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ORIGINAL RESEARCH

Oral Retinol, Alone or Combined with Medical Photoprotection, in Patients with Actinic Keratosis: A Randomized, Open-Label, Prospective, Multicentric Study

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ABSTRACT

Introduction: Actinic keratosis (AK) is a chronic ultraviolet-induced condition with potential progression to squamous cell carcinoma. This study assessed the efficacy and tolerability of oral retinol, alone or combined with broad-spectrum medical photoprotection containing piroxicam, in patients with mild-to-moderate AK.

Methods: In this multicenter, prospective, randomized, open-label study, 117 patients with up to six AK lesions were assigned to oral retinol 50,000 international units (IU)/day (group A), oral retinol plus medical photoprotection (group B), or standard photoprotection recommendations (group C). Treatment lasted 6 months, followed by 3 months of follow-up. Assessments were performed at baseline and at months 3, 6, and 9. The primary endpoint was change in Actinic Keratosis Area and Severity Index (AKASI). Secondary outcomes included global clinical efficacy, lesion clearance, tolerability, and exploratory line-field confocal optical coherence tomography findings.

Results: All 117 patients were included in the intention-to-treat analysis, and 99 in the per-protocol analysis. AKASI scores decreased significantly in group A at month 6 by −19.3% (mean difference (MD) 0.61, 95% confidence interval (CI) 0.11–1.11; $p<0.05$) and at month 9 by −22.5% (MD 0.71, 95% CI 0.18–1.25; $p<0.01$). In group B, significant reductions were observed at all time points (T3: −24.1%; MD 0.90, 95% CI 0.42–1.39; $p<0.0001$; T6: −34.9%; MD 1.31, 95% CI 0.86–1.76; $p<0.0001$; T9: −38.8%; MD 1.45, 95% CI 0.95–1.95; $p<0.0001$). No significant changes occurred in group C. Reductions were earlier and greater with the combined strategy. Global clinical efficacy was rated good or

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very good in 69% of patients in group A and 88% in group B, while lesion clearance rates were 56% and 82%, respectively. Tolerability was generally good, and no treatment-related adverse events were formally recorded. In the imaging substudy, significant reductions in epidermal and stratum corneum thickness occurred only in group B.

Conclusions: Oral retinol combined with medical photoprotection was associated with earlier and greater improvements than oral retinol alone or standard photoprotection recommendations. These findings support further controlled studies to confirm efficacy and clarify the contribution of each intervention.

Trial Registration: Trial registration number ISRCTN42565762, retrospectively registered on 18 May 2026.

Keywords: Actinic keratosis; Oral retinol; Medical photoprotection; AKASI score

Key Summary Points

Why carry out this study?
Actinic keratosis is a common manifestation of chronic ultraviolet-induced skin damage and requires long-term management strategies to reduce lesion burden and progression risk.
Adherence to topical therapies and photoprotection is often suboptimal, particularly in older patients and during periods of reduced sun exposure, potentially limiting treatment effectiveness.
This study evaluated whether oral retinol supplementation (50,000 IU/day), alone or in combination with medical photoprotection (piroxicam 0.8% combined with sun protection factor (SPF) 50+), could improve clinical outcomes in patients with mild-to-moderate actinic keratosis.
What was learned from the study?
Oral retinol supplementation significantly reduced AKASI scores in patients with mild-to-moderate actinic keratosis, with earlier and greater improvements observed when combined with a film-forming medical photoprotection containing piroxicam 0.8% and SPF50+.
The combination strategy was well tolerated and was associated with exploratory LC-OCT changes suggestive of morphological improvement, supporting its potential role as a complementary approach for patients with suboptimal adherence to topical therapies.

INTRODUCTION

Actinic keratosis (AK) represents a common manifestation of chronic ultraviolet (UV)-induced skin damage. It is characterized by a field of cancerization where subclinical lesions coexist with visible keratoses, carrying a risk of progression to invasive squamous cell carcinoma (SCC) [1, 2]. Current management strategies include both lesion-directed and field-directed therapies, such as cryotherapy, photodynamic therapy, and topical agents [3]. Despite their efficacy, recurrence rates remain high and repeated treatments are often required [4].

In this context, oral preventive strategies have gained increasing attention. Retinoids, including vitamin A (retinol), play a central role in the regulation of keratinocyte proliferation, differentiation, and apoptosis, providing a strong biological rationale for their use in UV-induced skin damage and carcinogenesis [5, 6], and substantial data supports its potential preventive role in UV-induced skin carcinogenesis. In a randomized, double-blind, placebo-controlled trial involving more than 2000 moderate-risk subjects with a history of multiple AKs, daily oral retinol supplementation at a dose of 25,000 IU significantly reduced the incidence of first new SCC compared with placebo, with a hazard ratio of 0.74 (95% CI

0.56–0.99; $p = 0.04$), whereas no significant effect was observed on basal cell carcinoma [7]. These findings provide clinical support for a potential preventive role of oral retinol in SCC development and reinforce the concept that modulation of keratinocyte biology may translate into clinically meaningful effects on malignant progression.

