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REVIEW

Systematic review of randomized controlled trials of topicals for actinic keratosis field therapy

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Abstract

Cutaneous field cancerization in dermatology describes the anatomic region of photodamaged skin with actinic keratoses (AKs) or cutaneous squamous cell carcinoma (cSCC) that is surrounded by cellular atypia, forming a dysplastic field. The concept of field cancerization is especially relevant in dermatology, as actinic keratoses and the surrounding dysplastic region can progress to carcinomas, necessitating the treatment of the field. Recent research has focused on field-directed therapy using topical agents. This study aims to systematically review randomized controlled trials on topical treatments for actinic keratosis field cancerization, following the PRISMA guidelines. Clinical recommendations were based on the Oxford Centre for Evidence-Based Medicine. We identified 20 original randomized controlled trials for topical cutaneous field therapy. 0.5% 5-Fluorouracil/salicylic acid and 0.5% 5-fluorouracil received a clinical recommendation grade of A, while diclofenac sodium received a clinical recommendation grade of B. Calcipotriol/5-fluorouracil, Imiquimod, sunscreen combination therapies, and tirbanibulin received a recommendation grade of C. This review provides a framework for clinicians when considering topical treatments for patients with field cancerization.

Keywords Cutaneous field therapy · Actinic keratosis · Cutaneous squamous cell carcinoma · Topicals

Introduction

Cutaneous field cancerization is defined as the anatomic region of photodamaged skin with actinic keratoses (AKs) or cutaneous squamous cell carcinoma (cSCC), surrounded by multifocal cellular atypia [1]. The global market size of treatments for AKs was 6.25 billion USD in 2017 and is estimated to be 9.25 billion USD in 2030. This primarily arises from photodamage due to chronic ultraviolet (UV) radiation exposure [2]. As cells in the exposed area accrue genetic alterations and divide, a dysplastic field emerges [3]. AK lesions, also known as solar keratosis, may initially develop with a dysplastic field without invasive features; however, as these cells continue to be exposed to carcinogenic elements and accrue more genetic mutations, there is potential for the eventual manifestation of carcinoma [3–5]. Although AKs are visible clinically, precancerous cells within the photodamaged periphery may only be revealed through histopathology [2]. Additionally, no reliable method exists to predict the progression of AKs to cSCC [2].

While AKs are commonly regarded as precancerous, the targeted treatment of isolated lesions does not target other nearby preneoplastic cells in its neighboring cancerized field [4, 6]. Therefore, a definitive approach is needed to treat all AKs and their surrounding dysplastic field, limiting the utility of cryotherapy, which is targeted therapy not beneficial for field therapy. Cutaneous field therapy refers to the treatment approach aimed at treating an entire field of skin, rather than individual lesions, to minimize the risk of new precancerous or cancerous lesions from developing [7]. While photodynamic therapy (PDT), a second-line non-topical therapy for cutaneous field cancerization, is safe and effective, PDT is not readily available to many patients in rural areas and was only available in 41.6% of metropolitan counties in 2017 [8]. Also, an analysis of the cost-effectiveness of different

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topical agents vs PDT for the treatment of AKs revealed PDT had a higher cost than topical agents, which increases healthcare spending and insurance companies may require patients to try topical agents first [9]. The limited availability of PDT necessitates the evaluation of topical agents for cutaneous field cancerization as topical agents are readily available across the United States.

The first line topical treatment for cutaneous field therapy is 5% 5-fluorouracil (5-FU), a highly effective and established treatment that has been extensively reviewed in the past. Second-line topical treatments include imiquimod and diclofenac sodium [10, 11]. Second-line treatment previously included ingenol mebutate; however, there are long-term safety concerns linking ingenol mebutate with skin cancer, prompting the European Union to suspend its use in 2020, with the manufacturer discontinuing production shortly afterwards [12]. While field therapy is effective in the treatment of field cancerization, long duration treatments, such as with 5-FU, may prevent patients from adhering to treatment [13]. Patients also prefer topical treatments that require fewer applications [13]. There is tremendous interest in topicals for cutaneous field therapy. 5-FU has been shown to be superior in efficacy compared to imiquimod (IMIQ), ingenol mebutate, and methyl aminolaevulinate PDT (MAL-PDT) [14]. The purpose of this study is to provide comprehensive review of current topical treatments for cutaneous field therapy and offer clinical recommendations based on efficacy and safety data. In addition, we aim to assess our clinical recommendations with those established by Jansen et al., while adding any additional topical treatment options [14].

