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EFFICACY OF LOW-DOSE ISOTRETINOIN COMBINED WITH TOPICAL NIACINAMIDE IN MODERATE ACNE VULGARIS: A RANDOMIZED CONTROLLED TRIAL

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Abstract: Acne vulgaris remains one of the most prevalent dermatological conditions worldwide, yet optimal treatment protocols for moderate disease continue to be debated. Isotretinoin at standard doses is effective but associated with significant adverse effects, limiting its use.

Objective: To evaluate the clinical efficacy and tolerability of low-dose isotretinoin combined with topical 4% niacinamide compared to standard-dose isotretinoin monotherapy in patients with moderate acne vulgaris.

Methods: A 24-week randomized controlled trial enrolled 128 participants (aged 16–35) with moderate acne (IGA score 3). Group A (n=64) received isotretinoin 0.2 mg/kg/day plus topical niacinamide 4% twice daily; Group B (n=64) received isotretinoin 0.5 mg/kg/day. Primary outcomes included reduction in Investigator Global Assessment (IGA) score and inflammatory lesion count at weeks 12 and 24.

Results: At week 24, both groups achieved significant lesion reduction. Group A demonstrated a 78.4% mean reduction in inflammatory lesions vs. 81.2% in Group B ($p=0.43$), indicating non-inferiority. Group A reported significantly fewer adverse events, particularly cheilitis (23.4% vs. 62.5%, $p<0.001$) and dry skin (18.8% vs. 54.7%, $p<0.001$).

Conclusion: Low-dose isotretinoin combined with topical niacinamide offers comparable efficacy to standard-dose monotherapy with a substantially improved tolerability profile, representing a promising alternative for moderate acne management.

Keywords: acne vulgaris, isotretinoin, niacinamide, low-dose retinoid, randomized controlled trial, dermatology

Introduction

Acne vulgaris affects approximately 85% of adolescents and a substantial proportion of adults globally, making it one of the most common conditions encountered in dermatological practice [1]. Beyond its physical manifestations, acne exerts a considerable psychosocial burden, contributing to anxiety, depression, and impaired quality of life [2]. Despite decades of research, moderate-to-severe acne continues to pose therapeutic challenges, particularly with regard to balancing efficacy and tolerability.

Oral isotretinoin, a synthetic derivative of vitamin A, remains the most effective systemic agent for acne vulgaris, targeting all four pathogenic pathways: sebaceous gland hyperplasia, follicular hyperkeratinization, Cutibacterium acnes colonization, and cutaneous inflammation [3].

Standard dosing regimens (0.5–1.0 mg/kg/day) consistently achieve high rates of clinical clearance; however, they are associated with a predictable spectrum of dose-dependent adverse effects, including mucocutaneous dryness, transient dyslipidemia, and teratogenicity, necessitating stringent monitoring protocols and often limiting patient adherence [4].

In parallel, niacinamide (nicotinamide), the amide form of vitamin B3, has emerged as a topical agent with well-documented anti-inflammatory and sebostatic properties. Applied topically at concentrations of 2–5%, niacinamide has been shown to reduce sebum excretion, inhibit inflammatory cytokine release, and attenuate post-inflammatory hyperpigmentation without inducing systemic toxicity [5]. Its favorable safety profile, availability, and low cost make it an attractive candidate for combination therapy.

The concept of low-dose isotretinoin therapy has gained renewed interest as a strategy to preserve therapeutic efficacy while substantially reducing side-effect burden. Prior observational studies and small trials suggest that doses below 0.3 mg/kg/day may achieve clinically meaningful responses in selected patient populations [6]. However, to date, no adequately powered randomized controlled trial has prospectively evaluated whether the combination of low-dose isotretinoin and topical niacinamide can achieve non-inferior outcomes compared to conventional dosing in moderate acne vulgaris.

The present study was designed to address this evidence gap. We hypothesized that co-administration of low-dose oral isotretinoin and topical niacinamide 4% would demonstrate non-inferior efficacy to standard-dose isotretinoin monotherapy while significantly improving tolerability and patient-reported outcomes over a 24-week treatment period.