Further support for this strategy derives from subsequent interventional studies exploring dose–response relationships and mechanistic endpoints. In a randomized study evaluating oral retinol at doses ranging from 25,000 to 75,000 IU/day in subjects with sun-damaged skin, higher doses were associated with significant reductions in actinic damage at the cellular level and upregulation of retinoid receptors, without a corresponding increase in clinically relevant toxicity [8]. These data suggest a dose-dependent biological activity of oral retinol on UV-damaged skin, providing mechanistic plausibility for its clinical effects.

In parallel, medical photoprotection strategies combining high-SPF sunscreens with anti-inflammatory agents such as piroxicam have emerged as promising tools for the management of actinic field damage. Piroxicam is a non-steroidal anti-inflammatory drug that acts as a non-selective cyclooxygenase inhibitor, predominantly targeting the cyclooxygenase (COX) COX1/COX2 axis, which is implicated in ultraviolet-induced inflammation and skin carcinogenesis. The upregulation of cyclooxygenase pathways, particularly COX2, has been associated with the development of AK and non-melanoma skin cancer, providing a biological rationale for the use of topical COX inhibitors in field cancerization [9].

Although established field-directed treatments such as 5-fluorouracil, imiquimod, and photodynamic therapy remain central options for AK clearance, in different clinical studies, piroxicam 0.8% combined with SPF50+ photoprotection was associated with a marked reduction in AK lesions, improvement in dermoscopic and reflectance confocal microscopy features, and favorable effects on field cancerization, with good tolerability [9–13].

Against this background, the clinical outcomes associated with combining systemic retinoid-mediated modulation of keratinocyte biology with topical photoprotective and anti-inflammatory intervention remain insufficiently explored.

The present study was designed to evaluate the efficacy and tolerability of oral retinol (50,000 IU/day), administered alone or in combination with a film-forming broad-spectrum medical device containing SPF50+ sunscreen and piroxicam 0.8%, in subjects with mild-to-moderate AK. In addition, an exploratory line-field confocal optical coherence tomography (LC-OCT) substudy was conducted to assess early morphological changes associated with treatment.

Study Aim

The aim of this study was to evaluate the efficacy and tolerability of oral retinol (50,000 IU/day), administered alone (“In” strategy) or in combination with medical photoprotection (film-forming medical device containing SPF50+ sunscreen and piroxicam 0.8%, “In&Out” strategy), in modulating the progression of actinic damage in subjects with mild-to-moderate AK, compared with a control group.

METHODS

Study Design

This was a multicenter, prospective, randomized, open-label, three-arm study with a treatment duration of 6 months, followed by a 3-month post-treatment follow-up. The study was conducted across four Italian dermatology clinics between April 2023 and March 2026.

The study was conducted in accordance with Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki and its later amendments. The study protocol was approved by an external independent review board in January 2023 (DC-01-2023, 12 January 2023). The trial registration number is ISRCTN42565762. Before enrolment, all participants provided fully informed written consent

to participate in the study and for the publication of their clinical photographs.

A total of 117 subjects (68 men and 49 women; mean age 70.5 ± 8.0 years) with mild-to-moderate AK who met all inclusion and exclusion criteria were enrolled after providing written informed consent.

Eligible participants were adults aged 18 to 80 years with up to six clinically diagnosed AK lesions located on the face and/or scalp. Exclusion criteria included the use of nicotinamide within 6 months prior to enrollment, history of skin cancer, any cause of systemic immunosuppression (including organ transplantation, chronic hematological malignancies, or ongoing immunosuppressive therapies), and pregnancy or lactation. Participants were randomized into three groups using a computer-generated allocation sequence. Thirty-nine subjects were assigned to group A and received oral retinol (50,000 IU daily for six consecutive months), in addition to standardized sun-protection recommendations. These included limiting sun exposure, avoiding direct sunlight between 10:00 and 14:00, wearing protective clothing and wide-brimmed hats, avoiding tanning devices, and applying sunscreen with SPF ≥ 30 daily. Forty-one subjects were assigned to group B and received oral retinol at the same dosage in combination with medical photoprotection, consisting of a film-forming medical device containing SPF50+ sunscreen and piroxicam 0.8%, applied twice daily to the face and scalp for 6 months. Thirty-seven subjects were assigned to group C (control group) and received only standardized sun-protection recommendations. Participants attended four study visits: baseline/randomization (T0), month 3 (T3), month 6 (T6, end of treatment), and month 9 (T9, follow-up).

Study Outcomes

The primary outcome was treatment efficacy, assessed using the validated Actinic Keratosis Area and Severity Index (AKASI) score [14], which quantifies the severity and extent of AK on the face and scalp on a scale ranging from 0 to 18.