Methods

We systematically searched PubMed, Embase, and Cochrane on August 31, 2023 for topical treatments for field therapy, per the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Search terms *field cancerization, field carcinogenesis, field change cancerization* or *cancer field effect* were combined with *topical* (Fig. 1). All articles resulting from 1973 to 2023 were independently reviewed by PP and JW. PP and JW scanned bibliographies of the included articles for additional relevant reports. Included articles were randomized controlled trials (RCTs) utilizing topical agents for AK cutaneous field therapy, with comparison arms including a vehicle or 5% 5-FU. Research that included non-topical agents (such as oral medications, bleaching agents, chemical peels, drugs administered intralesionally, laser treatments, and light-based therapies), whether used independently or in combination, were not considered. The studies that utilized proprietary formulations were not included, to better evaluate the isolated effects of the treatment. Studies that did not have preexisting AKs in a field as part of the inclusion criteria were not included. Reviews, conference abstracts, non-human studies, non-randomized controlled trials, non-English articles, basic science, case reports, and case series were excluded. Clinical recommendations were made per the *Oxford Centre for Evidence-Based Medicine* guidelines (Table 1) [15].

Results

Our systematic search yielded 1275 articles. After screening titles, abstracts, and full text articles, we identified 20 articles that met our inclusion criteria (Fig. 1). Investigated treatments included 5-FU/10% salicylic acid or 0.5% 5-FU (4), diclofenac sodium (3), 0.005% calcipotriol/0.5% 5-FU (1), imiquimod (8), sunscreen combination therapy (3), and 1% tirbanibulin (1). No studies utilizing 5% 5-FU for cutaneous field therapy was directly compared with placebo, but our review evaluated 0.5% 5-FU. Table 2 summarizes the included studies, highlighting evidence grades, designs, treatment parameters, results, and adverse effects.

0.5% 5-Fluorouracil

5-FU is a cytotoxic medication that can treat AKs by inhibiting cellular thymidylate synthase, leading to disruption of DNA replication [16]. 5% 5-FU is a well-established treatment for cutaneous field cancerization. Recently, many clinical trials have studied various doses and formulations of 5-FU [17–20]. In one 20-week RCT involving 166 patients with AKs, subjects received 0.5% 5-FU and 10% salicylic acid (SA) or vehicle cream once daily for 12 weeks. At 12 weeks, 49.5% of 0.5% 5-FU/10% SA patients achieved complete clearance of their AKs (AKCLEAR100), while 18.2% of the vehicle group had AKCLEAR100 [17].

In another RCT, 470 patients received 0.5% 5-FU/10% SA once daily for 12 weeks, 3% diclofenac sodium/HA twice daily for 12 weeks, or placebo. After 20 weeks, AKCLEAR100 was 55.45%, 32.0%, and 15.1%, respectively. Application site-reactions were greater in participants receiving 5-FU than diclofenac sodium [18].

Another RCT involving 207 patients compared the efficacy of 0.5% 5-FU with vehicle cream by adjusting the duration of treatment. The patients received 0.5% 5-FU or vehicle cream once daily for 1, 2, or 4 weeks. AKCLEAR100 was 14.9%, 37.0% and 57.8% in 1-, 2-, and 4-week treatment groups 4 weeks after treatment was completed, while 0% of those who received vehicle cream achieved AKCLEAR100 at all time points [19].

