Dermatology Practical & Conceptual

# Management of Local Skin Reactions Caused by 5-FU 4% Cream for the Treatment of Actinic Keratosis: A Delphi Consensus

Gabriella Brancaccio[1]*, Giulia Briatico[1]*, Zoe Apalla[2], Reinhard Dummer[3], Jan Eklind[4], Nicole Basset Seguin[5], Brigitte Dreno[6], Maria Concetta Fargnoli[7], Pascale Guitera[8], Markus V. Heppt[9], Christoph Hoeller[10], Thomas Jouary[11], Aimilios Lallas[12], Ulrikke Lei[13], Ulrike Leiter[14], Josep Malvehy[15], David Moreno Ramírez[16], John Paoli[17], Ketty Peris[18], Susanna Puig[15], Philippe Saiag[19], Eggert Stockfleth[20], Wilhelm Stolz[21], Alexander J. Stratigos[22], Class Ulrich[23], Ann-Marie Wennberg[24], Iris Zalaudek[25], Giuseppe Argenziano[1]

*equally contributed

1 Dermatology Unit, University of Campania, Naples Italy

2 Second Dermatology Department, Aristotle University of Thessaloniki, Thessaloniki, Greece

3 University Hospital Zurich and Kantonsspital, Aarau, Switzerland

4 Diagnostiskt Centrum Hud, Stockholm, Sweden

5 Dermatology Department, Saint-Louis Hospital, Paris, France

6 Nantes Université, INSERM, CNRS, Immunology and New Concepts in ImmunoTherapy, INCIT, Nantes, France

7 San Gallicano, Dermatological Institute, IRCCS, Rome, Italy

8 Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital, and Melanoma Institute Australia and Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

9 Department of Dermatology, Uniklinikum Erlangen, Friedrich-Alexander University (FAU), Erlangen, Germany; Comprehensive Cancer Center Erlangen-European Metropolitan Area of Nuremberg (CCC ER-EMN) and CCC Alliance WERA, Erlangen, Germany; Bavarian Cancer Research Center (BZKF), Erlangen, Germany

10 Department of Dermatology, Medical University of Vienna, Vienna, Austria

11 Dermatology Unit, Hospital Francois Mitterrand, Pau, France

12 First Dermatology Department, Aristotle University of Thessaloniki, Thessaloniki, Greece

13 Department of Dermatology and Allergy, Copenhagen University Hospital – Herlev and Gentofte, Copenhagen, Denmark

14 Center for Dermatooncology, Department of Dermatology, University Hospital of Tuebingen, Tuebingen, Germany

15 Dermatology Department, Hospital Clínic de Barcelona, Universitat de Barcelona, IDIBAPS, Barcelona, Spain

16 Medical-&-Surgical Dermatology Service. Hospital Universitario Virgen Macarena, Sevilla, Spain

17 Department of Dermatology and Venereology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden and Region Västra Götaland, Sahlgrenska University Hospital, Department of Dermatology and Venereology, Gothenburg, Sweden

18 Dermatologia, Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy; UOC di Dermatologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Rome, Italy

19 Department of General and Oncologic Dermatology, Ambroise Paré hospital, APHP, & EA 4340 "Biomarkers in cancerology and haematooncology", UVSQ, Université Paris-Saclay, Boulogne-Billancourt, France

20 Department of Dermatology, Ruhr-University, Bochum, Bochum, Germany

21 Department of Dermatology, Faculty of Medicine, Ludwig-Maximilians-University, Munich, Germany

22 1st Department of Dermatology-Venereology, National and Kapodistrian University of Athens, Andreas Sygros Hospital, Athens, Greece

23 Charite-Universitiitsmedizin Berlin, Berlin, Germany

24 Department of Dermatology and Venereology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

25 Department of Dermatology and Venereology of the Hospital Clinics Giuliano Isontino (ASUGI), Maggiore Hospital, Trieste, Italy

**Key words:** Actinic keratosis, 5-fluorouracil, Local skin reactions

**Citation:** G Brancaccio, G Briatico, Z Apalla, et al. Management of Local Skin Reactions Caused by 5-FU 4% Cream for the Treatment of Actinic Keratosis: A Delphi Consensus. *Dermatol Pract Concept*. 2025;15(2): 5787. DOI: https://doi.org/10.5826/dpc.1502a5787

**Accepted:** March 18, 2025; **Published:** April 2025



**Funding:** Article processing charges were covered with the unconditioned support of Pierre Fabre Laboratories. The funder had no role in writing or reviewing the article, or in determining its contents. The views and ideas expressed herein are those of the authors alone. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Competing Interests:** None.