Secondary outcomes included multiple complementary assessments. Global clinical efficacy was evaluated by investigators in active treatment groups using a five-point scale ranging from “very good” to “very poor,” based on overall changes in AK lesions. Global lesion clearance was assessed in active treatment groups using a similar five-point scale, specifically focused on lesion resolution. The need for additional treatments, including photodynamic therapy or cryotherapy, was recorded in all groups as an indirect measure of treatment failure or insufficient response. Treatment tolerability was assessed using a four-point scale, where 0 indicated excellent tolerability (no symptoms) and 3 indicated poor tolerability (severe pain, itching, or burning). Safety was evaluated through systematic documentation of all adverse events throughout the study period using case report forms (CRFs). In addition, an exploratory between-group comparison of AKASI score changes over time in the intention-to-treat (ITT) population was conducted. To reduce assessment bias, the clinical evaluations were performed by an independent investigator blinded to treatment allocation. Whenever possible, baseline and follow-up AKASI assessments were performed by the same assessor at each site. Finally, in a predefined subgroup of 13 patients from groups A and B, a noninvasive imaging analysis was performed using LC-OCT at month 3 (T3). The assessment included measurement of epidermal and dermal thickness, stratum corneum thickness, and evaluation of keratinocyte atypia, graded as mild, moderate, or severe. The LC-OCT substudy was conducted at the participating center where LC-OCT was available. Patients were included according to feasibility and availability of imaging, without separate randomization or stratification.

Statistical Analysis

Sample size calculation was based on available evidence on the efficacy of topical photoprotection in reducing AK severity. Previous studies have shown that topical medical photoprotection is associated with a reduction in AKASI

score ranging from approximately 26% to 31% [15, 16]. In particular, on the basis of data from Veronese et al., topical photoprotection corresponds to an estimated effect size (Cohen's *d*) of approximately 0.6 [16].

Assuming a greater efficacy for the combined strategy of oral retinol plus medical photoprotection, an effect size of 0.8 was hypothesized for the comparison between combination treatment and control. With a two-sided alpha level of 0.05 and a statistical power of 95%, a total of 70 participants (35 per group) were estimated to be required for this primary comparison (G*Power statistical software version 3.1.9.4, Heinrich Heine University, Kiel, Germany). In addition, a third exploratory group receiving oral retinol alone was included to further investigate the independent contribution of systemic supplementation. Therefore, a total of at least 105 participants is required, allocated across three treatment groups in a 1:1:1 ratio.

Statistical analyses were conducted using GraphPad statistical software version 9.0 (GraphPad Software Inc., La Jolla, CA, USA). A mixed-effects model for repeated measures (analysis of variance (ANOVA) test) was used to compare data at baseline and at the end of treatments. Between-group comparisons of AKASI score reduction over time were performed within the ITT population using repeated-measures ANOVA. Data are expressed as mean ± standard deviation (SD), and a p value < 0.05 was considered significant.

The primary efficacy analysis was conducted in the ITT population, which included all randomized patients. Missing data were handled using the last observation carried forward (LOCF) method. A per-protocol (PP) analysis, including patients who completed the study without major protocol deviations, was performed as an exploratory sensitivity analysis to assess the consistency of the ITT findings.

RESULTS

A total of 117 participants were enrolled and randomized into the three study groups. The study population included 68 men and 49 women, with a mean age of 70.5 ± 8.0 years. At baseline, the mean AKASI score was 3.2 ± 1.8. Consistent with the eligibility criteria, the study population represented a mild-to-moderate AK cohort, with a low baseline AKASI score and a limited number of clinically evident lesions. Table 1 shows demographics and baseline characteristics of the studied population.

All randomized participants (n = 117) were included in the ITT analysis, whereas 99 participants (85%) who completed the study according to the protocol were included in the PP analysis (Fig. 1).

Changes in AKASI score over time differed across the three study groups (Table 2). In group A, a progressive reduction in AKASI score

Table 1 Demographics and baseline characteristics

	Total	Group A (oral retinol)	Group B (oral retinol + MP)	Group C (Control)
Patients	117	39	41	37
Age (mean ± SD)	70.5 ± 8.0	71.8 ± 8.2	71.1 ± 7.2	68.5 ± 8.5
Sex				
Female	49	16	18	15
Male	68	23	23	22
AKASI (mean ± SD)	3.2 ± 1.8	3.2 ± 2.1	3.7 ± 1.8	2.7 ± 1.4

MP medical photoprotection (sunscreen SPF50+ and piroxicam 0.8%), *AKASI* Actinic Keratosis Area and Severity Index, *SD* standard deviation

