REVIEW ARTICLE

Evaluating the Efficacy and Safety of 4% 5-Fluorouracil Cream in Patients with Actinic Keratosis: An Expert Opinion

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Actinic keratosis is a lesion that develops in sun-exposed areas of the skin and is considered to be a precancerous condition or an early *in situ* squamous cell carcinoma. Treatment of actinic keratosis is important for reducing skin cancer risk, with treatment choice based on patient-, lesion- and treatment-related considerations. Of the topical treatments used for field-directed therapy, those containing 5-fluorouracil are among the most effective and widely prescribed. The most recently developed topical 5-fluorouracil preparation (Tolak®; Pierre Fabre, France) contains 4% 5-fluorouracil in an aqueous cream. This narrative review discusses data on 4% 5-fluorouracil cream to treat actinic keratosis, and provides the authors' expert opinion on issues associated with it use. The effect of the cream has been evaluated in phase 2 and 3 trials of adult patients with actinic keratosis on the face, ears or scalp. These trials included patients with severe baseline disease, defined by high lesion counts and large-size treatment fields, which possibly affected the proportion of patients who were able to achieve complete clearance. Other efficacy parameters (e.g. percentage change in lesion count, ≥75% clearance of lesions or clinically significant changes in validated severity scales) should also be assessed to fully evaluate 4% 5-fluorouracil treatment efficacy in these patients. Nevertheless, 4% 5-fluorouracil is associated with high efficacy, a low level of recurrence and a satisfactory safety profile.

Key words: field cancerization; fluorouracil; keratosis, actinic; safety; treatment efficacy.

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SIGNIFICANCE

Actinic keratoses are lesions that appear on photodamaged skin (e.g. face, neck and upper limbs) preceding or accompanying invasive skin cancer and are typically treated with creams containing 5-fluorouracil. This article reviews clinical trial data on how a new cream containing 4% 5-fluorouracil performed in adults with actinic keratosis. Treatment with 4% 5-fluorouracil cream was highly efficacious, safe, and prevented disease recurrence in approximately 27% of patients who achieved complete clearance of lesions in phase 3 studies. However, all trials were performed in patients with severe disease and numerous actinic keratosis lesions, making it more difficult for more patients to achieve complete clearance. Thus, other endpoints, such as percentage change in lesion count, ≥75% clearance of lesions or clinically significant changes in validated severity scales,may better reflect the efficacy of 4% 5-fluorouracil.

Actinic keratosis (AK) is a lesion that develops in sun-exposed areas of the skin, such as the face, neck, arms and hands, especially in fair-skinned individuals (1, 2). AK is one of the most common skin conditions seen in dermatology practice, with a prevalence of ~30% among adults attending dermatology clinics in Europe (3, 4). The prevalence of AK increases with age; it is higher in elderly individuals, particularly bald men (3–8).

AK occurs as a result of cumulating DNA mutations caused by ultraviolet (UV) radiation (9), and is considered to be a precancerous condition or an early *in situ* squamous cell carcinoma, since it can develop into cutaneous squamous cell carcinoma (cSCC) (10). It is noteworthy that, all AK lesions have the potential for progression to invasive cSCC, regardless of the thickness of the cutaneous changes (11). According to a systematic review, the rate of conversion from AK to cSCC varies from 0% to 0.075% per lesion per year in patients with no history of non-melanoma skin cancer (NMSC), but is higher (0.53% per lesion per year) in patients with a history of NMSC (10). Not only does the risk of cSCC among patients with AK increase with skin cancer history, but it also increases with age, immunosuppression, and the extent (lesion count and size of the affected area) of the AK (2, 5).

