Dermatology Practical & Conceptual

Comparative Efficacy and Tolerability of Imiquimod 3.75% Cream vs 5-Fluorouracil 4% cream in the Treatment of Actinic Keratosis: A Split-Face Study

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ABSTRACT

Introduction: Actinic keratosis (AK) is a common precancerous skin lesion that arises on chronically UV-exposed skin and that can progress to keratinocyte carcinoma.

Objective: The aim of this study was to compare the efficacy, safety, local skin reaction, time to wound healing, and patient preference of imiquimod (IMQ) 3.75% vs 5-fluorouracil (5-FU) 4% cream treatment for AKs.

Methods: Two symmetrical contralateral areas of approximately 25 cm^2 harboring a similar (≥5) number of AKs were selected and randomly assigned to IMQ 3.75% or 5-FU 4% cream treatment. The total number of AKs for each patient was evaluated at baseline (T0) and 90 days after the end of treatments (T1). Local skin reaction (LSR) score was registered the day after the end of both treatments. Complete remission rate of lesions, cosmetic outcome, and patient preference of treatment were assessed after 90 days (T1).

Results: The mean variation (ΔT0-T1) of AKs was not significantly different in patients treated with IMQ 3.75% vs 5-FU 4% ($P = 0.35$). The mean LSR was not significantly different between patients treated with IMQ 3.75% and those with 5-FU 4% (p=0.63). No difference in cosmetic outcome was observed in the two groups. Patient preference was equally distributed between the treatments. The mean time to wound healing after the end of the treatment was similar with IMQ 3.75% and with 5-FU 4% ($P = 0.83$).

Conclusions: This study reports a non-superiority of efficacy, tolerability, wound-healing time, and cosmetic outcome of topical IMQ 3.75% treatment compared to topical 5-FU 4% treatment in AK management.

Introduction

Actinic keratosis (AK) is a common precancerous skin lesion whose incidence is increasing due to ageing populations and greater exposure to ultraviolet light. It results from the accumulation of genotoxic DNA damage and requires removal due to the risk of progressing to invasive squamous cell carcinoma [1]. AKs commonly appear in fair-skinned individuals in areas of the body that have experienced the most exposure to solar damage over time. These areas often include the head, ears, neck, dorsal parts of the arms and hands, and the lower extremities. The scalp is a particularly common site for AKs, especially in areas where there is hair loss [2].

Because several treatment options are available for AKs, each with its own advantages and disadvantages, determining the most effective and tolerable treatment can be challenging for clinicians.

Guidelines and meta-analyses primarily focus on clinical efficacy and safety, but practical considerations such as treatment duration, complexity, and local skin reaction may play a significant role in treatment outcomes and patient satisfaction [3]. AK treatment can be either directed at the individual lesions or at the entire affected area (field-directed therapy). While single lesion treatment (e.g., cryotherapy, curettage, surgery, CO2 laser ablation) may be appropriate for certain patients with a limited number of lesions, field-directed therapy (e.g., 5-fluorouracil, imiquimod, diclofenac, terbanibulin, ingenol mebutate, and photodynamic therapy) is often preferred for patients with multiple lesions or a history of AKs, as it can help to manage multiple AKs and keratinocyte changes in a contiguous area. Additionally, field treatment approaches may provide benefits in reducing the risk of developing new AKs, limiting AK recurrence, and mitigating subclinical damage [4]. The topical application of creams, gels, and solutions is a common approach for managing AKs in dermatology practice. These agents can be applied locally or to broad areas and are especially useful for treating AKs in areas with high density or indistinct clinical borders. However, topical agents used in AK treatment are known to cause considerable local skin reaction, which may result in treatment discontinuation before achieving the desired therapeutic outcome. Therefore, it is the clinician's responsibility to collaborate with the patient to create an individualized treatment plan that is effective and well-tolerated.

Among the topical treatments for actinic keratoses (AKs), there is strong evidence supporting the use of 5-fluorouracil (5-FU) and imiquimod (IMQ). However, due to the different commercial preparations of these drugs, treatment regimens often vary in concentration, dosing intervals, and duration [4]. We decided to use 4% 5-fluorouracil (5-FU) and 3.75% imiquimod formulations, as these are widely used in clinical practice in Italy, where we conducted the study.

Objectives

The aim of this study was to compare the efficacy, safety, local skin reaction, time to wound healing, and patients' preference for IMQ 3.75% cream versus 5-FU 4% cream with an independent, non-sponsored single-center prospective open-label split-face clinical trial.

