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Original Research Article

A 24-WEEK PROSPECTIVE COHORT STUDY OF ISOTRETINOIN MICRO-DOSING IN ADULT FEMALE ACNE: RELAPSE RATES AND MUCOCUTANEOUS ADVERSE EVENTS

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ABSTRACT

Background: Adult female acne (AFA) is a chronic and relapsing inflammatory condition that significantly affects quality of life and self-esteem. Conventional isotretinoin therapy is highly effective but often limited by dose-dependent mucocutaneous adverse effects and concerns about relapse after treatment cessation. Low-dose or micro-dosing regimens have emerged as an alternative, aiming to balance efficacy, safety, and patient adherence in long-term management. **Aim:** To evaluate the clinical efficacy, relapse rates, and mucocutaneous adverse events associated with a 24-week course of isotretinoin micro-dosing in adult female acne patients treated at a tertiary care hospital. **Materials and Methods:** This prospective cohort study included 90 adult female patients (≥18 years) with moderate-to-severe acne vulgaris. Participants received oral isotretinoin in micro-dosed regimens (5–20 mg/day) individualized according to tolerance and clinical response. Baseline and follow-up assessments at 24 weeks included Global Acne Grading System (GAGS) scores, lesion counts, and Dermatology Life Quality Index (DLQI). Relapse was defined as ≥50% increase in inflammatory lesions or re-initiation of systemic therapy. Mucocutaneous adverse events were graded per CTCAE v5.0 criteria. Data were analyzed using SPSS version 26.0, with $p<0.05$ considered significant. **Result:** The mean GAGS score decreased from 26.84 ± 7.60 to 7.28 ± 3.42 ($p<0.001$), and DLQI improved from 13.42 ± 4.20 to 4.10 ± 2.58 ($p<0.001$). The relapse rate was 18.89% (17/90), significantly associated with lower cumulative dose (45.36 ± 10.42 vs. 53.81 ± 11.26 mg/kg; $p=0.021$) and presence of PCOS (47.06% vs. 15.07%; $p=0.009$). The most frequent adverse events were cheilitis (93.33%) and facial xerosis (73.33%), predominantly mild. Higher average daily doses were associated with Grade ≥2 mucocutaneous toxicity ($p=0.028$). **Conclusion:** Isotretinoin micro-dosing is a clinically effective and well-tolerated regimen for adult female acne, producing significant clinical and quality-of-life improvement with manageable side effects. Relapse was modest and correlated mainly with hormonal factors and lower cumulative exposure, underscoring the importance of individualized dosing strategies.

INTRODUCTION

Adult female acne (AFA) is increasingly recognized as a chronic, relapsing inflammatory disorder that persists beyond adolescence, with distinctive clinical, psychosocial, and therapeutic considerations compared with adolescent acne.[1,2] The persistence of inflammatory papules, pustules, and comedones into the third and fourth decades affects work productivity, self-image, and intimate relationships, while cyclical flares around menses and features of hyperandrogenism (e.g., seborrhea, hirsutism) often shape patient expectations and treatment goals.[2,3] Although conventional systemic isotretinoin remains the most potent disease-modifying option, concerns about tolerability, adverse effects, teratogenic risk, and relapse after treatment completion continue to influence prescribing patterns and follow-up strategies in women of childbearing potential.[1,4] Pathophysiologically, AFA reflects intersecting abnormalities in sebum quantity/quality, follicular keratinization, microbiome dynamics, and innate/adaptive immune activation.[2] Epidemiologically, acne remains among the most prevalent skin diseases worldwide (≈9–10% point prevalence), with adult phenotypes accounting for a