Thus, early and consequent AK treatment is considered to be an important strategy for reducing the risk of skin cancer (2), with the choice of treatment based on patient-, lesion- and treatment-related considerations (**Fig. 1**) (12). For patients with few isolated lesions, treatment can be lesion-directed, and may include cryotherapy, laser treatment, surgery (excision, curettage), photodynamic therapy or topical medications (2, 12–14). In practice, however, patient discomfort, potential adverse events, and the time required by the physician imply that there is a limit to the number of lesions that can be treated indi-

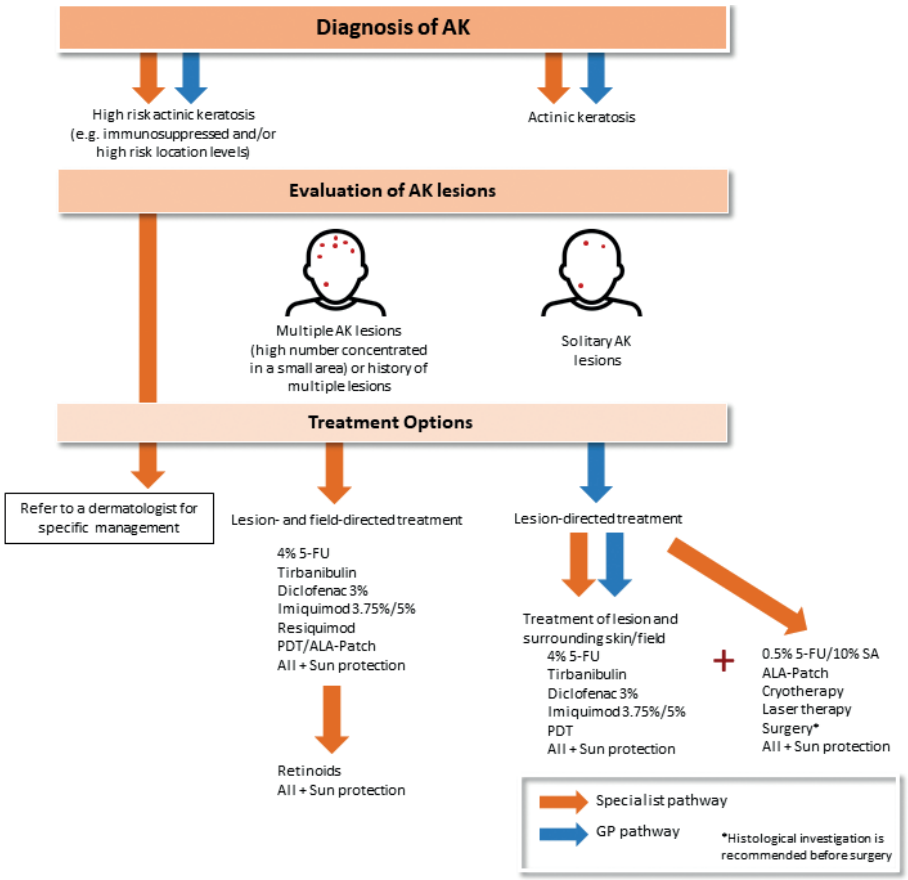

Fig. 1. Suggested treatment algorithm for actinic keratosis (AK) based on disease severity and patient characteristics (23). Figure adapted from Fig. 1 of Stockfleth E, et al. Eur J Dermatol. 2008; 18; 651–659, with permission from John Libbey Eurotext Plc. 5-FU: 5-fluorouracil; ALA: aminolaevulinic acid; GP: general practitioner; PDT: photodynamic therapy; SA: salicylic acid.

vidually (2). Therefore, for most patients, a field-directed approach is preferred, often combined with lesion-directed therapy (Fig. 1) (12, 13). This is particularly true for patients whose AK lesions are surrounded by areas of UV-related skin damage, such as telangiectasia, atrophy or dyspigmentation, which indicate field cancerization and significant UV-induced damage (12).

Of the topical treatments used for field-directed therapy, those containing 5-fluorouracil (5-FU) are among the most effective and widely prescribed (15–19). The most recently developed topical 5-FU preparation (Tolak®; Pierre Fabre, France) contains 4% 5-FU in a moisturizing aqueous cream and is applied once daily for 4 weeks (compared with the 5% 5-FU cream, which is typically applied 1–2 times daily). The aim of this narrative review is to allow the expert authors to examine the most recent clinical trial data with 4% 5-FU cream, focusing on the study endpoints and patient inclusion criteria, and how these may influence interpretation of the study results.

PRINCIPLES OF TOPICAL TREATMENT OF ACTINIC KERATOSIS

As part of the continuum of actinic skin damage, AKs are managed rather than cured (13). Moreover, the natural history of AK is dynamic, and characterized by spontaneous regression and recurrence, even in the absence of active treatment (10, 20). The aim of AK treatment is to eradicate as many lesions as possible, including subclinical lesions in the field of cancerization, to maintain the longest possible recurrence-free interval, reduce the need for additional spot treatments and decrease the risk of the patient developing an invasive SCC (21, 22).