Methods

Patients

The study enrolled adult patients with Fitzpatrick skin phototype I-IV who had multiple superficial non-erythematous AKs with a fairly symmetrical distribution on their face, scalp, or cheeks graded as Olsen's grade I or II [5]. The patients were recruited from the Dermatologic Department of the University of Brescia, which is a tertiary referral center in northern Italy. The diagnosis of AKs was confirmed visually and through dermoscopy. Exclusion criteria were: invasive tumors within the treatment area, concomitant clinically significant unstable medical conditions, active severe systemic infectious disease, current participation in another clinical study, chemical dependency or alcoholism, known allergies to any molecule in the study drugs, pregnancy or lactation, any other dermatological disease in the treatment area or within a distance of 3 cm in the six months prior to topical treatment for AK, and likelihood of poor compliance.

The study was held at the Dermatologic Department of the University of Brescia from January to November 2022 in accordance with the Declaration of Helsinki, and it was approved by the Local Ethics Committee. All patients were given verbal and written information on the nature of the study, and they signed an informed consent form before enrollment. Furthermore, we obtained permission from the patients or the publication of Figure 2.

Treatment Procedure

At baseline, two contralateral and symmetrical target areas on the face, scalp, or cheeks covering approximately 25 cm^2 and harboring more than five AKs were selected, and digital pictures were taken for accurate count of the lesions and for the subsequent follow-up. Randomization with a 1:1 allocation ratio of the contralateral areas to the treatment options was done with a computer-generated list using random permuted blocks of six to ensure concealment of allocation. Patients and treating physicians were not blinded to group assignment. Both treatments were delivered according to the protocol status of the European Medicines Agency and Italian Medicines Agency [6,7]. IMQ 3.75% cream was self-applied at night by patients on the affected area once a day in two 14-day cycles separated by 14 days of rest. 5-FU 4% cream was self-applied at night by patients on the affected area for

28 consecutive days. Patients with an incomplete response in multiple lesions after three months were treated with cryotherapy or a session of photodynamic therapy according to the number of lesions and the patient's preferences.

Clinical Assessment

The total number of AKs for each patient in the area of both treatments was evaluated at baseline (T0) and after 90 days from the end of each treatment (T1) and graded as Olsen I or Olsen II. The degree of local skin reaction (LSR) was assessed the day after the end of the treatment (EOT), i.e., at day 43 for IMQ 3.75% and at day 31 for 5-FU 4% from baseline. LSR were rated on a scale ranging from 0 to 4 (with higher numbers indicating greater severity) for the following six responses: erythema, flaking or scaling, crusting, swelling, vesiculation or pustulation, and erosion or ulceration (maximum composite score, 24) [8].

The patients were instructed to keep track of the number of days needed for their wound to fully heal and to contact the treating center if they experienced any local or systemic adverse events during the follow-up period, regardless of whether or not these events were linked to the treatment. Ninety days after the end of both treatments, an investigator who was blinded at the initial treatment allocation assessed the efficacy and cosmetic outcome.

The clinical response of lesions was evaluated at T1 using two categories: complete response (CR), which referred to the complete disappearance of the lesion on both visual assessment and palpation, and no response (NR), which meant that the lesion did not disappear or only partially disappeared. The overall cosmetic outcome of patients assessed at T1 was graded into one of four categories: excellent (no or mild redness or change in pigmentation), good (moderate redness or change in pigmentation), fair (slight-to-moderate scarring, atrophy, or induration), and poor (extensive scarring, atrophy or induration) [9]. At the same examination, patients completed a questionnaire anonymously to report which treatment they preferred, with a dichotomic choice between IMQ 3.75% cream and 5-FU 4% cream.

Statistical Analysis

Statistical analysis was performed with the SPSS™ (v27.0; IBM SPSS, Armonk, NY, USA) software program. Aiming for a significance level of 0.05 and a power of 0.80 and on the assumption that the smallest clinically important mean difference was 15% and the standard deviation of the difference in response was 17%, we calculated that at least 22 patients should be included in the study [10].

The normal distribution of collected data was analyzed by the Kolmogorov-Smirnov test. Categorical variables were summarized by using percentages and continuous variables by calculating medians, means, and range (minimum and maximum values). Medians and continuous variables were compared by using the Wilcoxon test and Mann-Whitney test. The chi-squared test was used for percentage comparison and associations. All results were considered statistically significant at $P \leq 0.05$ level.