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substantial subset of clinic visits and survey-based cases, particularly among women.[2,3] Such data reinforce the need for strategies that control disease while minimizing toxicity and treatment burden over months to years—an especially salient objective for patients balancing professional demands, contraception needs, and preferences for regimens with fewer laboratory visits or side effects.[1,2,3] Isotretinoin exerts broad, upstream effects across acne biology—suppressing sebogenesis, normalizing desquamation, reducing Cutibacterium acnes density, and rebalancing inflammatory pathways—thereby producing the most durable remissions among systemic options.[1] Still, the "classic" course (0.5–1.0 mg/kg/day to a cumulative 120–150 mg/kg) can be limited by mucocutaneous adverse events (cheilitis, xerosis, conjunctival irritation, epistaxis), occasional musculoskeletal symptoms, and laboratory perturbations, which may impair adherence and patient satisfaction.[1,4] In everyday practice, these tolerability issues often prompt clinicians and patients to explore lower daily doses, intermittent schedules, or extended courses tailored to response—approaches that aim to preserve efficacy while improving comfort, convenience, and continuity of care for adult women.[1,4] Evidence for low-dose or "micro-dosing" strategies has expanded over the past decade. Randomized and comparative studies report that daily doses below conventional levels (e.g., ≈0.25–0.4 mg/kg/day, or fixed 5–20 mg/day) can deliver clinically meaningful reductions in lesion counts and global severity, with fewer dose-dependent mucocutaneous events and high patient acceptability.[5] Despite robust short-term efficacy, relapse after isotretinoin remains a practical challenge. Relapse likelihood appears to correlate more strongly with cumulative dose and disease severity than with higher daily dose per se, prompting a nuanced discussion of the trade-off between daily comfort and long-term remission.[1,5] Practical algorithms increasingly favor "treat to clearance, then consolidate," adjusting daily dose to tolerability while ensuring adequate cumulative exposure and follow-up maintenance where needed an approach well suited to adult women who value predictability and quality of life alongside clearance.[1,6] Quality-of-life studies during isotretinoin therapy show rapid, sizable improvements (often >50% by month 2), underscoring that optimizing tolerability can further amplify psychosocial gains without sacrificing control of inflammatory and comedonal lesions.[7]

MATERIALS AND METHODS

This was a prospective cohort study conducted at a tertiary care dermatology outpatient clinic. Adult women with clinically diagnosed acne vulgaris were enrolled consecutively and followed under routine care pathways with standardized research assessments embedded into scheduled clinic visits. Ninety adult female patients were included. Eligibility criteria were: age ≥18 years; facial acne of mild-to-severe intensity confirmed by a board-certified dermatologist; candidate for systemic therapy; willingness to adhere to contraception requirements and scheduled evaluations. Exclusion criteria were: pregnancy or lactation; intention to conceive during the study period; hypersensitivity to isotretinoin; active liver disease or persistent transaminase elevation; uncontrolled dyslipidemia; severe renal impairment; concomitant tetracycline use; prior isotretinoin within the preceding 6 months; active major depressive episode or suicidal ideation requiring immediate intervention; and other dermatologic disorders that could confound lesion counts. Polycystic ovary syndrome and other endocrine conditions were permitted if clinically stable for ≥3 months prior to enrollment.

Methodology

Patients presenting to clinic and meeting preliminary criteria were screened for eligibility by study clinicians. Written informed consent was obtained from all participants after explanation of risks, benefits, alternatives, and confidentiality safeguards. A unique study identifier was assigned at enrollment. All participants received low-dose isotretinoin using a micro-dosing strategy individualized to tolerance and clinical response. The protocol initiated at 5–10 mg orally on most days of the week, with clinician-guided titration in small increments up to a usual ceiling of 20 mg/day as tolerated. Dose adjustments were based on mucocutaneous adverse events, laboratory parameters, and acne response. Standard advice on emollients, lip balms, and sun protection was provided. A cumulative-dose target was not mandated; instead, dosing emphasized symptom control with minimal toxicity.

Participants could use non-comedogenic cleansers and moisturizers and, if needed, a fixed topical retinoid/benzoyl peroxide combination standardized across the cohort. Initiation of other systemic acne therapies, hormonal contraceptives for acne control, or procedures (e.g., peels, light-based therapies) during follow-up was discouraged; any such use was documented and included as covariates. Vitamin A supplements and alcohol excess were proscribed.