Patients can often be managed by primary care physicians (13, 23), with referral to a specialist when the lesions do not respond to conventional treatments, are multiple and/or relapsing and/or difficult to treat, are present in immunosuppressed patients, or when there is concern that the lesions are not actually AK but rather cSCC (13). Treatment decisions should consider clinical presentation, comorbidities, risk factors (e.g. immunosuppression), and life expectancy, but should also take into account how the patient feels about the AK (cosmetic burden, skin cancer risk) and treatment strategy, method of application, expected efficacy of treatment, burden of treatment (side-effects, frequency of administration), need for specialist referral and availability and cost of treatment (12, 13, 24). Topical therapies are commonly used because they do not require specialist referral and are suitable for lesion- or field-directed therapy (2, 13). They are particularly useful when there is a high density of AK lesions with indistinct borders and adjacent field cancerization (2).

Table I. Suggested outcomes for assessment of actinic keratosis (AK) treatment

Efficacy outcomes considered to be of critical importance by the European Academy of Dermatology of Venereology (EADV) (14)	Core set of outcomes developed by a US Delphi consensus group of dermatologists and patients with AK (25)
Mean reduction in lesion counts (absolute [preferred] or percentages)	Percentage of AKs cleared
Participant complete clearance rate (rate of participants with complete clearance of all lesions within a predefined field)	Complete clearance of AKs
Participant partial clearance rate (rate of patients with at least 75% reduction in AK lesion count within a predefined field)	Severity of adverse events
Investigator global improvement index (rate of participants rated as "completely improved" by the investigator)	Patient perspective on effectiveness
Participant global improvement index (rate of participants self-assessed as "completely improved")	Patient-reported future treatment preference
	Rate of recurrence

TOPICAL TREATMENT EFFICACY ASSESSMENT

The efficacy of topical therapy can be assessed in a number of ways (10); a systematic review by Reynolds et al. (2020) identified 137 unique outcome measures for AK treatment efficacy in the literature (25). The European Academy of Dermatology and Venereology (EADV) lists 5 outcomes as critically important in the assessment of AK treatment efficacy (**Table I**). While complete clearance rate (CCR) is one of these outcomes, the list also includes a partial (but clinically meaningful) clearance response (PCR) of ≥75% reduction in lesions within a predefined field, as well as the mean reduction in lesion counts from baseline (14). Reynolds and colleagues used a Delphi consensus process to define a set of core outcome measures for the assessment of AK (Table I) (25). These include the CCR and PCR for short-term efficacy assessment, but also include long-term outcomes, such as recurrence rate (25). Both sets of outcome measures include patient assessments of efficacy (14, 25), and the consensus set includes the patient's consideration of future treatment (25).

Regulatory agencies require assessment of the CCR of AK lesions as a key clinical trial outcome for the definition of short-term efficacy (4–12 weeks) (26). However, there are concerns that this "all or nothing" outcome measure is often unattainable, and therefore is too rigorous and may undervalue some effective treatments, particularly in patients with large-field disease where it is more difficult to achieve complete clearance (26). As a result, some dermatologists have recommended using absolute or percentage reductions in lesion counts, rather than using binary endpoints, such as CCR, to assess treatment efficacy in clinical practice (21,27).

CCR is affected by the size of the treated area and by the number of lesions present; this is not the case for the percentage reduction in lesion count (15, 27, 28). CCR decreases with an increasing number of baseline lesions (independent of treatment interventions), so patients with a higher number of lesions are less likely to achieve CCR, but may still derive substantial clinical benefit from treatment (28). This means that CCR is feasible in a small area, but is rarely attained over a wide area (e.g. whole face or scalp) (27). In addition, subclinical lesions may become apparent during treatment with some field-directed topical treatments (29), affecting the evaluation of CCR and giving a false-negative result.

Because CCR is highly dependent on the area treated and the baseline lesion count, it may not be able to accurately reflect the efficacy among distinct treatments, since clinical trial populations usually differ in their baseline disease characteristics (28). This phenomenon will be discussed in the context of the clinical trials with 4% 5-FU cream.

