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Randomized comparative study of 5-Fluorouracil 4%, tirbanibulin, and photodynamic therapy for relapsing actinic keratoses

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ABSTRACT

Background: Actinic keratosis (AK) reflects a field cancerization process in chronically sun-damaged skin, and relapse after diclofenac therapy is a frequent clinical scenario. Field-directed treatments such as 5-fluorouracil (5-FU), tirbanibulin, and photodynamic therapy (PDT) are widely used, yet comparative data in post-diclofenac relapse and the contribution of reflectance confocal microscopy (RCM) to therapeutic monitoring remain limited.
Objectives: To compare the clinical efficacy, tolerability, and subclinical response of 5-FU 4%, tirbanibulin 1%, and PDT in relapsing AK of the scalp, integrating RCM imaging to assess field response.
Methods: A prospective randomized (1:1:1) study was conducted in 45 patients who previously achieved complete clearance with diclofenac 3% and relapsed within 12 months. Endpoints included clinical clearance at 12 weeks, RCM normalization, recurrence at 6 months, and local skin response (LSR) severity.
Results: Twelve-week clearance rates were 73.3% for 5-FU, 66.7% for tirbanibulin, and 80.0% for PDT ($p=0.711$). RCM normalization occurred in 66.7%, 60.0%, and 73.3% of patients, respectively ($p=0.741$). Recurrence among responders at 6 months was low and comparable (9.1%, 10.0%, and 8.3%; $p=0.991$). Tirbanibulin showed significantly lower LSR scores versus 5-FU and PDT ($p<0.001$), indicating superior tolerability.
Conclusions: Short-term efficacy of 5-FU, tirbanibulin, and PDT was comparable, while tolerability differed markedly. Tirbanibulin demonstrated the most favorable inflammatory and cosmetic profile, whereas 5-FU and PDT may be preferred when a more intense field effect is desired. RCM detected subclinical persistence in select cases and may serve as an adjunctive imaging tool for monitoring and guiding retreatment in field cancerization.

1. Introduction

Actinic keratosis (AK) is a clinical manifestation of field cancerization in chronically sun-exposed skin, characterized by areas of subclinical and clinical UV-induced keratinocyte atypia that predispose to the development of multiple AKs and cutaneous squamous cell carcinoma (cSCC) [1–7]. Visible lesions and the surrounding clinically normal-appearing field often share similar oncogenic mutations, particularly involving tumor suppressor pathways such as p53, supporting the concept that lesion-directed therapy alone is insufficient for long-term cancer control [2–5,7–9]. This pathogenic continuity explains why patients with multiple AKs have a markedly increased risk of developing cSCC and why field-directed therapy has become central to contemporary management strategies [1,5,10,11]. Current consensus in the medical literature and treatment guidelines now emphasize the importance of field-directed therapies to address both visible and subclinical disease, aiming to reduce the overall burden of AKs and prevent progression to invasive carcinoma [1,4,5,10,12]. Field-directed treatment options for actinic keratosis include topical agents such as 5-fluorouracil (5-FU), imiquimod, tirbanibulin and diclofenac, as well as photodynamic therapy (PDT). Current guidelines emphasize field therapy with 5-FU, imiquimod, tirbanibulin or PDT as first-line options, whereas diclofenac may be considered when a milder inflammatory profile is desired [13,14]. Treatment selection is therefore individualized, balancing field response, tolerability, and patient preference rather than assuming superiority of a single modality [14]. Topical 5-FU 4% cream remains the most effective field therapy, achieving sustained clearance and significant reduction in lesion count at 12 months, as