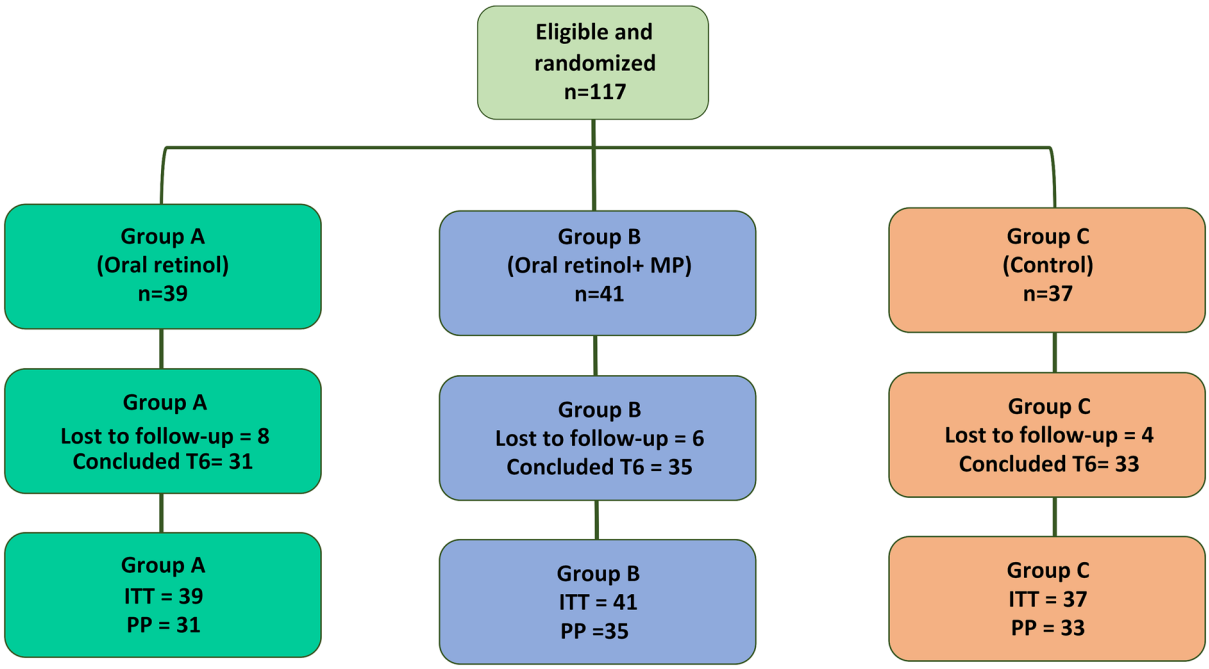

Fig. 1 Study flow diagram. A total of 117 participants were randomized and included in the intention-to-treat (ITT) analysis, while 99 participants who completed the study according to the protocol were included in the per-protocol (PP) analyses. *MP* medical photoprotection (sunscreen SPF50+ and piroxicam 0.8%)

was observed, reaching statistical significance at both T6 (−19.3%; mean difference 0.61, 95% CI 0.11–1.11; $p<0.05$) and T9 (−22.5%; mean difference 0.71, 95% CI 0.18–1.25; $p<0.01$) compared with baseline (T0). In group B, a more pronounced and earlier decrease in AKASI score was documented, with statistically significant differences already evident at T3 (−24.1%; mean difference 0.90, 95% CI 0.42–1.39; $p<0.0001$) and maintained at subsequent timepoints (T6: −34.9%; mean difference 1.31, 95% CI 0.86–1.76; $p<0.0001$; T9: −38.8%; mean difference 1.45, 95% CI 0.95–1.95; $p<0.0001$) compared with baseline. In contrast, group C did not show statistically significant changes in AKASI score at any timepoint during the study period. The percentage variation in AKASI score over time for each study group is shown in Fig. 2.

As an exploratory sensitivity analysis, the PP analysis showed results consistent with the primary ITT analysis. In the PP analysis, group A showed a statistically significant reduction in AKASI score at T6 compared with baseline ($p<0.01$), while group B confirmed significant improvements at all evaluated timepoints. No statistically significant changes were observed in group C.

Exploratory between-group analyses within the ITT population revealed significant differences in longitudinal AKASI score reduction across treatment groups. Group B demonstrated significantly greater improvement compared with group C at T3 (mean difference −0.71, 95% CI −1.37 to −0.06, $p<0.05$), T6 (mean difference −1.32, 95% CI −1.97 to −0.66, $p<0.0001$), and T9 (mean difference −1.41, 95% CI −2.06 to −0.76, $p<0.0001$). Group A also differed significantly from group B at T6 (mean difference 0.68, 95% CI 0.04 to 1.32, $p<0.05$) and from both groups B and C at T9 (mean difference 0.73, 95% CI 0.08 to 1.37, $p<0.05$; mean difference −0.68, 95% CI −1.34 to −0.03, $p<0.05$; for group B and C, respectively).

Regarding other secondary efficacy outcomes, global clinical efficacy was rated as good or very good in 69% of patients in group A and 88% in group B. Consistently, global AK lesion clearance was considered good or very good in 56%

Table 2 Change in AKASI score over time in the intention-to-treat population (ITT), with per-protocol (PP) sensitivity analysis

Group A (oral retinol)				Group B (oral retinol + MP)				Group C (control)			
T0	T3	T6	T9	T0	T3	T6	T9	T0	T3	T6	T9
ITT											
3.2 ± 2.1	2.7 ± 1.6	2.6 ± 1.3*	2.5 ± 1.3**	3.7 ± 1.8	2.8 ± 1.7****	2.4 ± 1.4****	2.3 ± 1.3****	2.7 ± 1.4	2.6 ± 1.3	2.8 ± 1.5	2.7 ± 1.4
PP											
3.2 ± 2.3	2.6 ± 1.7	2.5 ± 1.4**	–	3.8 ± 1.8	2.8 ± 1.6***	2.4 ± 1.3****	–	2.7 ± 1.4	2.6 ± 1.3	2.8 ± 1.6	–

MP medical photoprotection (sunscreen SPF50+ and piroxicam 0.8%)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$ *vs* T0

and 82% of patients in groups A and B, respectively. Treatment tolerability was generally good across the study population. Only three patients in group B reported a tolerability score of 1 or 2 at month 3, whereas two patients in group C reported a tolerability score of 1 at month 6. No patient reported severe symptoms corresponding to a tolerability score of 3. These symptoms were captured through the predefined tolerability scale and were not recorded as treatment-related adverse events in the CRFs. No treatment-related adverse events were formally recorded during the study period. The proportion of patients requiring additional AK-directed treatments was similar across groups, with three patients in each group (A, B, and C) undergoing further interventions.