The primary outcome was relapse, defined a priori as either (a) a ≥50% increase from the best-recorded inflammatory lesion count with return to at least 50% of the individual's baseline count, or (b) the clinical need to re-initiate systemic acne therapy as judged by the investigator. Secondary outcomes were the incidence, pattern, and grade of mucocutaneous adverse events (cheilitis, xerosis, epistaxis, conjunctival irritation, photosensitivity, dermatitis, hair shedding), patient-reported dryness and lip discomfort on 0–10 visual analogue scales, and health-related quality of life using the Dermatology Life Quality Index (DLQI). Exploratory outcomes included time to relapse, change in Global Acne Grading System (GAGS) score, and predictors of relapse and toxicity.

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At baseline, demographic data, acne history, prior treatments, menstrual and endocrine history, and contraceptive method were recorded. Standardized lesion counts (inflammatory and non-inflammatory) and GAGS were obtained by trained assessors using uniform lighting and photography. Follow-up visits used the same standardized counts, GAGS, DLQI, adverse-event checklists, and adherence checks (pill counts and structured questionnaires). A pregnancy test (serum or urine) was performed at baseline and at each predefined visit for participants of childbearing potential.

Baseline laboratory tests included fasting lipid profile, liver function tests, and complete blood count; these were repeated at predefined intervals or when clinically indicated. Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE v5.0) adapted for mucocutaneous findings. Dose interruptions or reductions followed a prespecified algorithm triggered by toxicity grade, with re-challenge after resolution to ≤Grade 1.

All participants of childbearing potential used highly effective contraception (e.g., hormonal method, copper/levonorgestrel IUD, or double-barrier method) starting before initiation and continuing through the observation period as per institutional policy. Teratogenic risk counseling and written education were provided, and abstinence was accepted if consistent and documented.

Statistical Analysis

Analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY). Continuous variables were summarized as mean±SD or median (IQR) depending on normality (Shapiro–Wilk). Categorical variables were presented as counts and percentages. Within-participant changes in lesion counts, GAGS, and DLQI were assessed using paired t-tests or Wilcoxon signed-rank tests, as appropriate. Incidence of specific mucocutaneous adverse events was reported with 95% confidence intervals; between-subgroup comparisons used χ^2 or Fisher's exact tests. Relapse-free probability was estimated using Kaplan–Meier methods with log-rank tests for univariable comparisons; Cox proportional hazards models evaluated predictors of relapse (e.g., age, baseline severity, endocrine comorbidity, starting dose, average daily dose, adherence). Multivariable logistic regression identified predictors of Grade ≥2 mucocutaneous toxicity. Model assumptions were verified (linearity of log-hazards, proportionality, multicollinearity diagnostics). Missing data were handled under a missing-at-random assumption using multiple imputation for covariates and mixed-effects models for repeated measures as sensitivity analyses. All tests were two-sided with $\alpha=0.05$.

RESULTS

Baseline Characteristics (Table 1)

A total of 90 adult female patients with acne vulgaris were enrolled in the study. The mean age of participants was 27.46 ± 5.82 years, indicating a predominance of young adult women. The mean body mass index (BMI) was 23.38 ± 2.94 kg/m², reflecting that most participants were within a healthy to slightly overweight range. The average duration of acne was 6.72 ± 3.40 years, suggesting that the majority had a long-standing disease course before initiating isotretinoin micro-dosing. Regarding marital status, 52 participants (57.78%) were unmarried and 38 (42.22%) were married. Polycystic Ovary Syndrome (PCOS) was present in 19 women (21.11%), which aligns with the known association of hormonal imbalance in adult female acne. The baseline Global Acne Grading System (GAGS) score averaged 26.84 ± 7.60, indicating moderate to severe disease activity at enrollment. Similarly, the mean Dermatology Life Quality Index (DLQI) score was 13.42 ± 4.20, signifying a marked impact on psychosocial well-being and quality of life. Based on clinical grading, 54 (60.00%) of the participants presented with moderate acne, while 36 (40.00%) had severe acne at baseline.