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demonstrated in a large multicenter trial [15]. PDT using methyl aminolevulinate (MAL) or aminolevulinic acid (ALA) is highly effective for both visible and subclinical lesions, with the added benefit of superior cosmetic outcomes, but pain during illumination is a notable limitation [10,15,16]. Diclofenac 3% gel offers a milder side effect profile and is suitable for patients who cannot tolerate more aggressive therapies, though its efficacy is lower than 5-FU, imiquimod, or PDT [10,16,17]. Tirbanibulin 1% ointment is a newer agent approved for field treatment of AKs on the face and scalp, with a short 5-day regimen and favorable tolerability, though long-term efficacy data are still emerging [1,18–21]. The choice among these options should be individualized, balancing efficacy, tolerability, cosmetic outcome, and patient adherence, as supported by recent comparative studies and reviews [10,15,16,22,23]. Patients who relapse after diclofenac represent a clinically relevant subgroup, as they have demonstrated initial treatment responsiveness but persistent field cancerization requiring further intervention. These cases provide an ideal scenario to evaluate comparative performance of field-directed options. Accordingly, this prospective randomized study compares 5-FU 4%, tirbanibulin 1%, and PDT as standalone field therapies in relapsing AKs of the scalp, integrating clinical and reflectance confocal microscopy (RCM) assessment. The primary objective is to evaluate short-term clinical clearance and tolerability; secondary objectives include subclinical response (RCM normalization) and 6-month recurrence within the treated field.

2. Materials and Methods

A prospective, randomized, study was conducted at the Oncologic Dermatology Unit, IRCCS Policlinico Sant'Orsola of Bologna, between January 2023 and March 2025. Inclusion criteria were patients $\geq$ 18 years with $\geq$ 5 clinically and dermoscopically confirmed AKs on the scalp, complete clearance after diclofenac 3% gel (twice a day per 3 months) and clinical relapse within 12 months post-therapy.

Exclusion criteria were immunocompromised status (including organ transplantation, systemic corticosteroids, biologics), photosensitivity disorders, invasive cSCC within the target area and a prior treatment with study drugs within 6 months. Patients (n = 45) were randomized (1:1:1) to one of three arms:

1. 5-FU 4% group: topical 5-FU applied once daily for 28 days.
2. Tirbanibulin group: tirbanibulin 1% ointment once daily for 5 consecutive days.
3. PDT group: PDT was performed using methyl 5-aminolevulinate 16% cream (Metvix®, Galderma, France), applied to the target field under occlusion for 3 hours, followed by illumination with red light at 630 nm, delivering a total light dose of approximately 37 J/cm².

Randomization was performed using a computer-generated 1:1:1 allocation sequence with sealed, sequentially numbered envelopes to ensure allocation concealment. Patients were evaluated at baseline, end of treatment, 12 weeks, and 6 months.

Evaluations included Clinical and dermoscopic scoring (AKASI score [24]), RCM imaging (VivaScope 3000) assessing keratinocyte atypia, parakeratosis, inflammatory infiltrate, and epidermal disarray [25–27]. The primary endpoint was complete clinical clearance at 12 weeks, defined as absence of visible AKs in the treated field. Secondary endpoints included RCM normalization, recurrence at 6 months, and local skin responses (LSR) severity score [28]. Treatment-related adverse events were recorded at each follow-up visit. LSR, including erythema, scaling, crusting, swelling, vesiculation, and erosion, were assessed using a standardized composite score [28]. Recurrence at 6 months was assessed only among patients who achieved complete clinical clearance at 12 weeks, as recurrence was defined as the reappearance of AK within a previously cleared treatment field. RCM outcomes were exploratory and the study was not powered to detect between-group differences for confocal endpoints.

Table 1
Baseline demographic and clinical characteristics of the study population according to treatment group. Values are presented as mean ± standard deviation or number (%), as appropriate.
Patients were randomized to receive 5-fluorouracil (5-FU) 4%, tirbanibulin 1%, or photodynamic therapy (PDT) (15 patients per group). Comparisons among groups were performed using one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. A p value < 0.05 was considered statistically significant.

Characteristic	Overall (n=45)	5-FU 4% (n=15)	Tirbanibulin (n=15)	PDT (n=15)	p value
Age, years	66.8 ± 7.3	68.6 ± 7.7	65.5 ± 6.2	66.4 ± 8.0	0.491
Male sex, n (%)	30/45 (66.7%)	7/15 (46.7%)	11/15 (73.3%)	12/15 (80.0%)	0.122
Lesion count, mean ± SD	6.9 ± 1.5	7.7 ± 1.4	6.1 ± 1.3	7.0 ± 1.5	0.012

Table 2
Clinical, confocal, and tolerability outcomes at follow-up according to treatment group. Complete clinical clearance and reflectance confocal microscopy (RCM) normalization were assessed at 12 weeks. Recurrence rates were calculated at 6 months among patients achieving complete clearance. Local skin reaction (LSR) severity is reported as mean ± standard deviation and median. Comparisons among treatment groups were performed using the chi-square test for categorical variables and the Kruskal–Wallis test for LSR scores.
A p value < 0.05 was considered statistically significant.