In the LC-OCT analysis, conducted in a predefined subgroup of patients at baseline (T0) and after 3 months (T3), both treatment groups showed a reduction in epidermal/dermal thickness and stratum corneum thickness over time (Fig. 3). However, these reductions reached statistical significance only in group B ($p < 0.05$). A decrease in keratinocyte atypia grade was observed in both groups, indicating a trend toward morphological improvement; however, these changes did not achieve statistical significance (data not shown).

Representative LC-OCT images of a patient in group B (Fig. 4), obtained at baseline and after 3 months of treatment, showed a reduction in stratum corneum and epidermal/dermal thickness together with a trend toward a more regular epidermal architecture. At baseline, LC-OCT imaging revealed features consistent with photodamaged skin, including irregularities of the stratum corneum, heterogeneity of the superficial signal, and a less organized epidermal–dermal architecture. The skin texture appeared heterogeneous, with reduced definition of the superficial layers and of the epidermal–dermal junction.

After 3 months of treatment, the images showed a more regular appearance of the stratum corneum and greater homogeneity of the epidermal–dermal architecture. Compared with baseline, a reduction in superficial irregularities and improved organization of skin layers could be observed, suggesting a trend toward

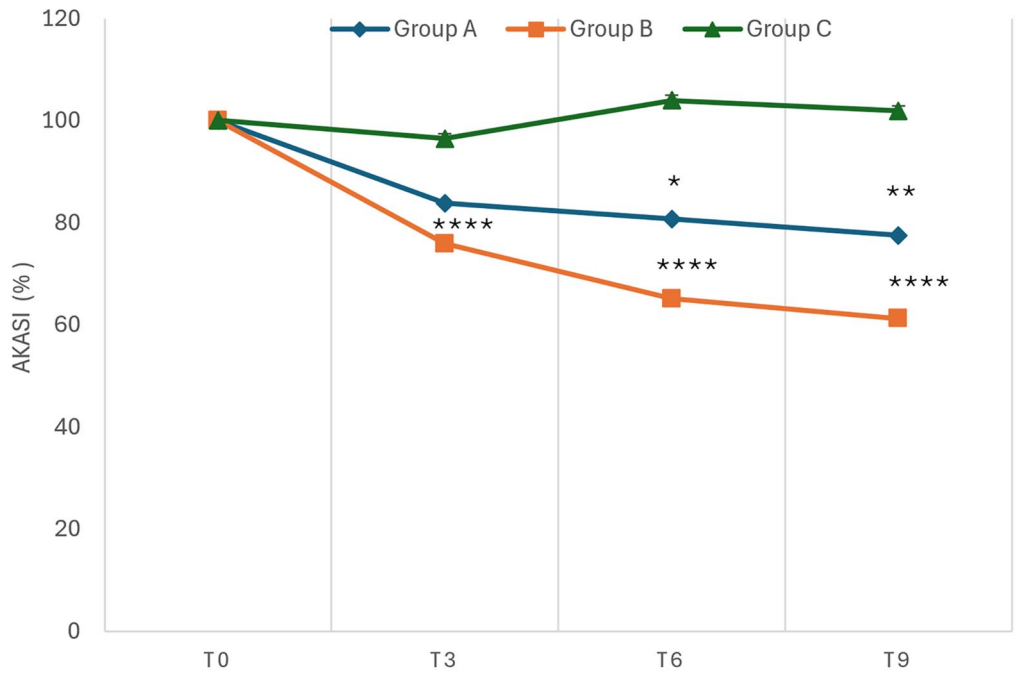

Fig. 2 Percentage reduction in AKASI score over time (expressed as % of baseline) for each study group. Group A, oral retinol; group B, oral retinol + medical photoprotection; group C, control group. *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$ vs T0