**Authorship:** All authors have contributed significantly to this publication.

**Corresponding Author:** Giulia Briatico, Dermatology Unit, University of Campania, Naples Italy. ORCID ID: (https://orcid.org/0000-0003-0421-3241),E-mail: giuliabriatico@gmail.com

## ABSTRACT

**Introduction:** Treatments such as 4% 5-fluorouracil (5-FU) cream have demonstrated strong efficacy in lesion clearance of actinic keratosis; however, local skin reactions (LSR) during treatment remain a significant challenge, potentially affecting patient adherence.

**Objective:** We sought to build consensus on management of LSR associated with 4% 5-FU using the Delphi methodology.

**Methods:** Twenty-eight expert dermatologists participated in a 3-round Delphi process. Experts evaluated LSR management strategies, including emollients, antibiotics, steroids, and treatment discontinuation. Agreement levels were measured using a 7-point Likert scale. Consensus was categorized as high if >80% of votes were within the 5–7 rating range and low when >25% were in the 1–3 rating range, with <25% of the votes in the 6–7 rating range. Other combinations of votes were considered as having moderate agreement.

**Results:** High agreement was achieved for the following statements: the approved daily schedule (once daily for 4 weeks) is the most appropriate (92.9%); mild LSR generally do not require intervention and do not impact treatment adherence (96.4%); severe LSR may benefit from temporary treatment interruption and emollient use, ensuring adherence without compromising efficacy (92.9%). The use of emollients (in parallel with the treatment with 5-FU) was considered not needed by most (moderate consensus, 64.3%). Experts emphasized the importance of clear communication about LSR during baseline consultation to enhance patient compliance.

**Conclusion:** This consensus provides practical guidance for managing LSR induced by 4% 5-FU, ensuring high adherence and optimizing treatment outcomes. Further research is needed to validate these findings and explore alternative management approaches.

## Introduction

Actinic keratosis (AK) presents as, dry, erythematous, scaly, and sometimes pigmented lesions developing in chronically sun-exposed body areas such as the face, scalp, neck, hands, and forearms. AKs result from abnormal proliferation of atypical epidermal keratinocytes, and they can progress into invasive cutaneous squamous cell carcinoma, which can produce distant metastasis [1]. It has been demonstrated that, in addition to clinically visible AK, subclinical or invisible lesions may also be present. If left untreated, these lesions contribute to field cancerization—an area of the epithelial surface more prone to developing multiple malignancies than normal skin due to DNA mutations caused by excessive sun exposure [2]. Therefore, timely treatment is crucial to improving patient outcomes.

Several studies have demonstrated the superiority of topical 5% 5-fluorouracil (5-FU) compared to 3% diclofenac, 5% imiquimod, and methyl aminolevulinate photodynamic therapy [3,4]. However, the occurrence of severe local skin reactions (LSR) during treatment can affect patient adherence [5] to therapy and therefore compromise efficacy. These reactions typically progress through three phases: an inflammatory phase characterized by intense erythema, an apoptotic phase marked by skin erosion, crusting, and scaling, and a healing phase during which epithelialization occurs. In 2020, the European Medicines Agency approved a novel 4% 5-FU formulation for the treatment of non-hyperkeratotic,

non-hypertrophic AK (Olsen grades I and II) [6]. The 4% formulation should be applied once daily, instead of twice daily application, as used for 5% 5-FU, for a maximum of 4 weeks. This schedule improves treatment compliance while maintaining high efficacy in clearance rate and risk of progression [7]. It was recently shown that the reduction in the treatment duration from 4 to 2-weeks can reduce the occurrence of severe LSR from 15% to 5% while maintaining an efficacy benefit [8].

To assess frequency and a standardized management of LSR, we performed a literature review including PubMed articles from 2017 to 2024 and combining MeSH terms "actinic keratosis' and "fluorouracil" and "skin reaction". In 2017, a case report [9] first underlined the need to be aware of LSR after the application of 5% 5-FU. A retrospective study [10] conducted in the Netherlands and enrolling 135 patients explored the frequency and severity of LSR and demonstrated that LSR affected almost 50% of the enrolled patients. The most common LSR was severe erythema, which was reported by 63 of 135 (46.7%) patients. Other commonly reported LSR were itching (28.9%), crusts (19.3%), burning sensation (21.5%), and scaling (18.5%).