CLINICAL TRIALS WITH 4% 5-FLUOROURACIL CREAM

The once-daily 4% 5-FU cream has been evaluated in a phase 2 trial and two phase 3 trials in adult patients with AK on the face and/or ears and/or scalp (**Table II**) (15, 30). The phase 2 study included patients with ≥5 to ≤20 lesions at baseline, but the two phase 3 studies

Table II. Clinical studies evaluating the efficacy of 4% 5-fluorouracil (5-FU) cream over 4 weeks in adult subjects (≥18 years) with actinic keratosis (AK) on the face and/or ears and/or scalp (15, 30, 31)

Study	Design	Treatments	N	Baseline lesion count Mean (SD)	CCR (100% clearance) % of patients	PCR (≥75% clearance) % of patients	% change from baseline in lesion count Mean (SD)
HDFUDR045[a]	Randomized, single-blind (phase 2)	4% 5-FU cream OD	20	11.6 (4.2)	80.0	100.0	98.1 (4.2)[c]
		5% 5-FU cream BID	20	10.5 (3.5)	75.0	95.0	95.1 (9.8)[c]
		Vehicle	20[c]	9.7 (2.2)[c]	15.0[c]	20.0[c]	23.0 (38.7)[c]
HDFUP3B048	Randomized, single-blind[b] (phase 3)	4% 5-FU cream OD	353	14.4 (10.8)	54.4	80.5	81.2 (37.3)
		5% 5-FU cream BID	349	14.8 (10.6)	57.9	80.2	80.0 (47.2)
		Vehicle	70[c]	16.2 (15.1)[c]	4.3[c]	7.1[c]	17.7 (35.4)[c]
HDFUP3S049	Randomized, double-blind (phase 3)	4% 5-FU cream OD	50	19.2 (15.0)	24.0	74.0	56.9 (104.9)[c]
		Vehicle	50[c]	23.2 (18.5)	4.0[c]	10.0[c]	4.3 (61.0)[c]

[a]This study had two other treatment arms with non-approved regimens (4% 5-FU OD for 2 weeks, 4% 5-FU BID for 2 weeks and 4% 5-FU BID for 4 weeks) that are not reported in this table. [b]This study was double-blind except that subjects were not blinded to dosing frequency (via double-dummy methodology or similar); investigators were blinded to dosing frequency. [c]Pierre Fabre, Data on file.
BID: twice daily; CCR: complete clearance rate; OD: once daily; PCR: partial clearance rate (≥75% reduction from baseline in lesion count); SD: standard deviation.

had no upper limit for AK lesions, so any patient with ≥5 lesions could be included, irrespective of the total number they had, and, as such, the total size of the treated fields could be large. AK lesions had to be ≥ 4 mm in diameter, but no larger than 1 cm (30).

In all studies, the primary endpoint was the proportion of patients who achieved a CCR of 100% (i.e. clearance of all lesions) at the final follow-up visit 4 weeks after the end of treatment in the intent-to-treat population. Secondary endpoints included the proportion of patients with PCR, and the percentage change from baseline in lesion count at 4 weeks (30). Patients who achieved CCR in the two phase 3 studies could enter a long-term follow-up phase in which they were assessed at 12 months after treatment (31).

As shown in Table II, the mean baseline lesion count differed between the studies (15); patients in the phase 3 HDFUP3S049 study had the highest baseline lesion count (15). The disease severity also differed between these studies (32). For example, in the HDFUP3S049 study, only 26% of patients in the 4% 5-FU group had mild AK, compared with 48% of patients using 4% 5-FU and 44% using 5% 5-FU in the phase 3 HDFUP3B048 study (32). The CCR rate was lowest in the HDFUP3S049 study, in which patients had the highest baseline lesion count and most severe disease (15, 31).

A post-hoc analysis of the studies with 5-FU cream (including the 4% formulation) showed a marked negative correlation between mean baseline lesion count and CCR ($p<0.001$; **Fig. 2**a) (15). Secondary endpoints, such as PCR (≥75%) and the change from baseline in lesion count, also showed a relationship with baseline lesion count, but the impact of lesion count on these parameters was much less marked (Figs 2b–c).