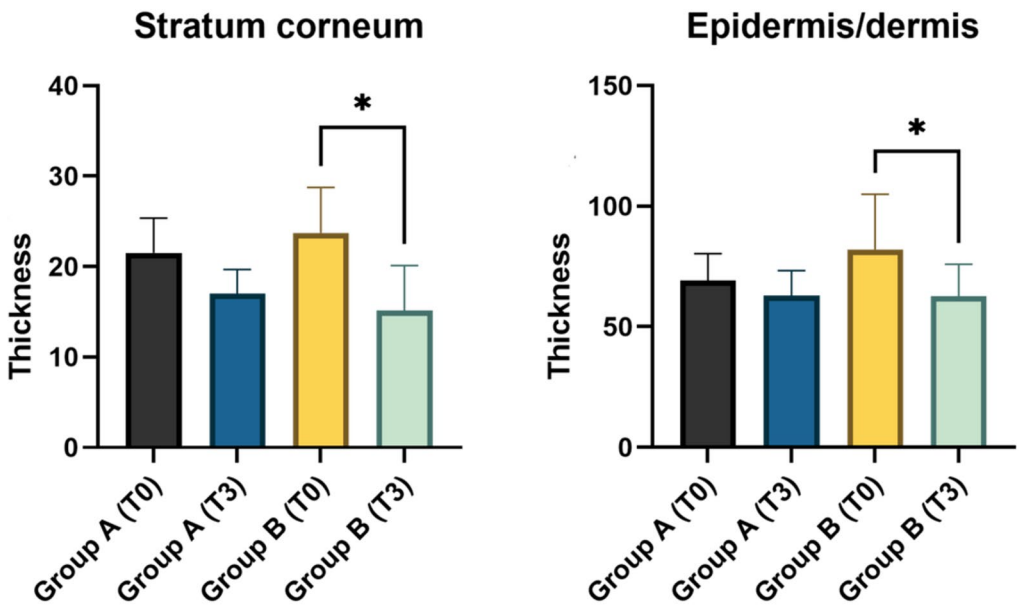

Fig. 3 LC-OCT measurement of epidermal and dermal thickness (µm) and stratum corneum thickness (µm) evaluated in group A (oral retinol, $n = 6$) and B (oral retinol + medical photoprotection, $n = 7$) at baseline (T0) and after 3 months (T3). *$p < 0.05$

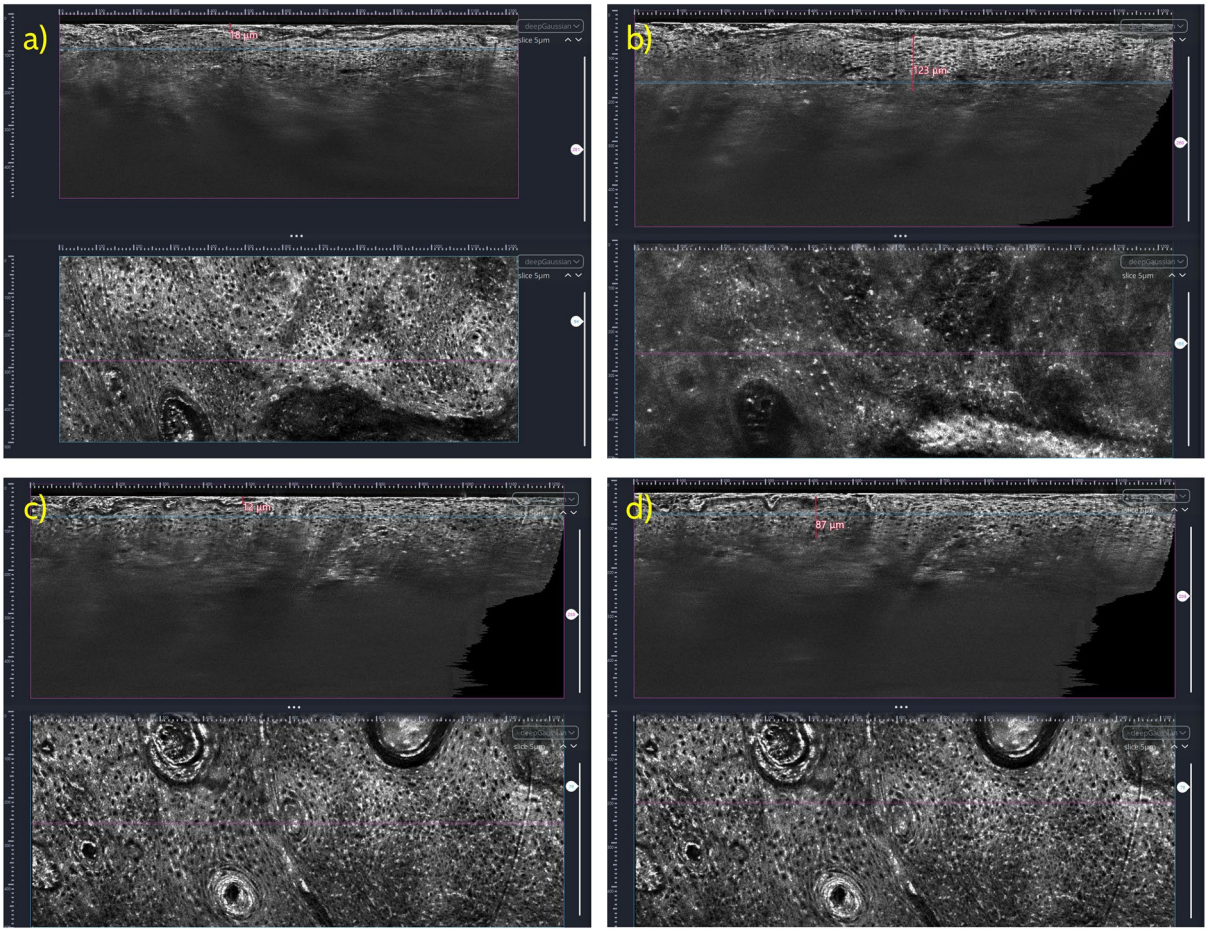

Fig. 4 Representative LC-OCT images of a patient in group B (oral retinol + medical photoprotection) at baseline (T0) and after 3 months of treatments (T3). **a** T0 stratum corneum; **b** T0 epidermal/dermal architecture; **c** T3 stratum corneum; **d** T3 epidermal/dermal architecture

morphological improvement of the actinic field. Post-treatment images also suggested reduced structural disorganization and a trend toward lower keratinocyte atypia. Although exploratory and qualitative, these observations are consistent with the quantitative LC-OCT findings and with the clinical improvement observed during the study.