After approval of the 4% 5-FU cream, the post hoc exploratory analysis of pooled data of safety populations from the two multicenter randomized phase 3 studies HD-FUP3B-048 and HD-FUP3B-049 compared LSR severity between 4% and 5% 5-FU [11]. For most LSR, severe ones were more common in patients treated with 5% 5-FU cream twice daily than in those treated with 4% 5-FU cream once daily. However, erythema and burning sensation were also reported in patients using 4% 5-FU cream [12] with the standard schedule. In this retrospective study on 98 patients, 67.3% reported burning sensation at four weeks, whereas 88.8% reported erythema. The authors concluded that both formulations could influence the adherence to the treatment because of LSR. In the literature, no specific strategies were found to reduce their impact. Only one study [13] explored adding emollients to prevent LSR, reporting no benefits.

In 2023, a qualitative analysis [14] was conducted on 10 participants treated with topical 5-FU who refused future treatment after discontinuation. The treatment's side effects were both physically and psychosocially burdensome for most participants. Following the treatment, most participants felt unprepared by their healthcare provider to deal with LSR.

## Objective

Since no specific recommendations for managing LSR following the application of 4% 5-FU were found in the literature, we aimed to identify procedures that would assist clinicians in maintaining high adherence to treatment by building consensus through a Delphi process.

## Methods

A Delphi method was chosen to investigate the extensive experience and opinions of international experts in the field regarding 4% 5-FU cream side effects management. The panel comprised 28 dermatologists working in referral centers for skin cancer prevention, diagnosis, and treatment. Three web-based surveys were conducted. The first and the second rounds were structured as open-ended or multiple-choice questions. First, the definition of LSR was established. LSR were defined according to the safety study [15] of 4% 5-FU formulation, in which LSR were evaluated by visual assessment of erythema, scaling/dryness, edema, crusting, and erosions. In this study, physicians used a four-point numerical scale to determine the average presence of these variables across all treated areas. The scale ranged from 0 to 3, where 0 indicated no reaction (no evidence of a response), 1 represented a mild reaction (faintly detectable), 2 signified a moderate reaction (clearly noticeable), and 3 denoted a severe reaction (marked, extensive, or bothersome). According to this description, clinical images were chosen and shown to qualify and quantify the three types of LSR (Figure 1). Then, in the first round, several questions were posed regarding the treatment schedule and the management of LSR, including the use of antibiotic therapy, steroids, emollients, or discontinuing the treatment. Participants were also asked whether AK clearance was achieved despite the presence of LSR or treatment discontinuation.

The second round was designed to clarify expert behavior in situations where an agreement had not been reached in the first round. Responses were analyzed, and a list of summarizing statements were prepared to evaluate the experts' agreement in the third round. Participants rated their agreement using a 7-point Likert scale (strongly agree, agree, somewhat agree, neither agree nor disagree, somewhat disagree, disagree, strongly disagree). Again, results were collected, analyzed, and finally reviewed.

Panel agreement was "high" if >80% of votes were within the 5–7 rating range. Agreement was low when >25% of votes were in the 1–3 rating range and <25% of the votes in the 6-7 rating range. Other combinations of votes were considered "moderate". The mean of the response of each question was calculated and interpreted following intervals with higher and lower limits of a 7-point Likert scale (Strongly Disagree: 1.00–1.86; Disagree: 1.87–2.72; Somewhat disagree: 2.73–3.58; Neutral: 3.59-–4.44; Somewhat agree: 4.44–5.30; Agree: 5.31–6.16; Strongly agree: 6.17–7.00).