Results

Twenty-four patients were enrolled in the study and completed the study in the period from January to November 2022. The main clinical details of patients are described in Table 1. The 25 cm^2 treated areas harbored a similar total number of AKs at baseline: 259 (177 Olsen I AKs and 82 Olsen II AKs) with IMQ 3.75% and 243 (169 Olsen I AKs and 74 Olsen II AKs) with 5-FU 4%.

The number of lesions treated per area was similar, with a mean of 10.79 [median 10, range 6–21] lesions in the areas treated with IMQ 3.75% and a mean of 10.13 [median 9.5, range 5–20] in the areas treated with 5-FU 4% ($P = 0.677$). No difference was observed in the analysis of the subpopulation AKs Olsen I ($P = 0.56$) and AKs Olsen II ($P = 0.60$). The total number of AKs at T1 was 71 (50 Olsen I AKs and 21 Olsen II AKs) with IMQ 3.75% and 78 (59 Olsen I AKs and 19 Olsen II AKs) with 5-FU 4%. The number of lesions per treated area was similar, with a mean of 2.96 [median 3, range 0–11] lesions in the areas treated with IMQ 3.75% and a mean of 3.25 [median 3, range 0–9] lesions in the areas treated with 5-FU 4% ($P = 0.38$). Patients experienced lno

Table 1. Major Clinical Details of Enrolled Patients at Baseline (T0).

Variable		Value (%)
Number of patients		24
Sex	M	21
	F	3
Median Age (years)		78
Age range (years)		65-90
Fitzpatrick skin phototype (%)	I	2 (8.3)
	II	13 (54.2)
	III	8 (33.3)
	IV	1 (4.2)
Total number of AKs at baseline	Number of AKs Olsen I	346
	Number of AKs Olsen II	156
Body site (%)	Scalp	13 (54.2)
	Forehead	7 (29.2)
	Cheeks	4 (16.6)

AK = actinic keratosis.

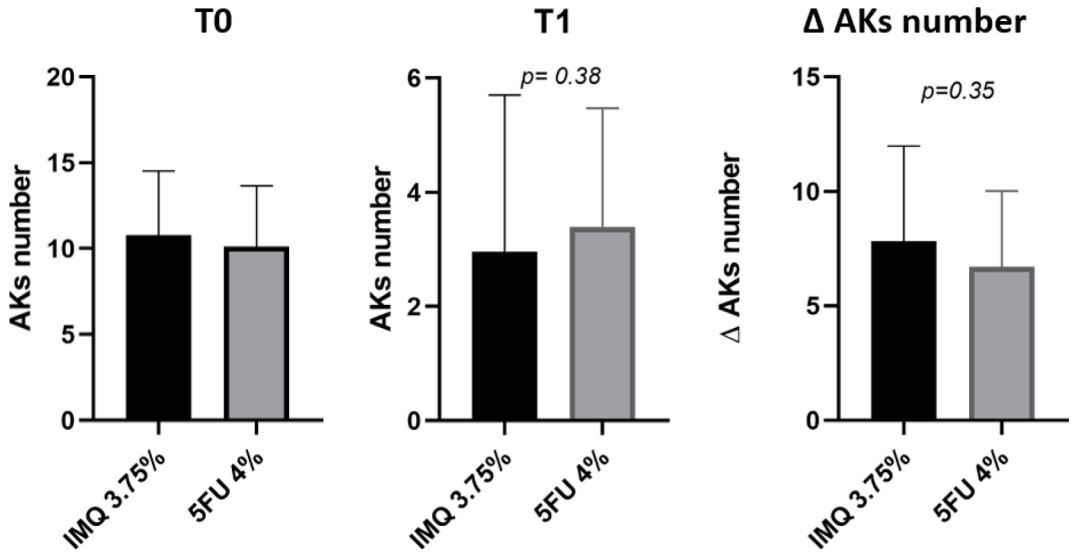

Figure 1. (A) Total number of actinic keratoses (AKs) at baseline (T0) in patients treated with imiquimod (IMQ) 3.75% cream and 5-fluorouracil (5-FU) 4% cream at baseline (T1), (B) 90 days after the end of both treatments (T1), and (C) the variation before and after treatment (ΔT0-T1).

local, systemic, acute or long-term adverse event related to the treatments.