Among the 204 patients who achieved CCR in the phase 3 studies, 56 (27.4%) remained clear of AK lesions at 12 months, and 110 (53.9%) had AK recurrence; the other 38 patients were lost to follow-up and could not be assessed at 12 months post-treatment (31).

Another factor that is relevant in AK treatment is the severity of local skin reactions that occur during topical therapy. When compared with twice-daily 5% 5-FU cream in the phase 2 study, once-daily 4% 5-FU cream was associated with a similar CCR, but had superior tolerability to 5% 5-FU, with a lower rate of application site skin irritation (30% vs 60%) and fewer adverse events overall (30). A post-hoc analysis of the two phase 3 studies with 4% 5-FU found that patients with ≥10 baseline AK lesions had more than twice the rate of severe scaling, and were more likely to experience moderate or severe pruritus or stinging, compared with patients who had <10 skin lesions at baseline (32). Therefore, the number of visible lesions at baseline influences not only the efficacy parameters but also the local tolerability assessments for field-directed therapies.

DISCUSSION

Baseline lesion count is an important consideration in both the clinical assessment of an individual patient with AK, and in the assessment of treatment efficacy. Patients who develop more invasive forms of skin cancer tend to have more severe AK (i.e. more lesions, redder or thicker lesions, wider area affected) (33, 34). Guidelines advocate that treatment decisions are based on AK severity and risk of malignant transformation (2, 12–14). Therefore, there is a greater clinical imperative to efficiently treat AK in patients with higher baseline lesion counts.

As described above, CCR is usually the primary endpoint of clinical trials to support the regulatory approval of AK treatment, but CCR is influenced by baseline lesion count, affecting any assessments of the comparative efficacy of AK treatment. Since few head-to-head comparative studies exist, network meta-analyses have been used to rank the efficacy of different treatments, but these evaluate CCR as the primary outcome measure without adjusting for baseline lesion count (16, 19, 35–37). Indeed, clinical trials of field-directed topical therapies for AK show marked heterogeneity in baseline lesion count (**Fig. 3**), with the mean ranging between 5 and 32 lesions (38). The three studies included in the current review all had mean baseline lesion counts of >10

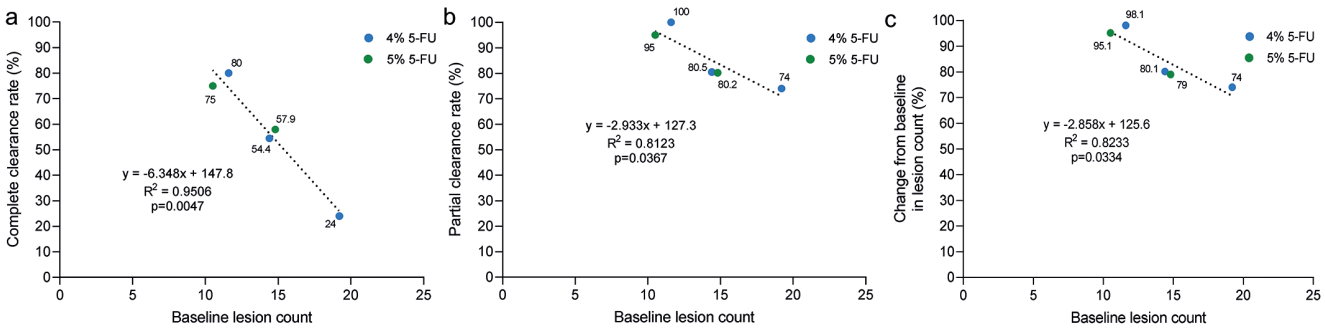

Fig. 2. Correlation between baseline lesion count and (a) complete clearance rate; (b) partial clearance rate (≥75% reduction in lesion count) and (c) percentage change from baseline in lesion count, in phase 2 and phase 3 studies of 4% 5-fluorouracil (4% 5-FU) cream once daily and 5% 5-fluorouracil (5% 5-FU) cream twice daily in patients with actinic keratosis (15). (a) is recreated from Fig. 1 of Ezzedine K, et al. J Mark Access Health Policy 2020; 8 (1): 1829884, which is published under a Creative Commons CC-BY-NC 4.0 license.

