductions, and cutaneous adverse events, with disagreements resolved by discussion. Where success was reported as a percentage, integer event counts were reconstructed from the percentage and the analysed denominator, rounded to the nearest participant and cross-checked against registry or label tabulations; the reconstruction arithmetic is provided in the supplementary file. Where a licensing report presented two independent pivotal trials with separate randomisation and non-overlapping populations, each was entered as a separate dataset, and a pre-specified sensitivity analysis later combined the paired trials within each programme. No trial contributed more than one tretinoin arm against a shared vehicle arm, so no unit-of-analysis error arose. Methodological quality was appraised independently by two reviewers using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2.0) across its five domains, with results displayed as a traffic-light matrix.

2.4. Synthesis

Because the primary outcome was dichotomous, the risk ratio (RR) was adopted and pooled on the natural-logarithm scale; the standardised mean difference and Hedges *g*, appropriate to continuous outcomes, were

considered but not applied, since the endpoint was binary and per-arm means and standard deviations for lesion counts were inconsistently reported. Study effects were combined with the Mantel–Haenszel method under a random-effects model using the DerSimonian–Laird estimator of the between-study variance (τ^2); no dataset contained a zero-event cell, so no continuity correction was required. Heterogeneity was quantified with the Q statistic, τ and τ^2, and the I^2 statistic with its 95% confidence interval, and a 95% prediction interval was calculated. The pooled control-arm event rate was combined with the relative effect to derive an absolute risk difference and number needed to treat. Robustness was tested by leave-one-out and combined-programme analyses; pre-specified subgroup analyses examined formulation and success definition, interpreted as non-randomised comparisons. Small-study effects were evaluated with a contour-enhanced funnel plot and the Egger test, acknowledged as underpowered below ten datasets. Analyses used R with the *meta* and *metafor* packages, with significance at a two-sided $p < 0.05$.

3. Results and Discussion

3.1. Study selection

The database searches and registry interrogation identified a large body of records addressing topical tretinoin in acne. After the removal of duplicates, the titles and abstracts were screened against the eligibility criteria, and the potentially relevant full-text reports were then assessed in detail. Records were excluded at full text principally because tretinoin was evaluated only within a fixed-dose combination without an isolable monotherapy arm, because the indication was non-acne (most often photoageing or melasma), because the design lacked a concurrent vehicle control, or because no dichotomous treatment-success outcome could be reconstructed even after interrogation of the corresponding registry entry or product label. Nine randomised, vehicle-controlled trial datasets ultimately met all criteria and were retained for quantitative synthesis. The complete flow of records through identification, screening, eligibility assessment and inclusion, with the numbers excluded at each stage and the reasons for exclusion, is shown in Figure 1.

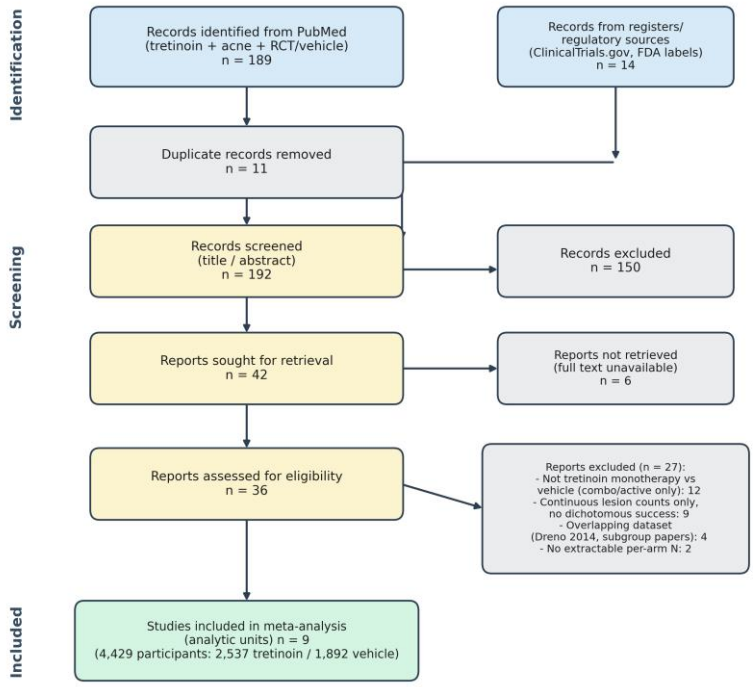

Figure 1. PRISMA 2020 flow diagram of study identification, screening and inclusion.