As for efficacy, 188/259 (73%) lesions treated with IMQ 3.75% and 165/243 (68%) lesions treated with 5-FU 4% were cleared at T1. The number of cleared Olsen I AKs was 127 with IMQ 3.75% and 110 with 5-FU 4%, and the number of cleared Olsen II AKs was 61 with IMQ 3.75% and 55 with 5-FU 4%. To compare the efficacy of the two treatment modalities, the variation (ΔT0-T1) in AK number was calculated .The mean variation (ΔT0-T1) in AK numbers in patients treated with IMQ 3.75% was 7.83 [median 7, range 3–21]. The mean variation (ΔT0-T1) in AK number in patients treated with 5-FU 4% was 6.87 [median 6.5, range 2–18]. No significant difference was found (P = 0.35) (Figures 1 and 2). When considering patients who achieved a reduction in the number of actinic keratoses (AKs) of at least 60%, IMQ 3.75% demonstrated non-inferiority compared to 5-FU 4%, with response rates of 75% and 79%, respectively. The 95% confidence interval ranged from -15.7 to 7.7, which falls well below the pre-defined non-inferiority threshold of 15%. The mean LSR recorded was 11.79 [median 12, range 6–16] for patients treated with IMQ 3.75% and 11.20 [median 12, range 6–16] for patients treated with 5-FU 4%; no significant difference was observed (P = 0.63).

The cosmetic outcome was rated as excellent in 12 skin areas that were treated with IMQ 3.75% and good in 12: none was rated fair or poor, whereas it was rated as excellent in 12 skin areas that were treated with 5-FU 4% and good in 12. (Figure 3).

Ten patients gave their overall preference to IMQ 3.75%, 12 to 5-FU 4%, and two expressed the same satisfaction with both treatments. The mean time to wound healing calculated in days after EOT (End Of Treatment) was similar after IMQ 3.75% as compared to 5-FU 4%, with the same median value of 10 days for both treatments (P = 0.83). The main results are summarized in Table 2.

Discussion

This study reports non-inferiority in terms of efficacy, tolerability, wound healing time, and the cosmetic result of topical IMQ 3.75% treatment compared to topical 5-FU 4% treatment in AK management. The strength of this study is the use of a split-face protocol that reduces the variability between patients, resulting in a more accurate evaluation of treatment outcomes. Various trustworthy guidelines for treating AKs have been established by various organizations in the United Kingdom, the United States of America, and Europe [4,11,12]. These guidelines, which rely on either evidence or expert consensus, provide clinicians with a range of treatment options based on the different clinical manifestations of AKs.

Nowadays, limited studies point to topical 5-FU therapy as the most effective treatment for AKs. The choice of the most appropriate therapy continues to be based on the clinical experience of the single physician and on expert consensus guidelines, taking into account the clinical presentation, clinical setting, patient type, and absolute and relative contraindications assessed on a case-by-case basis.

Strong recommendations are reported by various groups regarding the efficacy and safety of topical therapies for AKs with topical IMQ (3.75% or 5%) and topical 5-FU (4% or 5%) based on several randomized clinical trials (RCT) [4,11,12], although only a few small studies are present in