One RCT involving 24 patients directly compared the efficacy of 0.5% 5-FU and 5% 5-FU. Patients underwent

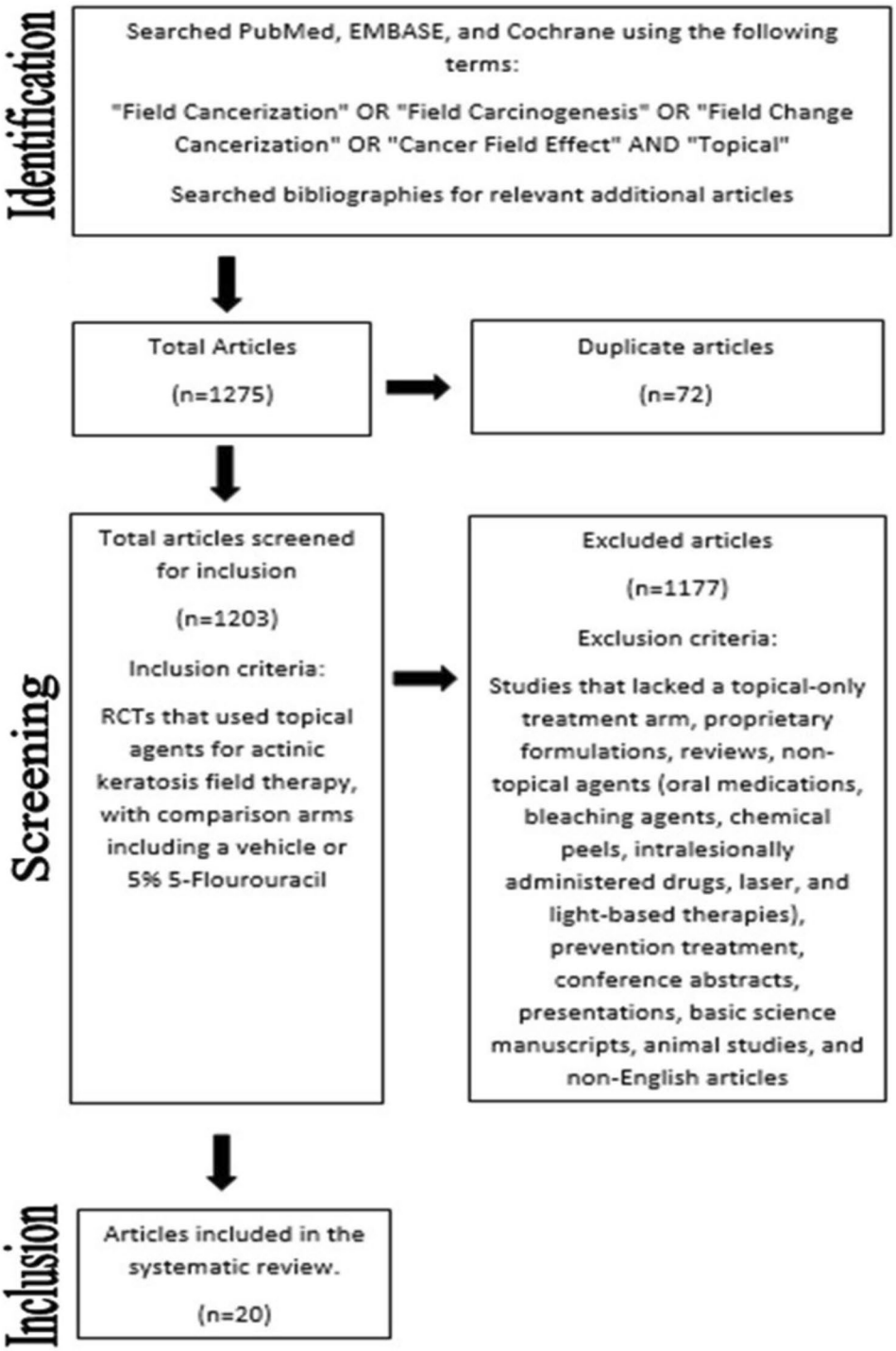

Fig. 1 PRISMA search strategy. Search strategy according to preferred reporting items for systematic reviews and meta-analysis (PRISMA) protocol

a split-face treatment, applying 0.5% 5-FU once daily or 5% 5-FU twice daily to either side of the face for 4 weeks. Both treatment arms achieved 43% AKCLEAR100 4 weeks after the end of treatment. Mild localized skin reactions were reported in both treatment arms, with no significant difference. Patients reported they preferred treatment with 0.5% 5-FU rather than 5% 5-FU [20].