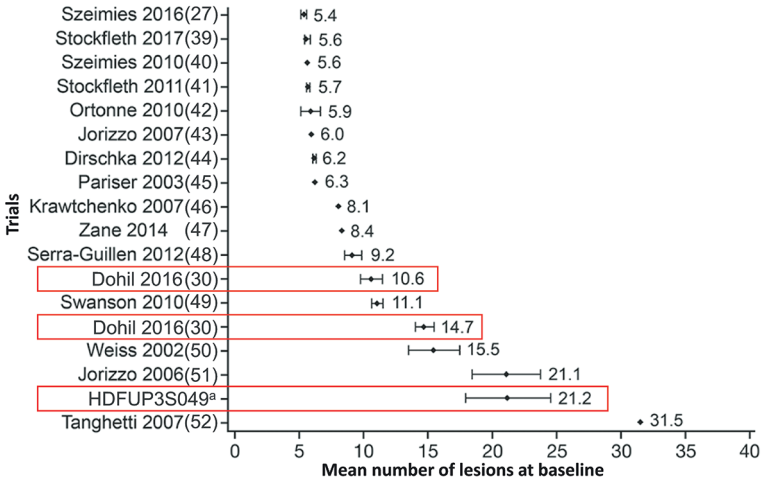

Fig. 3. Mean baseline lesion counts in a network meta-analysis of actinic keratosis (AK) treatments highlighting that trials with 4% 5-fluorouracil cream included patients with high actinic keratosis disease burden compared with other studies (38). Phase 2 and 3 studies with 4% 5-fluorouracil cream are highlighted. [a]Pierre Fabre, Data on file. Figure modified from Fig. 5 of Ezzedine K, et al. Acta Derm Venereol 2021; 101 (1): adv00358, by adding 3 red textboxes and reference numbers to the references on the y axis, which is published under a Creative Commons CC-BY-NC 4.0 license.

in the active treatment arms (15), which is at the upper end of the range typically used in clinical trials (38). As the clinical trials with 4% 5-FU have been conducted in patients with AK at the severe end of the scale (which is usually accompanied by field cancerization), this indicates that 4% 5-FU has confirmed efficacy in a population with high lesion counts and a large treatment field.

More appropriate endpoints are needed for the assessment of AK treatment efficacy, taking into account disease severity, and allowing for between-study comparisons. The Harmonisation of Outcome Parameters and Evaluation (HOPE) for actinic keratosis is underway to establish relevant, suitable, and standardized endpoints for assessing treatment efficacy in patients with AKs (53). For example, the percentage change in lesion count from baseline is relatively unaffected by the number of lesions present at baseline (28), and provides an assessment of net efficacy that accounts for the appearance of new lesions and spontaneous regression during treatment.

To date, a number of such scales have been developed, including the Actinic Keratosis Area and Severity Index (AKASI) (34), the Method of Assessing Skin Cancerization and Keratoses (MASCK) (54) and the Actinic Keratosis Field Assessment Scale (AK-FAS) (55), but these are not widely used in the clinical assessment of AK treatments, nor are they accepted endpoints for regulatory approval.

Since patients with a higher number of AK lesions are in greater need of treatment, we urge physicians to better understand the relationship between treatment efficacy and baseline lesion count and recognize the value of endpoints other than CCR in the assessment of treatment efficacy. In addition, as local skin tolerability can affect adherence, we recommend that all patients, particularly those with >10 lesions at baseline who may be at an increased risk of localized skin reactions during 4% 5-FU treatment, should be counselled prior to treatment initiation about potential adverse events and offered preventative measures (32).

In conclusion, several studies of 4% 5-FU cream have been performed in patients with AK, including in patients with severe disease who have high lesion counts and a large treatment field. Baseline lesion count affects the proportion of patients who are able to achieve CCR during field-directed AK therapy with topical 4% 5-FU, because complete clearance becomes more difficult to achieve in patients with a high number of lesions. We consider that this does not mean that treatment is less effective, but rather that other efficacy parameters, such as percentage change in lesion count, ≥75% clearance of lesions or clinically significant changes in validated severity scales, are needed to fully evaluate these treatments. Nevertheless, studies of topical 4% 5-FU indicate that this treatment is associated with a high level of efficacy, a low level of disease recurrence, and a satisfactory safety profile.

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