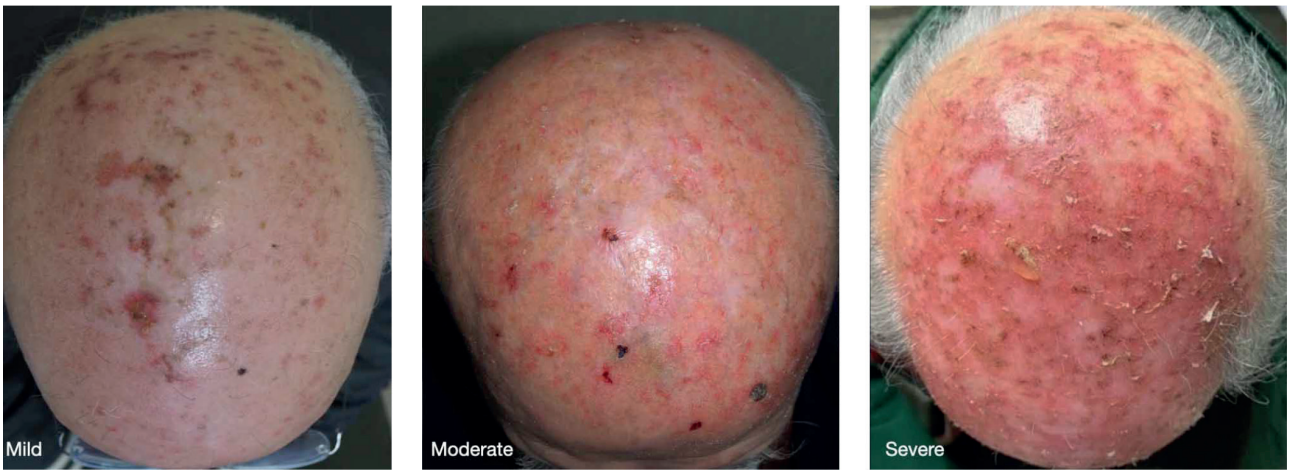


**Figure 1.** Three types of local skin reactions with 4% 5-fluorouracil cream: mild with small erythematous areas, moderate with larger involved areas, and severe with diffuse erythema, crusts, and scales.

## Results

Participants were based in Europe, with the addition of three Australian representatives. Almost half of them (46.2%) prescribed 4% 5-FU cream between five and 10 times/month, 30.8% more than 10 times/month, and 23% less than five times/month. Experts reported that 70% of patients experienced LSR. Among these, 20% had mild reactions, 30% moderate, and only 20% of patients had severe reactions.

The statements whose agreement rate was assessed in the third round are reported below and summarized in Figure 2.

1. **The conventional schedule of 4% 5-FU administration (daily for 4 weeks) is the most appropriate.**
   Most participants (92.9%) agreed with the statement, suggesting high consensus for the approved administration schedule. Overall, data showed support for the statement, with a mean of 5.8 (SD:1.33) and a mode of 6 (agree). Among the 7.1% that disagreed, the most frequently proposed alternative schedules were a 2-week treatment or continuation until a strong reaction occurred. However, there are no data in the literature regarding the efficacy of these alternative approaches.
2. **The use of emollients in parallel with the treatment with 5-FU is not necessary.**
   A moderate consensus was reached for this statement, with 64.3% agreement balanced by 28.6% of disagreement, a mean of 4.9 (SD:1.93) and a mode of 6 (agree). The strength of this statement is supported by a recent international phase 4 clinical trial[13] which was conducted to evaluate whether adding an emollient to topical 4% 5-FU could reduce the frequency and severity of LSR during a 4-week treatment period. The study compared the intervention group to a control group receiving 4% 5-FU alone in patients with AK. The primary goal was to measure the severity of LSR—such as erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration—at week 4 of treatment (or earlier, in cases of significant LSR). A total of 141 patients participated in the efficacy analysis, with 71 in the intervention group and 70 in the control group. Results showed no significant clinical difference between the groups regarding the total LSR score at week 4. Similarly, no difference was observed in individual LSR scores at any time point.

   Among the possible reasons explaining why this study showed no differences in the two groups, it is worth mentioning that the 4% 5-FU formulation contains highly purified peanut oil, which has effective moisturizing properties [15].
3. **Any potential LSR should be explained during the baseline examination.**
   All the participants strongly support this approach, with a mean of 6.8 (SD:0.4) and a mode of 7. All answers fell into the "strongly agree" and "agree" range.

   Several studies [9,10] highlighted the importance of informing patients about potential LSR when using topical 5-FU. They noted that the severity and frequency of LSR should be communicated clearly during consultations to avoid distress and treatment dropout, as unexpected reactions can lead to premature discontinuation of therapy. Moreover, explaining the mechanism of the drug —inflammation and visible reaction as a sign of its effectiveness [10]— can help patients view these symptoms as part of the healing process rather than a cause for alarm. This approach improved patient compliance and satisfaction with the treatment procedure.