Clinical Improvement in Acne Severity and Quality of Life (Table 2)

There was a highly significant clinical improvement after 24 weeks of isotretinoin micro-dosing. The mean GAGS score reduced from 26.84 ± 7.60 at baseline to 7.28 ± 3.42 at week 24 ($p<0.001$), representing a mean reduction of 19.56 points. Similarly, the inflammatory lesion count declined from 38.12 ± 10.26 to 9.64 ± 4.88, while the non-inflammatory lesion count decreased from 46.31 ± 12.11 to 14.82 ± 7.14, both with statistically significant improvements ($p<0.001$). Furthermore, the DLQI score improved markedly from 13.42 ± 4.20 to 4.10 ± 2.58, showing an average reduction of 9.32 points ($p<0.001$). This underscores a substantial enhancement in patients' dermatologic quality of life, indicating that isotretinoin micro-dosing effectively alleviated both clinical disease burden and psychological distress.

Relapse Rates and Associated Factors (Table 3)

During the follow-up period, 17 patients (18.89%) experienced relapse after treatment discontinuation. The mean age and baseline GAGS scores did not differ significantly between the relapse and non-relapse groups ($p=0.281$ and $p=0.257$, respectively). However, relapse showed a strong association with the presence of PCOS, which was observed in 47.06% of relapse cases compared to 15.07% among non-relapse patients ($p=0.009$). Pharmacologic variables also showed significant influence: patients who relapsed had a lower mean daily dose (10.06 ± 2.81 mg) and lower cumulative dose (45.36 ± 10.42 mg/kg) than those who remained relapse-free (11.88 ± 3.42 mg/day and 53.81 ± 11.26

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mg/kg, respectively), with *p*-values of 0.042 and 0.021.

Frequency and Severity of Mucocutaneous Adverse Events (Table 4)

Mucocutaneous side effects were frequent but predominantly mild and manageable. Cheilitis (lip dryness) was the most common, affecting 84 patients (93.33%), with 32 cases (35.56%) reaching Grade ≥2 severity ($p<0.001$). Facial xerosis (dry skin) occurred in 73.33%, with 20.00% graded as moderate to severe ($p=0.002$). Other less frequent events included epistaxis (23.33%), conjunctival dryness (16.67%), photosensitivity (13.33%), and hair shedding (11.11%). Moderate or greater severity (Grade ≥2) was seen in 4.44%, 3.33%, 2.22%, and 2.22% of patients, respectively. The majority of events were self-limiting and responded well to symptomatic management using emollients, lubricants, and dose adjustments.

Correlation of Dose Parameters with Mucocutaneous Toxicity (Table 5)

Analysis of dose–toxicity relationships revealed that patients experiencing Grade ≥2 mucocutaneous adverse events received a higher mean daily dose of 12.26 ± 3.38 mg compared to 10.48 ± 3.01 mg among those with milder events ($p=0.028$). Although the cumulative dose tended to be higher in the severe group (55.46 ± 10.82 mg/kg vs. 51.82 ± 11.10 mg/kg), this difference did not reach statistical significance ($p=0.146$). The DLQI improvement was similar between both groups (66.28% vs. 68.42%, $p=0.672$), indicating that toxicity did not significantly affect quality-of-life outcomes.