3.2. Study characteristics

As detailed in Table 1, the nine datasets were drawn from pivotal and investigator-initiated trials of tretinoin 0.05% lotion, tretinoin microsphere gel 0.1% and 0.04%, and tretinoin 0.025% gel, and together randomised 4,429 participants (2,537 to tretinoin and 1,892 to vehicle). The populations spanned preadolescents aged nine to eleven years through to adults, and baseline severity ranged from mild-to-moderate to moderate-to-severe facial acne. All trials applied the medication once daily for approximately twelve weeks and used an investigator global assessment as the success endpoint. Table 1 also gives the arm-level success counts, the per-dataset risk ratios with confidence intervals, and the random-effects weights. Each dataset is identified throughout by a single author-year (or product-programme) label, and the corresponding numbered reference is given in the table so that the datasets in Tables 2 and 4 can be mapped unambiguously onto those pooled in Table 1.

Table 1. Characteristics, treatment-success data, per-study risk ratios and random-effects weights of the included datasets.

Dataset (label used throughout)	Formulation	Population	Success/N (tretinoin)	Success/N (vehicle)	RR (95% CI)	Weight (%)
Tyring 2018 — Study 1[10]	Tretinoin 0.05% lotion	Age ≥9, moderate–severe	67/405	29/414	2.36 (1.56–3.57)	14.9
Tyring 2018 — Study 2[10]	Tretinoin 0.05% lotion	Age ≥9, moderate–severe	82/413	51/407	1.58 (1.15–2.19)	19.0
Retin-A Micro 0.1% — Study 1[11]	Tretinoin microsphere 0.1%	Adults	25/72	8/72	3.12 (1.51–6.46)	6.9
Retin-A Micro 0.1% — Study 2[11]	Tretinoin microsphere 0.1%	Adults	20/71	6/67	3.15 (1.35–7.35)	5.3
Retin-A Micro 0.04% — Study 1[11]	Tretinoin microsphere 0.04%	Adults	15/108	6/110	2.55 (1.03–6.32)	4.8
Retin-A Micro 0.04% — Study 2[11]	Tretinoin microsphere 0.04%	Adults	21/111	9/103	2.17 (1.04–4.51)	6.8
Eichenfield 2012[12]	Tretinoin microsphere 0.04%	Preadolescent 9–11 y	10/47	10/54	1.15 (0.52–2.52)	6.1
Jarratt 2012[13]	Tretinoin 0.025% gel	Age ≥12	105/464	43/242	1.27 (0.93–1.75)	19.2
Leyden 2006[14]	Tretinoin 0.025% gel	Age ≥12	122/846	34/423	1.79 (1.25–2.58)	17.1

Notes: RR, risk ratio for treatment success (tretinoin versus vehicle). Tyring 2018 datasets were reconstructed from the ClinicalTrials.gov results postings (NCT02932306, NCT02965456) and the corresponding publication;[10] the Retin-A Micro datasets from the United States Food and Drug Administration product label;[11] and the Eichenfield 2012, Jarratt 2012 and Leyden 2006 datasets from the primary publications and product labels.[12–14]

3.3. Risk of bias

Across the nine datasets the overall risk of bias was low to moderate, as displayed in Figure 2. Randomisation and blinding were generally well handled, consistent with the double-blind, vehicle-controlled design of the licensing trials; the most frequent concerns were missing outcome data from attrition over twelve weeks and, in a minority of datasets, selective reporting of the primary success definition among several plausible investigator scales. Because most datasets originated from industry-sponsored programmes, the potential for sponsor-related bias was considered throughout, although the double-blind, vehicle-controlled architecture mitigates the most direct forms of performance and detection bias.