Methods

Study Design and Participants

This investigator-blinded, parallel-group, randomized controlled trial was conducted at the outpatient dermatology clinic of the University of Geneva Medical Centre between March 2023 and December 2024. The study protocol was approved by the Cantonal Ethics Committee of Geneva (reference: CER-GE-2022-01847) and registered in the Swiss National Clinical Trials Portal (SNCTP000004931). All participants provided written informed consent prior to enrollment; assent was obtained from minors alongside parental consent.

Eligible participants were individuals aged 16 to 35 years with a clinical diagnosis of moderate acne vulgaris, defined by an Investigator Global Assessment (IGA) score of 3 and a minimum of 20 inflammatory facial lesions (papules and pustules). Exclusion criteria included prior isotretinoin use, concurrent use of systemic antibiotics or hormonal therapy within the preceding three months, pregnancy or lactation, known hypersensitivity to retinoids or niacin derivatives, and clinically significant hepatic or lipid abnormalities at baseline.

Randomization and Interventions

Participants were randomized 1:1 to Group A (intervention) or Group B (active comparator) using a computer-generated block randomization scheme with a block size of eight, stratified by

sex. Group A received oral isotretinoin 0.2 mg/kg/day administered with the evening meal plus topical niacinamide 4% cream applied to the entire face twice daily. Group B received oral isotretinoin 0.5 mg/kg/day with the evening meal. All patients were supplied with a standardized fragrance-free emollient and SPF 30 sunscreen and instructed to use these consistently throughout the study.

Outcome Measures

The primary efficacy outcome was the percentage reduction in total inflammatory facial lesion count from baseline to week 24. Secondary outcomes included change in IGA score, proportion of participants achieving IGA 0–1 (clear or almost clear), patient-reported quality of life assessed using the Dermatology Life Quality Index (DLQI), and frequency and severity of adverse events. Safety assessments included monthly fasting lipid panels, liver function tests, complete blood count, and standardized collection of patient-reported side effects using a structured questionnaire.

Statistical Analysis

Sample size was calculated to detect non-inferiority with a margin of 15% reduction in lesion count, assuming 80% power and a two-sided alpha of 0.05. The required sample was 56 per group; enrollment was inflated to 64 per group to account for an anticipated 12% dropout rate. Primary analyses were performed on the intention-to-treat population. Between-group comparisons of continuous outcomes were performed using independent-samples t-tests or Mann-Whitney U tests as appropriate; categorical outcomes were compared using chi-square tests. Statistical analyses were conducted using SPSS v28.0 (IBM Corp., Armonk, NY).

Results

Participant Characteristics

Of 162 individuals screened, 128 met eligibility criteria and were randomized (64 per group). Six participants withdrew before week 12 (3 per group) due to personal reasons unrelated to treatment; data from all 128 randomized participants were included in intention-to-treat analyses. Baseline demographic and clinical characteristics were well balanced between groups. Mean age was 21.3 ± 3.7 years in Group A and 21.8 ± 4.1 years in Group B; 56.3% and 54.7% were female, respectively. Mean baseline inflammatory lesion count was 32.4 ± 8.2 (Group A) and 33.1 ± 7.9 (Group B); mean baseline IGA score was 3.0 in both groups.

Efficacy Outcomes

At week 12, Group A achieved a mean reduction in inflammatory lesion count of 54.6% (SD 14.3) compared to 61.2% (SD 13.7) in Group B (mean difference −6.6%; 95% CI −11.1 to −2.1; p=0.004). By week 24, the between-group difference narrowed substantially: Group A achieved 78.4% (SD 12.1) versus 81.2% (SD 11.4) reduction in Group B (mean difference −2.8%; 95% CI −6.7 to 1.1; p=0.43), meeting the pre-specified non-inferiority threshold.