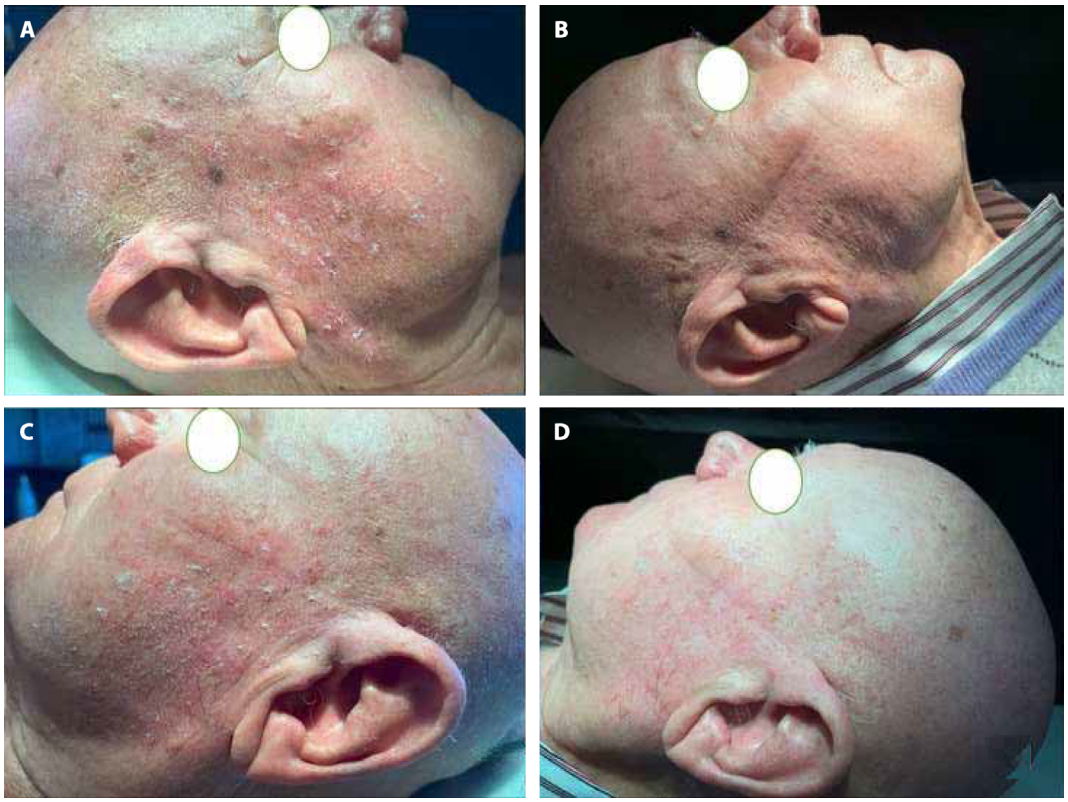

Figure 2. (A, B) Clinical photos in the same patient before and after treatment with imiquimod (IMQ) 3.75% cream applied on the right cheek and temporal area and (C, D) before and after treatment with 5-fluorouracil (5-FU) 4% cream applied on the left cheek and temporal area.

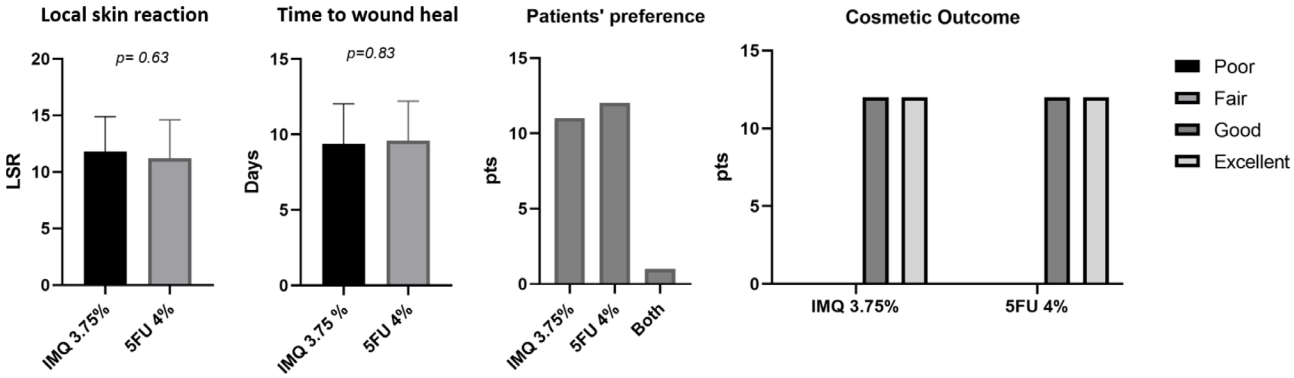

Figure 3. Graphic representation of (A) local skin reaction (LSR), (B) time to wound healing, (C) patients' preference and (D) cosmetic outcome after treatment in patients treated with imiquimod (IMQ) 3.75% cream and 5-fluorouracil (5-FU) 4% cream.

literature that directly compared the efficacy and safety of these therapies [4]. Numerous articles are available in the literature about the comparison of the various treatments for Aks, with discordant conclusions. A meta-analysis product by Gupta et al. assessed the efficacy of various interventions for the treatment of Aks, including topical 5-FU 5% and topical imiquimod 5% and determined that 5-FU was superior to all treatments [13]. In another systematic review, the authors did not suggest the superiority of 5-FU in achieving a higher percentage reduction in AKs compared to PDT (Photodynamic Therapy), cryotherapy, imiquimod, ingenol mebutate (IMB), trichloroacetic acid (TCA), and ablative fractional laser (AFXL) [14]. In another real-world, community-based cohort retrospective study, Neugebauer et al. compared the effectiveness of topical 5-FU versus topical IMQ for the treatment of AKs in a cohort of 5700 patients, and they found that 5-FU appeared to be significantly more effective than IMQ in the short-term (two years), but not long-term (five years) prevention of subsequent AKs. Unfortunately, this study lacks a standardized therapy regimen (concentration, dosing interval, and duration were not specified) and homogeneity between the two groups, making it

Table 2. Average Variation (ΔT0-T1) in Actinic Keratoses (AKs) Number, Local Skin Reaction Score (LSR), Cosmetic Outcome, and Time to Wound C healing in Days with Imiquimod (IMQ) 3.75% cream and 5-florouracil (5-FU) 4% Cream.