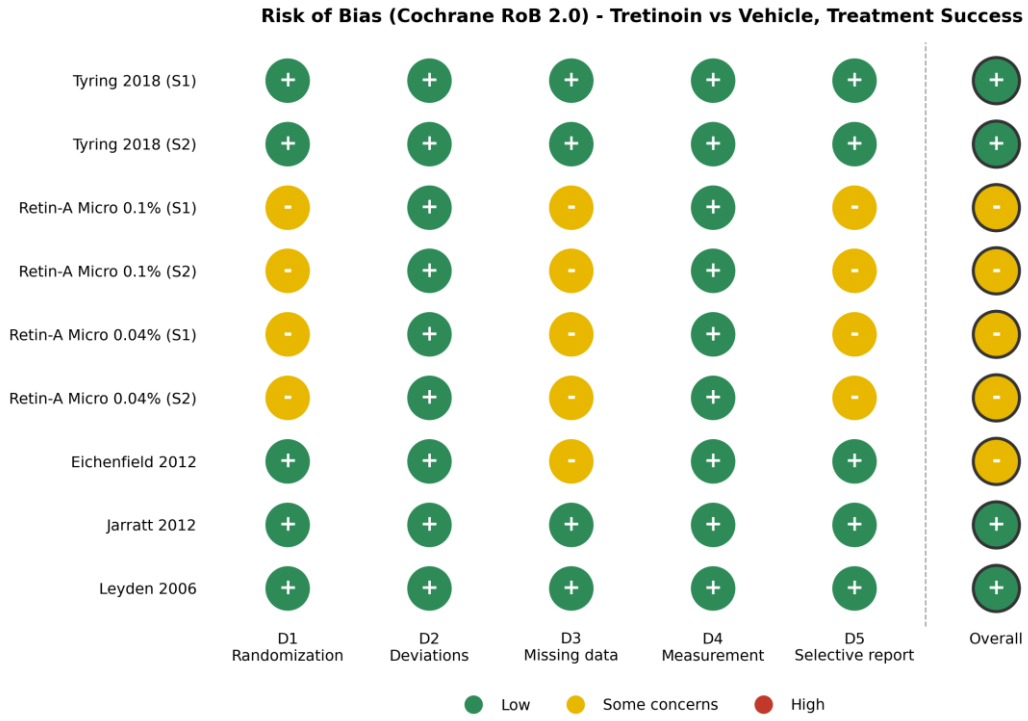

Figure 2. Cochrane RoB 2.0 risk-of-bias assessment across the five domains for each included dataset.

3.4. Primary meta-analysis

Pooling the nine datasets in a DerSimonian–Laird random-effects model, topical tretinoin monotherapy was associated with a significantly higher probability of treatment success than vehicle, with a pooled risk ratio of 1.83 (95% CI 1.48–2.27; z = 5.55; p < 0.001), as shown in the forest plot in Figure 3. In relative terms this corresponds to roughly a doubling of the likelihood of achieving investigator-rated clear or almost-clear skin. Between-study heterogeneity was moderate and non-significant (I^2 36.7%, 95% CI 0–70.9%; τ^2 0.036; τ 0.19; Q = 12.64, df = 8, p = 0.13); because the upper confidence limit of I^2 reached the substantial range, the heterogeneity is described as moderate rather than reliably low. The 95% prediction interval (1.11–3.04) excluded the null, indicating that a benefit would be expected in essentially all comparable future settings.