Grade of recommendation: a for the included 5-FU formulations for cutaneous field therapy based on 3 level 1b studies and 1 level 2b study. (See Table 2).

Table 1 Level of evidence and grades of recommendation per oxford center for evidence-based medicine [13]

Level of evidence (LOE)
1a. Systematic review of RCTs
1b. Individual RCT (with narrow confidence interval)
2b: Low quality RCT
2a: Systematic review of cohort studies
2b: Individual cohort study/low-quality RCT
3a. Systematic review of case–control studies
3b: Individual case–control study
4. Case series
5. Case reports, expert opinion, bench research
Grades of recommendation
A. Consistent Level 1 studies
B. Consistent Level 2 or 3 studies or extrapolations from Level 1 studies
C. Level 4 studies or extrapolations for level 2 or 3 studies
D. Level 5 evidence of troublingly inconsistent or inconclusive studies of any level

Diclofenac sodium

Diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAID), inhibits cyclooxygenase-2 to decrease cellular proliferation and induce apoptosis in AKs [10]. One RCT involving 96 patients analyzed the target lesion number score (TLNS) 3 months after patients were given 3% topical diclofenac sodium in 2.5% HA gel or vehicle gel. Patients who received diclofenac sodium had a significantly decreased TLNS compared to vehicle [21]. Mild applications site reactions were reported [21]. Another RCT involving 30 male patients, subjects received 3% diclofenac sodium and HA gel twice a day for 60 days or 5% 5-FU 5 days of the week for 4 weeks for field therapy. Patients who received 5-FU had a 57.13% reduction of their field cancerization, while those who received diclofenac sodium had 62.45% reduction two months after the end of treatment [22]. Field cancerization was measured by imaging AKs and the surrounding skin with reflectance confocal microscopy, which allows real-time rendering of cellular and subcellular skin comparable to histological examination. Reduction of field cancerization was assessed by measuring field cancerization at baseline and at the end of the trial [23]. No AEs were reported [22].

In another RCT, 195 patients received 3% diclofenac sodium/2.5% HA or vehicle gel twice a day for either 30 days or 60 days. AKCLEAR100 at 30 days after the final treatment was 14.3% and 33.3% in the 30- and 60-day treatment groups, respectively, with mild AEs [24]. Patients who received vehicle gel reported 4.1% and 10.2% AKCLEAR100 after 30 and 60 days, respectively [24].

Grade of recommendation: B for diclofenac sodium for cutaneous field therapy based on 1 level 1b study and 2 level 2b studies (see Table 2).

Calcipotriol/5% 5-FU

Calcipotriol, a vitamin D3 analog, has antiproliferative effects which has been used to treat psoriasis [25]. One RCT involving 131 patients who had previously received cryotherapy for cutaneous field cancerization treated subjects with 0.005% calcipotriol ointment with 5% 5-FU cream or petroleum jelly with 5% 5-FU twice a day for 4 days. After 8 weeks, subjects who received calcipotriol had an 87.8% reduction of AKs on their face, 76.4% on their scalp, 68.8% in their right upper extremity, and 79% on their left upper extremity. Patients who received petroleum jelly and 5% 5-FU had a 26.3% reduction of AKs on their face, 5.7% on their scalp, 9.6% on their right upper extremity, and 16.3% on their left upper extremity [26]. The combination of calcipotriol and 5% 5-FU demonstrated superior efficacy compared to 5% 5-FU alone; however, patients receiving calcipotriol experienced significantly more burning and skin redness [26].

Grade of recommendation: C for calcipotriol/5% 5-FU for cutaneous field therapy based on 1 level 2b study. (See Table 2).