**Figure 2.** Statement numbers corresponding to the following:

*Q1. The conventional schedule of 4% 5-FU administration (daily for 4 weeks) is the most appropriate:* 92.9% agreed that the daily administration for four weeks is the most appropriate (mean: 5.8, SD: 1.33). *Q2. The use of emollients in parallel with the treatment with 5-FU is not necessary:* a moderate consensus (64.3% agreement) indicated that emollients are not necessary from the first application (mean: 4.9, SD: 1.93). *Q3. Any potential local skin reactions should be explained during the baseline examination:* all participants (100%) agreed that potential LSR should be explained during the baseline examination (mean: 6.8, SD: 0.4). *Q4. The patient should be checked 4 to 8 weeks after baseline/treatment initiation:* 85.7% agreed on following patients 4-8 weeks post-treatment (mean: 5.75, SD: 1.4). *Q5. Mild LSR do not require intervention:* 96.4% agreed that mild LSR do not require intervention (mean: 6.3, SD: 0.9). *Q6. Even without intervention for mild LSR, most patients complete the treatment schedule:* 89.3% confirmed that patients generally complete the treatment schedule despite mild LSR (mean: 5.9, SD: 1). *Q7. Moderate LSR do not require intervention:* 71.4% agreed that moderate LSR do not require intervention (Mean: 5.1, SD: 1.5). *Q8. Even without intervention for moderate LSR, most patients complete the treatment schedule:* 67.9% indicated that patients usually complete treatment despite moderate LSR (mean: 5.2, SD: 1.4). *Q9. In case of severe LSR, treatment should be paused for a few days during which emollients may be prescribed. The treatment schedule should then be completed:* 92.9% agreed that treatment should be paused for severe LSR, with the possibility of using emollients (mean: 5.9, SD: 1.3). *Q10. The use of local steroids is not recommended in case of severe LSR:* 57.1% agreed that local steroids are not recommended for severe LSR (mean: 4.8, SD: 1.7). *Q11. This approach for severe LSR controls the reaction while maintaining optimal treatment results:* 89.2% affirmed that pausing treatment ultimately leads to successful completion (mean: 5.9, SD: 0.8).

4. **The patient should be checked 4 to 8 weeks after baseline/ treatment initiation.**
   Regarding this, 85.7% of participants agreed that the patient should be visited at the end of the treatment or at least one month after (mean 5.75 with SD: 1.4, and mode: 6). Among those who provided different approaches (10.71%), some panelists stated they do not visit the patient routinely after 5-FU prescription or do so only upon patient's request. Otherwise, (s)he will be examined at the next routine base skin check.