	IMQ 3.75%	5-FU 4%	P-Value
Average variation (ΔT0-T1) in AK number	7.83 [median 7, range 3-21]	6.87 [median 6.5, range 2-18]	0.35
Local skin reaction (LSR) score	11.79 [median 12, range 6-16]	11.20 [median 12, range 6-16]	0.63
Cosmetic outcome	Excellent 12	Excellent 12	
	Good 12	Good 12	
Mean time to wound healing in days	10 [median 10, range 5-16]	10 [median 10, range 6-15]	0.83

difficult to compare the efficacy and tolerability of the two treatments [15].

This study compared the efficacy of 5-FU 4% versus IMQ 3.75% with a split-face protocol. Only a few RCTs are available in the literature that directly compare the efficacy and tolerability of topical IMQ and topical 5-FU. An RCT published by Tanghetti et al. compared IMQ 5% cream applied twice weekly for 16 weeks versus 5-FU 5% cream applied twice daily for 2–4 weeks in 36 patients with four or more AKs randomly assigned. Tanghetti et al. concluded in their study that 5-FU 5% was more effective than IMQ 5% in exposing what were presumed to be subclinical AKs and in reducing the final AK count, while tolerability was shown to be similar [16]. However, the protocol of this study, applied to a small sample size, may have been affected by high variability among enrolled subjects, making it difficult to compare outcomes in a homogeneous manner. In another RCT, Jansen et al. found topical 5-FU to be superior to topical IMQ, MALT-PDT, and IMB [17].

Krawtchenko et al., in their RCT, compared the effectiveness of topical 5% IMQ cream applied three times per week for four weeks, topical 5% 5-FU ointment applied twice daily for four weeks, and cryosurgery, concluding that imiquimod treatment of AK resulted in superior sustained clearance and cosmetic outcomes compared with cryosurgery and 5% 5-FU [18].

This study makes a valuable contribution to the evaluation of the effectiveness of different treatments available for AKs by facilitating the comparison of two of the most commonly used and effective treatments through a split-face protocol. This protocol enhances the validity of the results obtained by improving internal control within the examined sample, as both treatments are performed on the same patient. This eliminates the variability stemming from individual differences such as age, sex, skin phototype, photodamage, disease burden, the influence of prior treatments, and so on. This, in turn, enhances the reliability and significance of the results [19]. Furthermore, the split-face protocol, as the same individual undergoes both treatments, mitigates the bias related to personal preferences or patient expectations, thereby contributing to more objective results. Additionally, the outcomes of the two treatments become simultaneously visible on the same patient, allowing for a direct and visual assessment of treatment efficacy by the clinician.

Limitations

The current study has certain limitations. First, it was not fully blinded, since only the investigator who assessed the treatment results was blinded, whereas the patients and other specialists were not. Second, the follow-up period was relatively short, which prevented us from assessing the occurrence of late relapses, the potential preventive effect on new lesion development, and the effectiveness in reducing or eliminating the risk of progression towards invasive SCC. One more limitation of our study is that we only treated two small areas (25 cm^2). This was done to compare the two treatments based on their approval status by The European Medicines Agency (EMA). However, in daily clinical practice, this scenario is rather unrealistic, as patients often have multiple AKs that spread over large areas of the face, scalp, hands, and sometimes other parts of the skin.

Conclusion

This study reports non-superiority in terms of efficacy, tolerability, wound healing time, and cosmetic outcome of topical IMQ 3.75% treatment compared to topical 5-FU 4% treatment in AK management. Furthermore, this randomized clinical trial conducted with a split-face modality was valuable in providing insights not only into effectiveness and safety but also into cosmetic outcomes, LSR, time to wound healing, and patients' preference. These factors significantly affect the patients' adherence to the treatment, particularly among elderly or frail patients, and may substantially influence the treatment's effectiveness.

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