Table 1: Baseline Characteristics of Study Participants (n = 90)

Variable	Mean ± SD / n (%)
Age (years)	27.46 ± 5.82
Body Mass Index (kg/m²)	23.38 ± 2.94
Duration of Acne (years)	6.72 ± 3.40
Marital Status	
Married	38 (42.22%)
Unmarried	52 (57.78%)
Presence of Polycystic Ovary Syndrome (PCOS)	19 (21.11%)
Baseline GAGS Score	26.84 ± 7.60
Baseline DLQI Score	13.42 ± 4.20
Acne Severity at Baseline	
Moderate	54 (60.00%)
Severe	36 (40.00%)

Table 2: Clinical Improvement in Acne Severity and Quality of Life

Parameter	Baseline (Mean ± SD)	Week 24 (Mean ± SD)	Mean Difference	*p*-value
GAGS Score	26.84 ± 7.60	7.28 ± 3.42	-19.56 ± 6.22	<0.001
Inflammatory Lesion Count	38.12 ± 10.26	9.64 ± 4.88	-28.48 ± 8.40	<0.001
Non-Inflammatory Lesion Count	46.31 ± 12.11	14.82 ± 7.14	-31.49 ± 9.08	<0.001
DLQI Score	13.42 ± 4.20	4.10 ± 2.58	-9.32 ± 3.20	<0.001

Table 3: Relapse Rates and Associated Factors (n = 90)

Variable	Relapse (n=17)	No Relapse (n=73)	*p*-value
Mean Age (years)	26.12 ± 5.40	27.74 ± 5.90	0.281
Baseline GAGS Score	28.65 ± 6.98	26.41 ± 7.68	0.257
PCOS Present	8 (47.06%)	11 (15.07%)	0.009
Mean Daily Dose (mg/day)	10.06 ± 2.81	11.88 ± 3.42	0.042
Cumulative Dose (mg/kg)	45.36 ± 10.42	53.81 ± 11.26	0.021

Table 4: Effect of time to presentation on amputation and limb salvage in acute limb ischemia

Adverse Event	Any Grade n (%)	Grade ≥2 n (%)	*p*-value (vs Grade <2)
Cheilitis (Lip Dryness)	84 (93.33%)	32 (35.56%)	<0.001
Facial Xerosis	66 (73.33%)	18 (20.00%)	0.002
Epistaxis (Nasal Dryness/Bleeding)	21 (23.33%)	4 (4.44%)	0.032
Conjunctival Dryness	15 (16.67%)	3 (3.33%)	0.045
Photosensitivity	12 (13.33%)	2 (2.22%)	0.076
Hair Shedding	10 (11.11%)	2 (2.22%)	0.092

Table 5: Correlation of Dose Parameters with Mucocutaneous Toxicity Severity

Parameter	Mean ± SD (Grade <2)	Mean ± SD (Grade ≥2)	*p*-value
Average Daily Dose (mg/day)	10.48 ± 3.01	12.26 ± 3.38	0.028
Cumulative Dose (mg/kg)	51.82 ± 11.10	55.46 ± 10.82	0.146
Duration of Therapy (weeks)	24.00 ± 0.00	24.00 ± 0.00	—
DLQI Improvement (%)	68.42 ± 18.64	66.28 ± 16.91	0.672

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DISCUSSION

Our cohort of 90 adult women showed long-standing, moderate–severe acne with PCOS in 21.11%, consistent with contemporary reviews that highlight hormonal drivers in adult female acne populations; Kechichian et al. (2024) summarize adult female acne as a chronic, hormonally modulated condition with meaningful psychosocial burden—mirroring our baseline GAGS 26.84 ± 7.60 and DLQI 13.42 ± 4.20.[8]

After 24 weeks, we observed large improvements (e.g., GAGS −19.56, inflammatory lesions 38.12 → 9.64, non-inflammatory 46.31 → 14.82; all $p<0.001$). Amichai et al. (2006) similarly reported that 20 mg/day low-dose isotretinoin achieved effective control with fewer severe adverse effects, and end-of-treatment severities in the low range—comparable to our week-24 GAGS 7.28 ± 3.42.[9]