Figure 5 shows representative clinical photographs of a patient in group B (oral retinol + medical photoprotection) at baseline (T0) and after 9 months (T9).

DISCUSSION

The present study evaluated the efficacy and tolerability of oral retinol, administered alone or in combination with a topical medical photoprotection, in patients with mild-to-moderate AK. Within this selected population, AKASI scores decreased over time in the active treatment groups, with a more rapid and pronounced effect observed in the combination group ("In&Out" strategy). In contrast, no significant changes were observed in the control group receiving standard photoprotection alone. The magnitude and temporal pattern of AKASI reduction differed between the two active treatment arms.

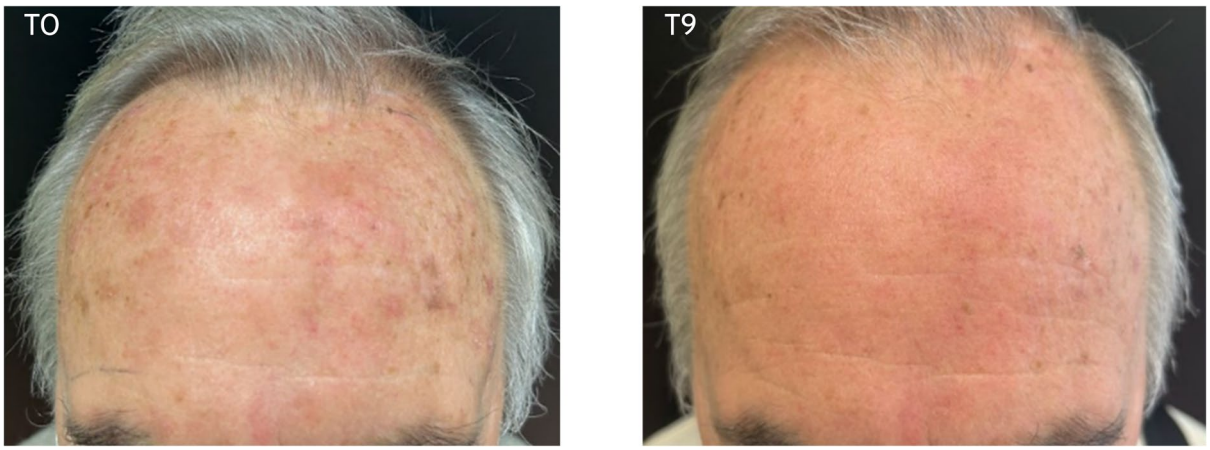

Fig. 5 Representative clinical photographs of a patient in group B (oral retinol + medical photoprotection) at baseline (T0) and at month 9 (T9, follow-up visit)

While oral retinol alone was associated with a gradual improvement that became significant at later timepoints, the combination with medical photoprotection resulted in an earlier and more sustained clinical response.

This finding is compatible with a potential complementary effect between systemic modulation of keratinocyte differentiation and local photoprotective or anti-inflammatory mechanisms. However, because the study did not include a medical photoprotection-only arm, the present data cannot determine whether the greater reduction observed in the combination group was driven by oral retinol, regular application of the dispensed SPF50+ product, piroxicam, or their combined use.

These results are consistent with previous evidence supporting a preventive role of oral retinol in UV-induced skin carcinogenesis. In a large randomized controlled trial, oral retinol supplementation significantly reduced the incidence of squamous cell carcinoma in moderate-risk individuals, while no effect was observed on basal cell carcinoma [7]. Additional studies have demonstrated dose-dependent biological activity of oral retinol on sun-damaged skin, including reduction of actinic damage at the cellular level and modulation of retinoid receptor expression [8]. Taken together, these data provide a strong biological and clinical rationale for the use of oral retinol as a field-directed strategy in patients with AK.

The findings of the LC-OCT substudy further support this interpretation. The significant reduction in epidermal and stratum corneum thickness observed in the combination group suggests a measurable impact on structural features of actinic damage. Although improvements in keratinocyte atypia did not reach statistical significance, the observed trend toward lower atypia grades is consistent with a potential normalization of epidermal architecture. Given the limited sample size, these results should be considered exploratory but provide preliminary mechanistic insight into the effects of treatment.