   As reported in the phase 3 study [6], the clearance of AK lesions should be evaluated at the end of the inflammation phase. LSR are transient and resolve within 2–4 weeks after the end of treatment. Consequently, follow-up eight weeks after starting the treatment can be considered adequate to evaluate both efficacy and safety.
5. **Mild LSR do not require intervention**
   Mild LSR, characterized by faintly detectable erythema or dryness, generally do not need clinical intervention. There was high agreement among panelists (96.4% agreement, mean: 6.3, and SD: 0.9) who underscored the transitory and self-limiting nature of mild reactions. Panelists also highlighted that the mild intensity of these symptoms often does not generate undue alarm in patients. Supporting this position, prior studies [6-10] indicated that minimal LSR are a natural response to the pharmacological action of 5-FU and are indicative of its activity against the targeted lesions. Local therapy with emollients and temporary suspension of 3–7 days were the most frequent approaches among those who support intervention in this category.
6. **Even without intervention for mild LSR, most patients complete the treatment schedule**
   With 68.7% of responses in the strongly agree/agree range and another 10.71% with moderate agreement (total 89.3%), the panelists confirmed that mild LSR do not impact adherence, thus permitting the treatment schedule to be successfully completed (mean 5.9, SD:1; mode 6).
7. **Moderate LSR do not require intervention**
   Reactions of moderate severity, such as clearly noticeable erythema, scaling, or localized swelling, elicited more variability in expert opinion. While 71.4% of the panelists agreed that intervention is generally not required (mean: 5.1, SD: 1.5, and mode: 6), a notable minority (21.4%) supported the use of emollients or temporary treatment suspension (up to 14 days) to mitigate symptoms. Experts highlighted that patients should be well-informed during baseline consultations about the potential for moderate reactions and reassured that such reactions are not typically harmful or treatment-limiting. Some panelists suggested dose adjustments, such as reducing application frequency to three times weekly, as an alternative management strategy for patients with persistent moderate LSR.
8. **Even without intervention for moderate LSR, most patients complete the treatment schedule**
   Despite the variability in management approaches, 67.9% of panelists agreed that patients experiencing moderate LSR usually complete their treatment schedule (mean: 5.2, SD: 1.4, mode: 6), while 21.4% of experts disagreed because moderate LSR could escalate and become severe or cause significant discomfort, leading to treatment discontinuation. These instances highlight the need for individualized patient support. Further research could explore predictors of non-compliance in this subset of patients to optimize intervention strategies.
9. **In case of severe LSR, treatment should be paused for a few days during which emollients may be prescribed. The treatment schedule should then be completed.**
   This statement reached a strong agreement (92.9%) among panelists (mean 5.9, SD:1.3, and mode: 6) following two rounds. In the first round, all the management possibilities of severe LSR were explored, then the various interventions were grouped into specific categories and resubmitted to achieve consensus in the second round. In detail, the experts agreed to pause the treatment until improvement of the symptoms, which usually occurs in seven days (93% of the answers). Only two experts proposed more than seven days of suspension (15 days). Insights into factors influencing the occurrence of severe LSR may help to understand the best approach. In the post hoc exploratory analysis[11] of the safety of 4% 5-FU, the authors found that the incidence of severe erythema was significantly higher in patients with at least 10 AK lesions (46%) than in patients with 5–10 lesions (28%; $P < 0.001$). Similar results were observed for the other LSR. This pre-treatment threshold of 10 lesions may assist healthcare professionals to prevent which patient could have severe LSR.
10. **The use of local steroids is not recommended in case of severe LSR**
    With 57.1% in agreement and 28.6% in disagreement (mean: 4.8, SD: 1.7, and mode: 6), this statement reached moderate agreement. Since erythema and scaling could be assimilated to a localized acute contact dermatitis, they may be successfully treated with mid- or high-potency topical steroids. However, since the effects disappear with the suspension of the drug, this intervention does not necessarily have to be considered mandatory.
11. **This approach for severe LSR controls the reaction while maintaining optimal treatment results.**
    Despite the differences in the use of steroids, almost all experts (89.2%) confirmed that pausing the treatment led to the completion of the treatment even in patients

who experienced severe LSR (mean: 5.9, SD: 0.8, and mode: 6). 4% 5-FU already showed[15] an improved safety profile compared with 5% 5-FU, with a lower rate of adverse events leading to treatment discontinuation (10.1% versus 14.9%, respectively), while maintaining optimal treatment results, with a 100% lesion clearance at four weeks of 54.4% versus 57.9%, respectively (≥75% lesion clearance achieved at four weeks in 80.5% versus 80.2%, respectively, and percentage change in AK lesions count from baseline of 80.1% versus 79.0%). For these reasons, a few days' suspension do not impact the total efficacy of the treatment.

## Conclusions

This study addresses the challenge of managing LSR associated with topical 4% 5-FU treatment of AK. Through a Delphi method, agreement was established on key strategies to improve adherence and optimize treatment outcomes. High agreement among experts confirmed the efficacy of the approved treatment schedule (once daily for four weeks) and the transitory nature of mild LSRs, which generally do not require intervention. For severe LSR, temporary interruption of treatment combined with emollient application emerged as the preferred approach, allowing patients to resume therapy without compromising its efficacy. The use of emollients (in parallel with the 5-FU treatment) was not considered necessary by most panelists (moderate agreement). The study also highlighted the critical role of clear patient education during baseline consultations, particularly regarding the expected progression of LSR and their association with treatment efficacy. These findings might be helpful for clinicians managing LSR with 4% 5-FU and maintaining high treatment adherence. However, the need for further research remains, particularly to validate alternative schedules and management strategies.