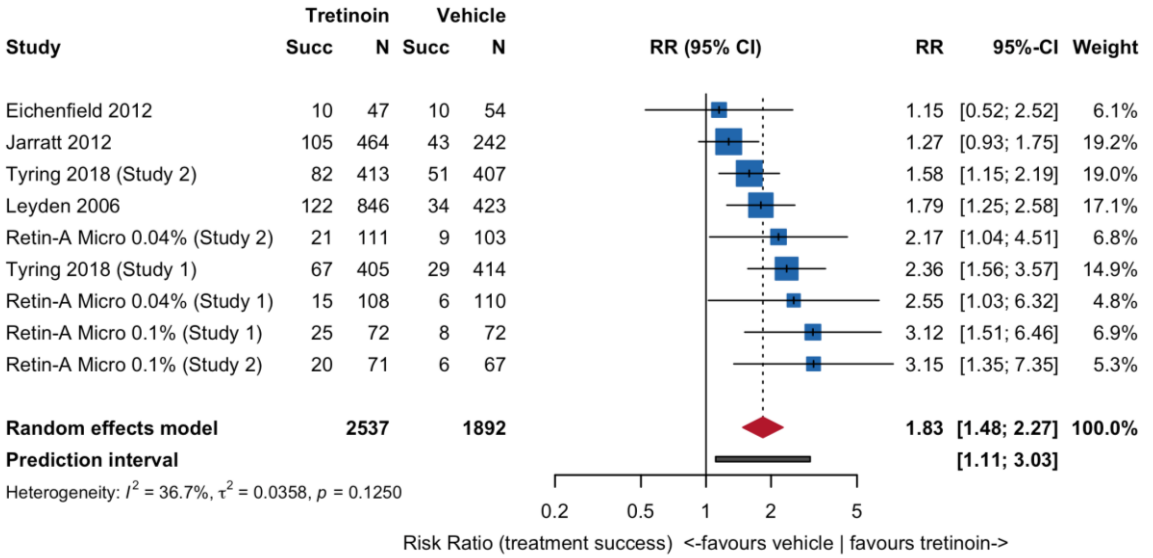

Figure 3. Forest plot of the random-effects meta-analysis of treatment success, topical tretinoin versus vehicle (pooled RR 1.83, 95% CI 1.48–2.27; prediction interval 1.11–3.04).

3.5. Absolute effect

Across the vehicle arms, 196 of 1,892 participants achieved treatment success (10.4%), whereas 467 of 2,537 tretinoin-treated participants did so (18.4%); these totals correspond exactly to the arm-level counts in Table 1. The absolute risk difference was therefore approximately 8 percentage points, and the number needed to treat to achieve one additional success was approximately 12. Because the absolute benefit scales with the underlying success rate, it will be larger where the baseline response is higher and smaller where the success definition is more stringent. A number needed to treat of about twelve for a self-applied, inexpensive, once-daily topical agent with a benign safety profile compares favourably with many interventions in general dermatology, and it provides a concrete figure that clinicians can convey to patients when setting expectations at the point of prescription.

3.6. Continuous efficacy outcomes

Although per-arm means and standard deviations were too inconsistently reported to permit a pooled continuous analysis, every trial that reported lesion counts showed a greater reduction with tretinoin than with vehicle; the direction and magnitude of these reductions are summarised in Table 2. Representative figures included inflammatory-lesion reductions of 38.2% with the microsphere 0.04% gel versus 19.2% with vehicle, of 46.3% and 30.6% with the micronised 0.05% gel across two adolescent trials versus 37.1% and 10.9% with vehicle, and of 52% with the 0.05% lotion, with non-inflammatory reductions following the same pattern, indicating that the categorical endpoint if anything understates the breadth of improvement. Table 2 draws on a wider set of trials than the nine pooled datasets; the final column states, for each entry, whether that trial contributed to the meta-analysis in Table 1.

3.7. Subgroup analyses

Pre-specified subgroup analysis by formulation, summarised in Table 3, showed a consistent direction of effect across all preparations, with point estimates of 1.89 for the 0.05% lotion, 3.13 for the microsphere 0.1% gel, 1.81 for the microsphere 0.04% gel and 1.50 for the 0.025% gel; the between-subgroup difference was not significant (p = 0.17), indicating that formulation did not materially modify the relative benefit and that formulation choice may be guided by tolerability and patient preference. Subgroup analysis by the trial-specific success definition showed a significant between-groups difference (p = 0.046), interpreted as a non-randomised, confounded comparison that most plausibly reflects the stringency of the investigator scale rather than a qualitative difference in efficacy, since every subgroup favoured tretinoin.

Table 2. Narrative summary of reported percentage lesion-count reductions (tretinoin versus vehicle).