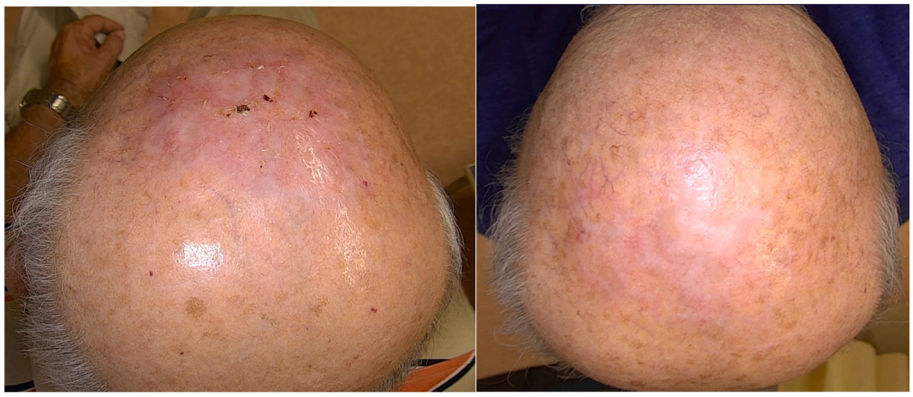
Outcome	Overall (n=45)	5-FU 4% (n=15)	Tirbanibulin (n=15)	PDT (n=15)	p value
Complete clearance at 12w, n (%)	33/45 (73.3%)	11/15 (73.3%)	10/15 (66.7%)	12/15 (80.0%)	0.711
RCM normalization at 12w, n (%)	30/45 (66.7%)	10/15 (66.7%)	9/15 (60.0%)	11/15 (73.3%)	0.741
Recurrence at 6m among responders, n (%)	3/33 (9.1%)	1/11 (9.1%)	1/10 (10.0%)	1/12 (8.3%)	0.991
LSR score, mean ± SD	9.6 ± 3.7	11.4 ± 2.6	5.7 ± 1.3	11.7 ± 3.0	<0.001
LSR score, median [IQR]	9 [7–12]	11 [10–13]	5 [5–6]	11 [10–13]	

2.1. Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range), and categorical variables as number (%). Comparisons among treatment groups were performed using one-way analysis of variance for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate. Local skin reaction scores were compared using the Kruskal–Wallis test. Complete clinical clearance and reflectance confocal microscopy (RCM) normalization at 12 weeks, as well as recurrence at 6 months among responders, were compared across treatment groups using chi-square or Fisher's exact tests. All tests were two-sided, and a p value < 0.05 was considered statistically significant. Statistical analyses were performed using **Stata/SE (StataCorp LLC, College Station, TX, USA)**.