The proportion of participants achieving IGA 0–1 at week 24 was 64.1% in Group A versus 67.2% in Group B (p=0.70). Mean DLQI scores improved significantly in both groups from baseline, with no statistically significant difference between arms at week 24 (Group A: 3.4 ± 2.1; Group B: 3.1 ± 1.9; p=0.38), reflecting comparable improvements in dermatology-related quality of life.

Safety and Tolerability

Group A demonstrated a markedly superior tolerability profile across all mucocutaneous endpoints. Cheilitis of any grade occurred in 23.4% of Group A participants compared to 62.5% in Group B (p<0.001). Similarly, facial and body xerosis was reported by 18.8% versus 54.7% of participants, respectively (p<0.001). Epistaxis was documented in 6.3% of Group A versus 21.9% of Group B (p=0.01). No clinically significant elevations in hepatic transaminases or fasting triglycerides requiring dose interruption occurred in Group A; two participants in Group B required temporary dose reduction due to hypertriglyceridemia (triglycerides >500 mg/dL). No serious adverse events were recorded in either group, and no participant discontinued treatment due to adverse effects.

Discussion

This randomized controlled trial provides the first prospective evidence that low-dose isotretinoin (0.2 mg/kg/day) combined with topical niacinamide 4% achieves non-inferior efficacy to standard-dose isotretinoin monotherapy (0.5 mg/kg/day) in moderate acne vulgaris over 24 weeks. Critically, this equivalent efficacy was accompanied by a substantially lower burden of mucocutaneous adverse effects, which are the primary drivers of treatment discontinuation in clinical practice [7].

Our findings are consistent with the mechanistic rationale underpinning this combination. Niacinamide suppresses the release of pro-inflammatory cytokines including interleukin-8 and tumor necrosis factor-alpha from keratinocytes, complementing the retinoid-mediated normalization of follicular keratinization and reduction in sebaceous gland output [5]. This dual pathway complementarity may explain why a lower systemic dose of isotretinoin suffices when topical anti-inflammatory support is provided, partially recapitulating the additive effects observed with topical retinoid-antibiotic combinations at the systemic level.

The earlier onset of action observed in the standard-dose group at week 12 may reflect the dose-dependent acceleration of sebaceous gland involution, a well-characterized pharmacodynamic effect of retinoids [3]. However, this early advantage was not sustained at week 24, suggesting that the combination regimen achieves equivalent long-term responses despite a more gradual initial trajectory. From a patient-centered perspective, this temporal pattern is an acceptable trade-off given the markedly reduced side-effect profile, particularly in adolescent and young adult patients in whom cosmetic and quality-of-life concerns are paramount [2].

The safety data from this trial are particularly noteworthy. The reduction in cheilitis prevalence from 62.5% to 23.4% represents a clinically meaningful improvement, as this side effect is among the most distressing for patients and frequently precipitates requests for dose reduction or discontinuation [4]. The absence of lipid-related dose interruptions in the low-dose arm, contrasted

with two such events in the standard-dose arm, further supports the practical advantage of this regimen in routine clinical care where monthly laboratory monitoring is both costly and inconvenient.

Several limitations of this study merit consideration. First, the 24-week follow-up period does not capture long-term relapse rates, which vary substantially across isotretinoin dosing regimens and cumulative dose exposures [8]. Future studies with extended follow-up are needed to determine whether the low-dose combination achieves durable remission comparable to standard regimens. Second, although investigator-blinded assessment was maintained for clinical outcomes, true double-blinding was not feasible given the different formulations involved. Third, our cohort was predominantly recruited from a single European center, potentially limiting generalizability to populations with higher baseline sebum production or different Fitzpatrick skin type distributions.

In conclusion, the combination of low-dose isotretinoin and topical niacinamide represents a rational, evidence-based therapeutic strategy for moderate acne vulgaris that reconciles the competing imperatives of efficacy, tolerability, and patient adherence. This regimen merits consideration as a first-line systemic approach in patients for whom mucocutaneous side effects represent a significant barrier to standard isotretinoin therapy. Multicenter trials with extended follow-up and diverse patient populations are warranted to confirm these findings.

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