Dataset	Inflammatory (tretinoin vs vehicle)	Non-inflammatory (tretinoin vs vehicle)	Contributes to Table 1?
Berger 2007 (microsphere 0.04%)[15]	38.2% vs 19.2%	33.6% vs 20.4%	No — narrative only
Lucky 2011 (micronised 0.05%, study 1)[16]	46.3% vs 37.1%	45.7% vs 27.9%	No — narrative only
Lucky 2011 (micronised 0.05%, study 2)[16]	30.6% vs 10.9%	39.1% vs 16.9%	No — narrative only
Tyring 2018 (lotion 0.05%)[10]	52% vs vehicle (p < 0.001)	46% vs vehicle (p < 0.001)	Yes — datasets 1–2
Eichenfield 2012 (microsphere 0.04%)[12]	Favours tretinoin (NS, static)	LS-mean −19.9 vs −9.7 (p = 0.04)	Yes — dataset 7
Trifu 2011 (cream 0.05%)[17]	Significant vs placebo (p = 0.013)	Significant vs placebo (p = 0.002)	No — narrative only
Tirado-Sanchez 2013 (gel 0.05%)[18]	Greater than placebo	Greater than placebo	No — narrative only

Notes: *NS, not statistically significant; LS, least-squares. Values are percentage reductions from baseline at approximately 12 weeks as reported in the source trials. Dataset numbering in the final column refers to the row order of Table 1.*

Table 3. Pre-specified subgroup analysis by tretinoin formulation.

Formulation subgroup	k	Pooled RR (95% CI)	I^2 (%)
Tretinoin 0.05% lotion	2	1.89 (1.28–2.79)	55.3
Tretinoin microsphere 0.1%	2	3.13 (1.81–5.44)	0
Tretinoin microsphere 0.04%	3	1.81 (1.13–2.91)	3.8
Tretinoin 0.025% gel	2	1.50 (1.07–2.09)	49.0
All formulations (overall)	**9**	**1.83 (1.48–2.27)**	**36.7**

Notes: *Between-subgroup difference not significant (p = 0.17). RR, risk ratio; k, number of datasets. The overall estimate is shown for reference.*

3.8. Sensitivity analyses

The pooled estimate was robust to any single dataset: in leave-one-out analysis, with the between-study variance re-estimated at each iteration, the recomputed risk ratio ranged narrowly from 1.75 to 1.95 and remained significant throughout, and I^2 ranged from 8.3% to 44.5%. When the two pivotal trials within each licensing programme were combined into a single unit, reducing the analysis from nine datasets to six, the pooled risk ratio was essentially unchanged at 1.80 (95% CI 1.41–2.30), confirming that entering paired trials separately did not inflate the apparent precision.

3.9. Publication bias

The contour-enhanced funnel plot in Figure 4 showed a broadly symmetrical distribution of datasets, and the Egger test did not detect a significant small-study effect (intercept 1.72; t = 1.79; p = 0.12). With only nine datasets both assessments were underpowered and are reported for completeness rather than as reliable evidence of the absence of bias; the recovery of licensing-trial data does not preclude unpublished null vehicle-controlled studies.

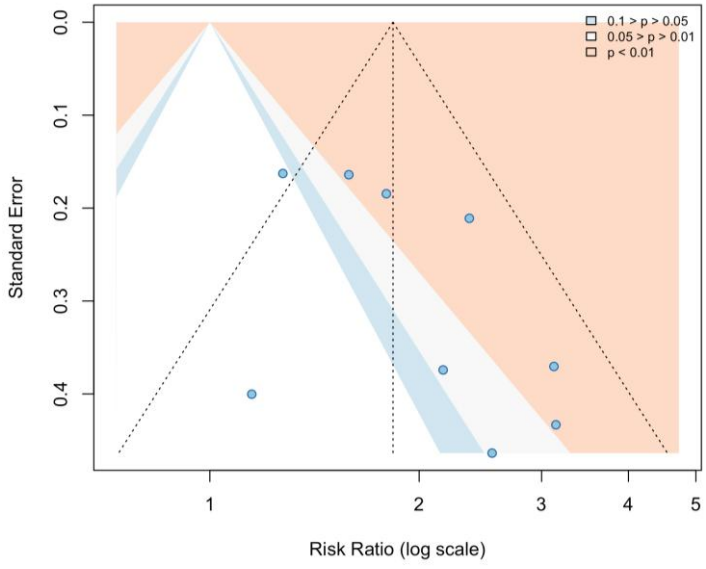

Figure 4. Contour-enhanced funnel plot of the included datasets; shaded regions denote conventional significance contours (0.1 > p > 0.05, 0.05 > p > 0.01, p < 0.01).