An additional clinically relevant aspect concerns treatment adherence, although this was not formally assessed in the present study. Topical therapies, including photoprotective agents, are highly dependent on patient compliance, which may be suboptimal in older populations. Factors such as difficulty in consistent application, sensory characteristics of topical products, comorbidities, and reduced perception of disease severity may contribute to poor adherence. Moreover, seasonal variations may further influence treatment behavior, with reduced use of topical photoprotection during periods of lower perceived sun exposure. In this context, the oral component of an "In&Out" strategy may have practical relevance as part of a multimodal approach in clinical settings where adherence to topical regimens is suboptimal. Future studies should include predefined adherence measures

to determine whether this strategy offers any real-world adherence advantage over topical regimens alone.

The clinical tolerability profile was favorable over 6 months, with no treatment-related adverse events formally recorded in the CRFs. These findings are consistent with previous evidence supporting the acceptable tolerability of moderate-dose oral retinol supplementation. In particular, Alberts et al. evaluated oral vitamin A at doses ranging from 25,000 to 75,000 IU/day for 12 months in 129 subjects with severe sun-damaged skin and found no significant increase in clinical or laboratory toxicities compared with placebo, even at higher dose levels. The study also reported no clear dose–response relationship for adverse events, supporting the short- to medium-term safety of oral retinol supplementation in this setting [8]. Nevertheless, potential long-term safety concerns associated with chronic retinoid exposure, including metabolic alterations and possible effects on lipid profile and bone metabolism, should still be considered in clinical practice, particularly in older patients and during prolonged treatment courses. Therefore, prolonged oral retinol supplementation in patients who are older or polymedicated should be considered cautiously and ideally accompanied by appropriate clinical and laboratory monitoring in future studies and in clinical practice.

Some limitations should be acknowledged. The open-label design may have introduced performance and assessment bias, particularly for investigator-rated outcomes. However, to increase the internal validity of our results, we adopted the assessor-blinded approach for the evaluation of the clinical endpoints. The absence of a control group for certain secondary endpoints limits the interpretability of comparative analyses.

In addition, the study did not include a treatment arm receiving medical photoprotection alone. Consequently, the study cannot isolate the independent contribution of the topical medical device, the sunscreen component, piroxicam, or oral retinol within the combined strategy. Nevertheless, previous clinical data have suggested that piroxicam may have activity in AK, including a preliminary open-label study of piroxicam 1% gel showing regression of a proportion of treated lesions [17], and several studies have reported clinical improvement with formulations combining piroxicam 0.8% and SPF50+ photoprotection [9–13]. In addition, the clinical use and labelling of topical non-steroidal anti-inflammatory drugs for AK emphasize strict avoidance of ultraviolet exposure during treatment, supporting the broader rationale for combining anti-inflammatory topical strategies with photoprotection. Therefore, the present study was primarily designed to evaluate the clinical outcomes associated with adding oral retinol to a combined "In&Out" strategy, rather than to deconstruct the independent efficacy of each topical component. Finally, adherence to photoprotection and oral supplementation was not formally measured, which further limits the interpretation of between-group differences and should be addressed in future trials.

Furthermore, participants had mild-to-moderate AK, a limited number of clinically evident lesions, relatively low baseline AKASI scores, and no previous history of skin cancer. As a result, the findings may not be directly generalizable to patients with high-risk clinical settings. The relatively small sample size, short follow-up, and the exploratory nature of the LC-OCT substudy (that restrict the generalizability of mechanistic findings) are other limitations. Despite these limitations, the consistency of clinical improvement, the supportive mechanistic signals, and the favorable safety profile collectively suggest that oral retinol supplementation, particularly when combined with medical photoprotection, may represent a rational and clinically relevant strategy in the management of AK. Further randomized controlled trials with larger sample sizes and longer follow-up are warranted to confirm these findings and to better define the role of systemic retinoid-based approaches in the prevention and treatment of actinic damage.

CONCLUSIONS

This study provides evidence that oral retinol supplementation in mild-to-moderate patients with AK, alone or in combination with medical photoprotection, is associated with a reduction

in clinical severity of AK, as assessed by AKASI score. The combination approach was associated with a more rapid and consistent clinical improvement compared with oral supplementation alone. In addition to its clinical efficacy, oral retinol may offer practical advantages in real-world settings, particularly in older populations, where adherence to topical treatments is often suboptimal and may further decline during periods of reduced perceived sun exposure, such as the winter months. The favorable tolerability profile observed in this study supports the feasibility of this approach, although long-term safety considerations should be taken into account. Overall, these findings support the rationale for integrating oral retinol into a multimodal management strategy for AK. Further randomized controlled studies, including a medical photoprotective-only arm and patients who are higher-risk, are warranted to confirm these results and to better define the role of systemic supplementation in the prevention and treatment of actinic damage.

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Declarations

Conflict of Interest. Massimo Milani, Stefano Alfano, and Francesca Colombo are employees of Cantabria Labs Difa Cooper that commercialized the tested products. Marco Ardigò, Martina Burlando, Elena Campione, Gianluca Nazzaro, Giulio Foggi, and Angelo V. Marzano, declare no conflicts of interest related to this manuscript.

Ethical Approval. The study was conducted in accordance with Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki and its later amendments. The study protocol was approved by an external independent review board in January 2023 (DC-01-2023, 12 January 2023). The trial registration number is ISRCTN42565762. Before enrolment, all participants provided fully informed written consent to participate in the study and for the publication of their clinical photographs.

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