Imiquimod

Imiquimod (IMIQ) can be used for the treatment of cutaneous malignancies by binding to toll-like receptors and inducing apoptosis and the release of immunomodulatory cytokines [27]. Eight RCTs used 5% IMIQ for field therapy and compared IMIQ with vehicle cream. In a study involving 43 patients with kidney, heart, or liver transplants, patients received 5% IMIQ or vehicle cream for 3 days a week. After 16 weeks, 62.1% of IMIQ patients had AKCLEAR100 compared to 0% of vehicle cream patients [28]. Another study involving 44 patients treated solar keratoses with 5% IMIQ or vehicle cream three times a week for 3 weeks. After

Table 2 Published clinical trials with topicals for cutaneous field therapy

Author	Patient population	# of patients	Study design	Follow-up	Primary outcome	Treatment	Treatment regimen	Results	Adverse effects
Stockfleth et al. [17]	18–85 y/o, 4–10 AKs in 25 cm^2 area on face, balding scalp, or forehead	166	DB, VC	20 weeks	AKCLEAR100	0.5% 5-FU/10% SA Vehicle	Once daily for 12 weeks Once daily for 12 weeks	49.5%# 18.2%	Erythema, pain, irritation, inflammation, scab, erosion, pruritus, dermatitis, bleeding, edema, ulcer, application-site exfoliation, nasopharyngitis, headache Erythema, pain, irritation, inflammation, scab, erosion, pruritus, dermatitis, bleeding, application-site exfoliation, nasopharyngitis, headache
Jorizzo et al. [19]	≥ 18 y/o, ≥ 5 AKs on face or scalp	207	DB, VC, parallel	4 weeks after treatment completion	AKCLEAR100	0.5% 5-FU 0.5% 5-FU 0.5% 5-FU Vehicle Vehicle Vehicle	Once daily for 1 week Once daily for 2 weeks Once daily for 4 weeks Once daily for 1 week Once daily for 2 weeks Once daily for 4 weeks	14.9%# 37.0%# 57.8%# 0% 0% 0%	89% facial irritation 98% facial irritation 96% facial irritation 65% facial irritation 65% facial irritation 65% facial irritation
Loven et al. [20]	≥ 18 y/o, ≥ 3 AKs on each side of the face, anterior bald scalp, or forehead	24	SB, comparative	4 weeks after treatment completion	AKCLEAR100	0.5% 5-FU 5% 5-FU	Once daily for 4 weeks Twice daily for 4 weeks	43% 43%	Erythema, erosion, dryness, burning, pruritus, pain, edema Erythema, erosion, dryness, burning, pruritus, pain, edema

Table 2 (continued)

Author	Patient population	# of patients	Study design	Follow-up	Primary outcome	Treatment	Treatment regimen	Results	Adverse effects
Stockfleth et al. [18]	18–85 y/o, 4–10 AKs on face/ forehead or scalp	470	DB, VC	20 weeks	AKCLEAR100	0.5% 5-FU/10% SA 3% Diclofenac Sodium/HA Vehicle	Once daily for 12 weeks Twice daily for 12 weeks Once daily for 12 weeks	55.4%*# 32.0%* 15.1%	92% ASR# 62.7% ASR 75.7% ASR
Mazzella et al. [22]	≥ 50 y/o male, > 3 AKs in 25 cm^2 area on bald scalp	30	OL	8 weeks after last treatment	% Reduction of field cancerization area	3% diclofenac sodium/HA gel 5% 5-FU cream	Twice a day for 60 days Once daily, 5 days a week for 4 weeks	62.45%* 57.13%*	None reported None reported
Rivers et al. [24]	≥ 18 y/o, ≥ 5 AKs in 1–3 5 cm^2 areas	195	DB, PC	30 days after last treatment	AKCLEAR100	3% diclofenac sodium/2.5% HA gel 3% diclofenac sodium/ 2.5% HA gel 2.5% HA gel 2.5% HA gel	Twice a day for 30 days Twice a day for 60 days Twice a day for 30 days Twice a day for 60 days	14.3%# 33.3%# 4.1% 10.2%	Pruritus, rash, dry skin, ASR, paresthesia, hyperesthesia, pharyngitis Pruritus, rash, dry skin, ASR, contact dermatitis, paresthesia, hyperesthesia, flu-like syndrome, infection, pharyngitis Pruritus, rash, dry skin, ASR, paresthesia, hyperesthesia, flu-like syndrome, infection, headache, pharyngitis, bronchitis Pruritus, rash, dry skin, ASR, contact dermatitis, acne, paresthesia, hyperesthesia, flu-like syndrome, infection, headache, pharyngitis