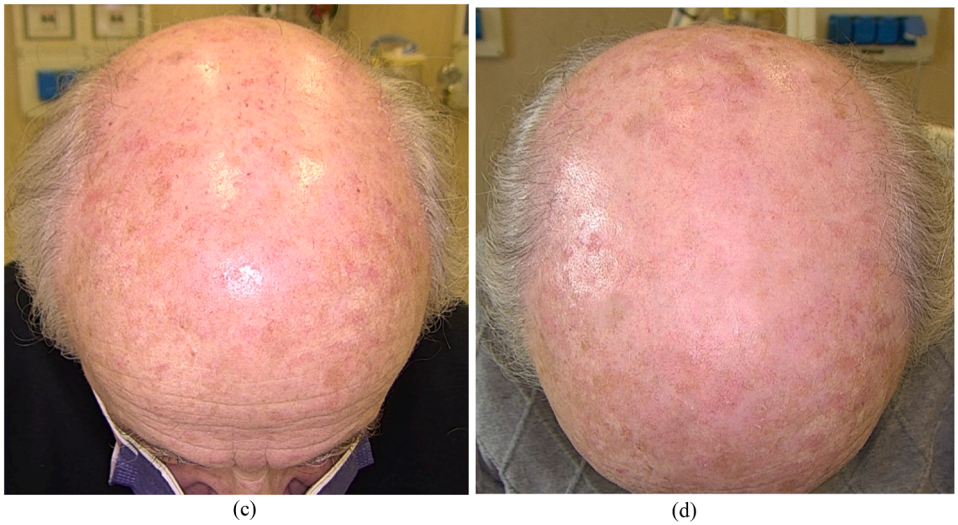
3. Results

A total of 45 patients were enrolled and randomized in a 1:1:1 ratio to treatment with 5-FU 4%, tirbanibulin 1%, or PDT, with 15 patients allocated to each group. All patients completed the assigned treatment and follow-up and were included in the final analysis. Baseline demographic and clinical characteristics are reported in Table 1. The three treatment groups were comparable with respect to age and sex distribution. The overall mean age was 66.8 ± 7.3 years, and most patients



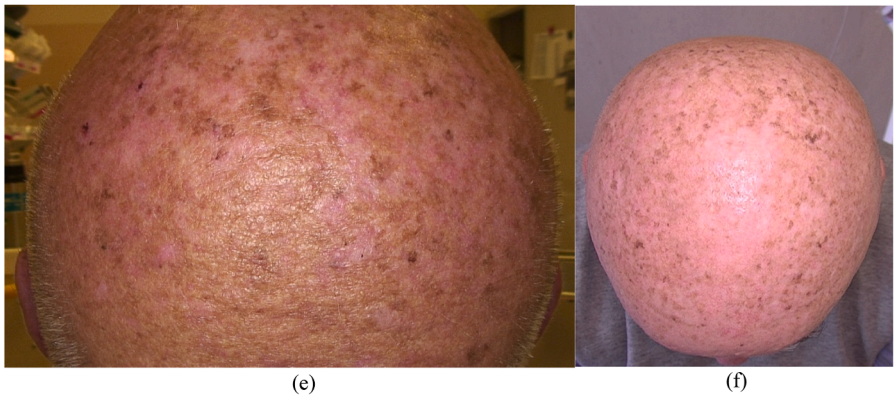
(a) (b)

(C–D) Tirbanibulin: baseline images showing clinically visible actinic keratoses with typical features, and follow-up images at 12 weeks revealing clinical resolution with minimal residual erythema.



(c) (d)

(E–F) Photodynamic therapy (PDT): baseline images illustrating multiple actinic keratoses in a cancerized field and image at 12 weeks showing substantial clinical improvement and.



(e) (f)

Clinical images were acquired under standardized lighting conditions. All post-treatment images were captured at the 12-week follow-up visit.

Figure 1. (A–B) 5-Fluorouracil (5-FU) 4%: baseline clinical appearance showing multiple erythematous, scaly actinic keratoses within a photodamaged field, and corresponding post-treatment images at 12 weeks demonstrating marked reduction of erythema and scaling with restoration of normal epidermal pattern. (C–D) Tirbanibulin: baseline images showing clinically visible actinic keratoses with typical features, and follow-up images at 12 weeks revealing clinical resolution with minimal residual erythema. (E–F) Photodynamic therapy (PDT): baseline images illustrating multiple actinic keratoses in a cancerized field and image at 12 weeks showing substantial clinical improvement and Clinical images were acquired under standardized lighting conditions. All post-treatment images were captured at the 12-week follow-up visit.

were male (66.7%), with no statistically significant differences among groups. Baseline lesion burden differed significantly across treatment arms, with a higher mean number of actinic keratoses in the 5-FU group compared with tirbanibulin and PDT ($p = 0.012$). At 12 weeks, complete clinical clearance of the treated field was achieved in 33 of 45 patients (73.3%). Clearance rates were 73.3% (11/15) in the 5-FU group, 66.7% (10/15) in the tirbanibulin group, and 80.0% (12/15) in the PDT group (Fig. 1). Differences in clearance rates among treatment arms were not statistically significant ($p = 0.711$; Table 2). RCM evaluation at 12 weeks demonstrated complete normalization of the epidermal honeycomb pattern in 30 of 45 patients (66.7%). Normalization was observed in 66.7% (10/15) of patients treated with 5-FU, 60.0% (9/15) treated with tirbanibulin, and 73.3% (11/15) treated with PDT. No statistically significant differences were detected among the three groups ($p = 0.741$; Table 2). Among patients who achieved complete clearance, recurrence within the previously treated field at 6-month follow-up occurred in 3 of 33 patients (9.1%). Recurrence rates were low and comparable across treatment groups: 9.1% (1/11) in the 5-FU group, 10.0% (1/10) in the tirbanibulin group, and 8.3% (1/12) in the PDT group, with no statistically significant difference observed ($p = 0.991$; Table 2). LSR severity differed significantly among treatment arms ($p < 0.001$; Table 2). Tirbanibulin was associated with substantially lower mean and median LSR scores compared with both 5-FU and PDT, whereas 5-FU and PDT showed comparable levels of local inflammatory response. No serious adverse events, treatment interruptions, or discontinuations were recorded during the study.