3.10. Safety and tolerability

Cutaneous adverse events were predominantly mild and transient and were confined largely to the application site, comprising dryness, scaling, erythema and a burning or stinging sensation that typically peaked within the first two weeks and improved thereafter, as summarised in Table 4. Where quantified, the micronised gel produced application-site dry skin in about 14%, burning in about 8% and erythema in about 5% of treated adolescents, and more than 70% of adolescents in the microsphere trials experienced no cutaneous adverse event; serious treatment-related events were not reported, and discontinuation for local intolerance was uncommon. In the preadolescent trial, irritation with the microsphere formulation was similar to vehicle, supporting acceptable tolerability even in younger skin.[12]

Table 4. Structured summary of cutaneous tolerability across representative datasets.

Dataset / formulation	Principal local reactions	Overall tolerability	Contributes to Table 1?
Tyring 2018 (lotion 0.05%)[10]	Application-site pain, dryness (mild, transient)	Well tolerated; no discontinuations for AE	Yes — datasets 1–2
Berger 2007 (microsphere 0.04%)[15]	Mild–moderate dryness, erythema, scaling	No significant difference vs vehicle at week 12	No — narrative only
Lucky 2011 (micronised 0.05%)[16]	Dry skin ≈14%, burning ≈8%, erythema ≈5%	Better tolerated than microsphere 0.1%	No — narrative only
Jorizzo 2008 (microsphere 0.04%, adolescents)[19]	>70% with no cutaneous AE	Low incidence; mostly mild	No — adolescent tolerability report from the microsphere 0.04% programme
Eichenfield 2012 (microsphere 0.04%, 9–11 y)[12]	Irritation signs and symptoms	Similar to vehicle	Yes — dataset 7

Notes: AE, adverse event. Values are as reported in the source trials. Dataset numbering in the final column refers to the row order of Table 1.

3.11. Quality of life

Several of the included trials, particularly those of the 0.05% lotion, collected acne-specific quality-of-life data using validated instruments and reported improvements that favoured tretinoin over vehicle, most consistently in the self-perception and acne-symptom domains. These outcomes were not amenable to pooling because of heterogeneous instruments and incomplete numerical reporting, but their direction was concordant with the efficacy findings and is clinically important, since for many patients, and especially in an aesthetic context, the improvement in quality of life is the outcome that matters most and often drives the decision to persist with treatment. The convergence of the dichotomous success endpoint, the narrative lesion-count reductions in Table 2 and these patient-reported gains lends internal coherence to the overall conclusion that tretinoin confers a clinically meaningful benefit over vehicle.

3.12. Interpretation and comparison with other evidence

This focused pairwise synthesis of nine randomised, vehicle-controlled datasets, comprising more than four thousand participants, found that topical tretinoin monotherapy approximately doubled the relative probability, and raised the absolute probability by about eight percentage points, of investigator-rated treatment success in facial acne vulgaris relative to vehicle, with a pooled risk ratio of 1.83 and a prediction interval that excluded the null. The number needed to treat of approximately twelve situates tretinoin monotherapy among the useful single-agent interventions in dermatology.[1,4] The magnitude and precision of this estimate, together with its robustness in the leave-one-out and combined-programme analyses and the consistency of the direction of effect across every formulation subgroup shown in Table 3, provide a contemporary quantitative anchor for the long-standing clinical impression that tretinoin is an effective foundation of acne therapy.