## References


1. Dianzani C, Conforti C, Giuffrida R, et al. Current therapies for actinic keratosis. *Int J Dermatol*. 2020;59(6):677-684. DOI:10.1111/ijd.14767.
2. Willenbrink TJ, Ruiz ES, Cornejo CM, Schmults CD, Arron ST, Jambusaria-Pahlajani A. Field cancerization: Definition, epidemiology, risk factors, and outcomes. *J Am Acad Dermatol*. 2020;83(3): 709-717. DOI:10.1016/j.jaad.2020.03.126.
3. Wu Y, Tang N, Cai L, Li Q. Relative efficacy of 5-fluorouracil compared with other treatments among patients with actinic keratosis: A network meta-analysis. *Dermatol Ther*. 2019;32(3): 1-6. DOI:10.1111/dth.12822.
4. Jansen MHE, Kessels JPHM, Nelemans PJ, Kouloubis N, Arits AHMM, van Pelt HPA, Quaedvlieg PJF, Essers BAB, Steijlen PM, Kelleners-Smeets NWJ MK. Randomized Trial of Four Treatment Approaches for Actinic Keratosis. *N Engl J Med*. 2019;7;380(10) DOI: 10.1056/NEJMoa1811850
5. Shergill B, Zokaie S CA. Non-adherence to topical treatments for actinic keratosis. *Patient Prefer Adherence 2013; 835–41*. DOI: 10.2147/PPA.S47126
6. Pierre Fabre Dermatologie. Tolak 40 mg/g cream: summary of product characteristics. 2020. https:// docetp.mpa.se/LMF /Tolak%20cream%20ENG% 20SmPC_09001bee809dbaa1.pdf. Accessed 8 Dec 2020. 20.
7. Ezzedine K, Painchault C BM. Systematic Literature Review and Network Meta-analysis of the Efficacy and Acceptability of Interventions in Actinic Keratoses. *Acta Derm Venereol*. 2021;101(1). DOI: 10.2340/00015555-3690
8. Heppt M V., Ulrich C. Does early discontinuation of topical 4% 5-fluorouracil affect lesion clearance for actinic keratosis? Results from a dose-ranging study. *J Eur Acad Dermatology Venereol*. 2024;(July):1-3. DOI:10.1111/jdv.20441.
9. Komal Chughtai, Rahul Gupta, Sunil Upadhaya SAH. Topical 5-Fluorouracil associated skin reaction,. *Oxford Med Case Reports*. 2017;(8). DOI: 10.1093/omcr/omx043
10. S. Ahmady, E.M.M. Oyen, M.H.E. Jansen, P.J. Nelemans, J.P.H.M. Kessels, N.W.J. Kelleners-Smeets KM. Patient-reported skin reactions to 5% 5-fluorouracil in treatment of actinic keratosis. *Br J Dermatol*. 2021;185(5):1050-1052. DOI: 10.1111 /bjd.20570
11. Stockfleth E, Bégeault N, Delarue A. Intensity of Local Skin Reactions During 5-Fluorouracil Treatment Related to the Number of Actinic Keratosis Lesions: A Post Hoc, Exploratory Analysis. *Dermatol Ther (Heidelb)*. 2022;12(2):467-479. DOI:10.1007 /s13555-021-00668-9.
12. Briatico G, Brancaccio G, Scharf C, et al. Real-World Experience With Topical 5-Fluorouracil 4 % (40 mg/g) Cream for the Treatment of Actinic Keratosis. 2023;13(2):4-9. DOI: 10.5826 /dpc.1302a151
13. Stockfleth E, Jouary T, Farnetani F, et al. Severity of Local Skin Reactions with 4% 5-Fluorouracil Plus Emollient versus 4% 5-Fluorouracil Alone in Patients with Actinic Keratosis: A Single-Blind Randomised Trial. *Dermatol Ther (Heidelb)*. 2023;13(4):1013-1027. DOI:10.1007/s13555-023-00902-6.
14. Singh R, McCain S, Feldman SR. Refusal of Retreatment With Topical 5-Fluorouracil Among Patients With Actinic Keratosis: Qualitative Analysis. *JMIR Dermatology*. 2023;6:1-9. DOI:10.2196/39988.
15. Dohil MA. Efficacy, Safety, and Tolerability of 4% 5-Fluorouracil Cream in a Novel Patented Aqueous Cream Containing Peanut Oil Once Daily Compared With 5% 5-Fluorouracil Cream Twice Daily: Meeting the Challenge in the Treatment of Actinic Keratosis. *J Drugs Dermatol* 2016 Oct 1;15(10)1218-1224 PMID 27741339.