4. Discussion

In this prospective randomized study, we compared three widely used field-directed therapies in patients with relapsing actinic keratoses following prior diclofenac treatment, integrating clinical assessment with RCM. All three field therapies demonstrated comparable short-term efficacy, with no statistically significant differences in clearance or recurrence. PDT showed the highest numerical clearance, but this did not translate into a significant advantage. These findings align with current evidence suggesting that, in relapsing AKs with field cancerization, treatment selection should prioritize patient-specific considerations. Notably, the absence of significant differences does not imply equivalence, as the study was not powered for non-inferiority or equivalence testing. RCM identified subclinical persistence in a subset of clinically cleared fields, and these abnormalities corresponded to cases that later recurred at 6 months. Although exploratory, this supports the hypothesis that RCM may function as an early marker of incomplete field response and potential relapse risk, warranting further study as a treatment monitoring and retreatment-guidance tool. Tirbanibulin demonstrated the most favorable tolerability profile, with significantly lower LSR scores compared with 5-FU and PDT. Conversely, 5-FU and PDT produced more intense inflammatory responses, which, although expected and manageable, may affect adherence in patients requiring repeated field treatment. In clinical practice, tirbanibulin may be prioritized when downtime and cosmetic acceptability are critical, while 5-FU and PDT remain valid options when pursuing a more aggressive field effect.

5. Conclusions

To conclude, in relapsing AKs following diclofenac, 5-FU, tirbanibulin, and PDT provide similar short-term clinical control. Tolerability profiles differ markedly and should guide treatment selection. RCM adds value in detecting subclinical persistence and may contribute to individualized retreatment strategies. Larger, longer studies are warranted to validate RCM as a stratification or predictive tool.

Strengths of this study include its prospective randomized design, standardized assessment time points, and the incorporation of RCM as an objective, non-invasive method to evaluate subclinical disease. The focus on patients relapsing after diclofenac therapy reflects a common and clinically relevant real-world scenario.

Limitations include the relatively small sample size, single-center design, and short follow-up duration, which limit statistical power and the ability to assess long-term outcomes, including progression to invasive squamous cell carcinoma. Additionally, baseline lesion burden differed among groups despite randomization, which may have influenced treatment response.

Future studies with larger cohorts, longer follow-up, and stratification by baseline lesion burden are warranted to further define the prognostic value of RCM normalization and to explore optimal sequencing or combination strategies for patients with recurrent or extensive field cancerization.

Author contributions

Conception and design: Venturi, Dika

Acquisition of data: Venturi, Magnaterra, Gualandi, Scotti, Baraldi, Alessandrini, Vaccari

Analysis and interpretation of data: Venturi, Dika

Drafting of the manuscript: Venturi, Dika

Critical revision of the manuscript for important intellectual content: Venturi, Dika

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

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The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

Ethics approval

The study was conducted in accordance with institutional ethics requirements

Informed Consent Statement

Informed consent was obtained from the subject involved in the study.

CRediT authorship contribution statement

Federico Venturi: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Elisabetta Magnaterra:** Writing – original draft, Methodology, Investigation. **Alberto Gualandi:** Validation, Software, Methodology, Investigation, Data curation. **Biagio Scotti:** Software, Methodology, Investigation, Conceptualization. **Carlotta Baraldi:** Writing – original draft, Methodology. **Aurora Alessandrini:** Software, Methodology, Investigation, Data curation, Conceptualization. **Sabina Vaccari:** Validation, Methodology, Investigation. **Emi Dika:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors have no relevant financial or non-financial interests to disclose.

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