The findings are coherent with the wider evidence base. Recent network meta-analyses of topical acne treatments have consistently placed topical retinoids, and their fixed-dose combinations with benzoyl peroxide, among the more effective options for mild-to-moderate disease, while noting that combination regimens generally outperform single agents.[6–8,20] The present analysis complements those broad syntheses by isolating the tretinoin-versus-vehicle contrast and expressing it as a single, interpretable relative and absolute effect. It is important to emphasise that this monotherapy estimate is not an argument for preferring monotherapy to combination therapy; rather, a clean estimate of tretinoin versus vehicle is a necessary reference point against which the incremental benefit of adding benzoyl peroxide or an antibiotic can be judged. The first fixed-dose triple combination of clindamycin, benzoyl peroxide and adapalene, for example, achieved treatment-success rates of roughly 50% in phase 2 and phase 3 trials, substantially above the monotherapy rate quantified here, underscoring the additive value of multi-targeted regimens.[21–23] Consistently, a pooled analysis of three phase 3 trials of a fixed clindamycin/tretinoin gel found the combination

superior to its tretinoin monotherapy component, further illustrating that the monotherapy effect quantified here is a floor upon which combination regimens build.[24]

Because topical retinoids are used over months, real-world effectiveness depends heavily on adherence, which is undermined by the very local irritation that the tolerability analysis in Table 4 characterises. A practical implication of the pooled data is that the irritation associated with tretinoin is predictable, early and self-limiting, typically peaking within the first fortnight and settling thereafter; clinicians who forewarn patients of this trajectory, and who recommend adjunctive moisturisation and, where necessary, a temporary reduction in application frequency, are likely to preserve adherence through the critical induction period and thereby to realise more of the efficacy demonstrated here.[25] The absence of a significant between-formulation difference in efficacy further implies that the choice between a conventional gel, a microsphere gel and a polymeric-emulsion lotion can reasonably be driven by tolerability and patient preference rather than by an expectation of superior response, which is a message of direct practical utility.[26,27]

The applicability of the findings to skin of colour and to adult acne, both prominent in aesthetic dermatology, deserves specific comment. One included trial was conducted in a darker-skinned population and reported benefit without undue irritant hyperpigmentation, and contemporary trials of retinoid-containing regimens in ethnically diverse and skin-of-colour populations have similarly demonstrated efficacy with acceptable pigmentary tolerability.[18,28,29] Nevertheless, patients with darker phototypes remained under-represented overall, and the potential for tretinoin-induced irritant hyperpigmentation warrants continued caution and individualised counselling. The efficacy estimate should therefore be applied to these groups with an awareness that the external validity of the pooled population, while broad, is imperfect. It should also be underscored that the twelve-week horizon of the included trials captures only the induction phase of treatment; arguably the greatest long-term value of topical tretinoin lies in maintenance, where it prevents the reformation of microcomedones after inflammatory lesions have resolved, a role emphasised in current guidance and newer retinoid programmes that the present short-term synthesis does not quantify.[4,5]

3.13. Heterogeneity and limitations

The moderate, non-significant heterogeneity observed (I^2 36.7%, with an upper confidence limit reaching the substantial range) is unsurprising given the clinical diversity of the included trials, which spanned four formulations, a wide age range and several distinct investigator scales. The subgroup analyses in Table 3 suggest that much of this variability was attributable to differences in the stringency of the success definition rather than to genuine differences in biological efficacy between formulations; however, because the success definition is confounded with formulation, era and sponsor, this interpretation is offered cautiously and the subgroup contrasts are treated as non-randomised comparisons. The numerically larger effect observed for the microsphere 0.1% datasets should be interpreted in the light of their small size, their use of an excellent-global-response definition, and their smallest analytic weight in Table 1, and not as evidence of true formulation superiority, particularly since the between-subgroup test was not significant.

Several limitations warrant emphasis. First, the primary outcome was a dichotomous investigator global assessment whose definition varied across trials; although this was addressed in a subgroup analysis, residual outcome heterogeneity cannot be excluded, and the absolute success rates are not directly comparable across studies. Second, a number of the included datasets were derived from industry-sponsored licensing programmes and from regulatory labels, which may be subject to sponsor-related and selective-reporting biases despite their double-blind design. Third, with only nine datasets the assessment of small-study effects through the Egger test and funnel plot in Figure 4 was underpowered, and the possibility of unpublished negative vehicle-controlled trials remains. Fourth, continuous outcomes such as the percentage reduction in inflammatory and non-inflammatory lesion counts, and patient-reported quality-of-life measures, could not be formally meta-analysed because per-arm means and standard deviations were inconsistently reported, so the pooled synthesis reflects the probability of a categorical response rather than the full spectrum of clinical improvement, although these outcomes were summarised narratively in Table 2. Fifth, the analysis was restricted to facial acne and to a twelve-week horizon, precluding conclusions about truncal disease and about long-term maintenance. Sixth, the paediatric evidence rested on a single preadolescent trial, so the reassuring tolerability finding in younger skin is hypothesis-generating rather than definitive.[12] Seventh, skin-of-colour and adult subpopulations, while represented, were not present in sufficient numbers to support subgroup estimates specific to them.