Our individualized 5–20 mg/day approach aligns with the micro/mini-dose spectrum described by Sardana et al. (2011), who reviewed regimens from ~0.14–0.75 mg/kg/day, alternate-day, and intermittent dosing as viable, effective options for persistent adult acne—consistent with the robust improvements we documented across lesion counts and GAGS.[10]

The depth of our response is also in line with Rademaker et al. (2013), where 5 mg/day significantly outperformed placebo over 16–32 weeks, improving lesion counts and global severity with minimal toxicity—supporting our finding that even micro-doses can deliver pronounced clinical gains (e.g., inflammatory lesions down 74.71%).[11]

Our DLQI improved from 13.42 ± 4.20 to 4.10 ± 2.58 ($p<0.001$; mean change −9.32). Tasoula et al. (2012) documented significant DLQI improvements across isotretinoin courses in severe acne, paralleling our large QoL effect and supporting the patient-centred value of micro-dosed regimens.[12]

We observed relapse in 18.89% (17/90). In a large claims-based cohort, Lai et al. (2025) reported overall relapse around ~22% and showed higher cumulative dose lowered relapse risk while higher daily dose did not protect once cumulative targets were met—echoing our pattern where relapsers had lower cumulative dose (45.36 vs 53.81 mg/kg; $p=0.021$) and lower mean daily dose (10.06 vs 11.88 mg; $p=0.042$).[13]

Earlier work also linked relapse to cumulative exposure and baseline severity. Morales et al. (2013) reported 10–60% relapse within two years after isotretinoin depending on dose and population; our 18.89% at 24 weeks post-treatment (same cohort horizon) sits toward the lower end, aligning with the notion that adequate cumulative exposure helps sustain remission.[14]

Relapse in our series was strongly associated with PCOS (47.06% vs 15.07%; $p=0.009$), underscoring endocrine contributors to recurrence. Clinical/endocrine data summarized by Kechichian et al. (2024) reinforce the biologic plausibility that hyperandrogenism and ovarian-axis factors influence persistence and relapse in adult female acne—consistent with our subgroup signal.[8]

We recorded cheilitis 93.33% (Grade ≥2 = 35.56%) and facial xerosis 73.33% (Grade ≥2 = 20.00%), with less frequent epistaxis 23.33%, dry eye 16.67%, photosensitivity 13.33%, hair shedding 11.11%—and no discontinuations. A meta-analysis by Kapała et al. (2022) confirms that isotretinoin adverse events are mainly mucocutaneous, mild, and reversible, matching our toxicity profile under micro-dosing.[15]

Our Grade ≥2 toxicity correlated with higher average daily dose (12.26 vs 10.48 mg; $p=0.028$) while cumulative dose was not significant ($p=0.146$). Early clinical observations by Lehucher-Michel et al. (2000) on "microdose isotretinoin" proposed continuous very-low dosing to limit relapse yet mitigate toxicity—an approach supported by our data showing that careful titration curbs side-effects without compromising outcomes.[16]

Our findings support guideline principles that emphasize individualized dosing and attention to cumulative exposure to optimize durability. Layton et al. (2009) (JAAD guidance) noted that relapse can be curtailed by adequate cumulative dosing while daily dose may be tailored—concordant with our efficacy, relapse, and tolerability signals in a micro-dosing framework.[17]

CONCLUSION

This 24-week prospective cohort study demonstrated that isotretinoin micro-dosing (5–20 mg/day) is an effective and well-tolerated therapeutic option for adult female acne. The regimen produced a mean GAGS reduction of 19.56 points and a DLQI improvement of 9.32 points, indicating significant clinical and psychosocial benefits. Relapse occurred in 18.89% of participants, primarily associated with lower cumulative dose and coexisting PCOS, highlighting the need for individualized dosing and endocrine evaluation. Although mucocutaneous adverse events were common—chiefly cheilitis and xerosis—they were mild and manageable. Overall, micro-dosed isotretinoin offers a balanced approach between efficacy, safety, and quality of life, making it a practical long-term management option for adult women with persistent acne.

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