3.14. Clinical implications

For dermatological, venereological and aesthetic practice these results reinforce the guideline-endorsed positioning of topical tretinoin as a first-line and maintenance agent for acne vulgaris.[4] The doubling of relative probability, and the eight-percentage-point absolute increase, in the likelihood of a clinically meaningful response, achieved with a predictable profile of mild, self-limiting local irritation and no serious treatment-related events, supports tretinoin monotherapy where a single-agent regimen is preferred and provides a defensible benchmark against which newer polymeric-emulsion and microencapsulated formulations, and fixed-dose combinations, can be judged.[27,30] The acceptable tolerability in preadolescent skin, while based on limited data, is reassuring for cautious extension to younger patients under

supervision and with attention to formulation, application frequency and adjunctive moisturisation. In everyday practice, the combination of a clear relative benefit, a tangible absolute gain, a predictable and self-limiting local reaction profile, and a low acquisition cost makes topical tretinoin a rational anchor for both the induction and the maintenance of acne control, whether used alone in milder disease or as the retinoid backbone of a fixed-dose combination in more extensive or treatment-resistant presentations.

4. Conclusion

This contemporary, focused meta-analysis of nine randomised, vehicle-controlled datasets demonstrated that topical tretinoin monotherapy significantly increased the probability of investigator-rated treatment success in facial acne vulgaris, with a pooled random-effects risk ratio of 1.83 (95% CI 1.48–2.27) and a prediction interval that excluded the null. Expressed in absolute terms, the success rate rose from about 10% with vehicle to about 18% with tretinoin, an absolute difference of approximately eight percentage points and a number needed to treat of approximately twelve. The effect was of moderate magnitude, robust to the exclusion of any individual dataset and to the combination of paired pivotal trials, and consistent in direction across tretinoin 0.05% lotion, microsphere 0.1% and 0.04% gels, and 0.025% gel, with non-significant between-formulation differences. Heterogeneity was moderate and appeared to be driven mainly by differences in the stringency of the success definitions. Cutaneous adverse events were largely limited to mild, transient application-site dryness, erythema, scaling and burning, with no serious treatment-related events, including in a preadolescent population. Taken together, these estimates provide quantitative support for the first-line and maintenance positioning of topical tretinoin that international guidelines already recommend, and a transparent benchmark against which newer formulations and fixed-dose combinations can be evaluated. The principal remaining uncertainties concern the harmonisation of success definitions, the paucity of long-term and paediatric data, the under-representation of skin-of-colour populations, and the inability to synthesise continuous outcomes. Adequately powered, independently funded trials reporting standardised endpoints beyond twelve weeks, and enrolling paediatric and skin-of-colour populations, would strengthen the evidence base; until then, the present synthesis offers clinicians a clear and defensible estimate of the benefit and tolerability of topical tretinoin to inform shared decision-making in acne care. By translating a fragmented and largely industry-generated evidence base into a single, transparent and reproducible pairwise estimate, expressed in both relative and absolute terms, this meta-analysis provides a practical reference point for dermatologists, venereologists and aesthetic physicians and a benchmark for the design and interpretation of future comparative trials.

Declarations

Ethical Approval. Not applicable. This study synthesised previously published aggregate data and did not involve new human participants, human material or animals; institutional ethics approval was therefore not required.

Conflict of Interest. The authors declare no conflict of interest. Several of the included primary trials were industry-sponsored; this potential source of bias is addressed in the risk-of-bias assessment and the discussion.

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Data Availability. The extracted dataset, the reconstruction arithmetic for event counts, and the analysis code are available from the corresponding author on reasonable request.

Use of Artificial Intelligence. None.

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