Table 2 (continued)

Author	Patient population	# of patients	Study design	Follow-up	Primary outcome	Treatment	Treatment regimen	Results	Adverse effects
Wolf et al. [21]	≥ 18 y/o, ≥ 5 AKs in 1–3 5 cm^2 areas	96	DB, PC	3 months	Target lesion number score	3% Diclofenac sodium/ 2.5% HA gel Vehicle	Twice daily for 90 days Twice daily for 90 days	50%# 20%	Pruritus, ASR, dry skin, rash, erythema, rash vesiculobullous, skin exfoliation, ulcerated skin Pruritus, ASR, dry skin, erythema
Cunningham et al. [26]	≥ 50 y/o, 4–15 AKs in 25 cm^2 area, history of cryotherapy	131	DB	8 weeks	% reduction of AKs	0.005% calcipotriol ointment with 5% 5-FU cream Petroleum jelly with 5% 5-FU cream	Twice daily for 4 days Twice daily for 4 days	87.8% face*#, 76.4% scalp*#, 68.8% RUE*#, 79% on LUE*# 26.3% face*, 5.7% scalp*, 9.6% RUE*, 16.3% LUE*	69% skin redness# 91% delayed erythema resolution pattern# 39% skin burning# scaling, itching 25% skin redness 6% delayed erythema resolution pattern 13% skin burning scaling, itching
Ulrich et al. [28]	4–10 AKs in 100 cm^2 area on face or balding scalp, history of kidney, liver, or heart transplant	43	DB	16 weeks	AKCLEAR100	5% IMIQ Vehicle	Once daily, 3 days a week for 16 weeks Once daily, 3 days a week for 16 weeks	62.1%# 0%	Fatigue, headache, diarrhea, nausea, rash, skin disorder, leukopenia None reported
Gebauer et al., [34]	≥ 18 y/o, 10–50 AKs on forearms	149	DB, VC	16 weeks	AKCLEAR 100	5% IMIQ 5% IMIQ 5% IMIQ 5% IMIQ Vehicle	Once daily twice a week for 8 weeks Once daily three times a week for 8 weeks Once daily five times a week for 8 weeks Once daily for 8 weeks For each of the treatment protocols	3.2% 6.9% 3.3% 6.7% 0%	58.1% ASR# 86.2% ASR# 83.3% ASR# 90% ASR# 13.8% ASR

Table 2 (continued)

Author	Patient population	# of patients	Study design	Follow-up	Primary outcome	Treatment	Treatment regimen	Results	Adverse effects
Chen et al. [29]	5–15 SKs on one treatment area (scalp, forehead/temples, or both cheeks)	44	DB, VC	4 weeks after treatment completion	AKCLEAR75	5% IMIQ Vehicle	Once daily 3x/week for 3 weeks Once daily 3x/week for 3 weeks	72% 27.3%	93% LSR 40% LSR
Swanson et al. [30]	≥ 18 y/o, 5–20 AKs in 25 cm^2 area on face or balding scalp	479	DB, VC	14 weeks	AKCLEAR100	2.5% IMIQ 3.75% IMIQ Vehicle	Once daily for 2 weeks, 2 week washout, once daily for 2 weeks Once daily for 2 weeks, 2 week washout, once daily for 2 weeks Once daily for 2 weeks, 2 week washout, once daily for 2 weeks	30.6%# 35.6%# 6.3%	Erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, erosion/ulceration Erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, erosion/ulceration, diarrhea, headache Flaking/scaling/dryness, headache
Jorizzo et al. [31]	≥ 18 y/o, 4–8 AKs in 25 cm^2 area on face or balding scalp	246	DB, VC	20 weeks	AKCLEAR100	5% IMIQ Vehicle	Once daily, 3 times per week for 4 weeks, 4 week washout, repeat 4-week cycle if no clearance Once daily, 3 times per week for 4 weeks, 4 week washout, repeat 4-week cycle if no clearance	53.7%# 14.6%	ASR# ASR

Table 2 (continued)

Author	Patient population	# of patients	Study design	Follow-up	Primary outcome	Treatment	Treatment regimen	Results	Adverse effects
Alomar et al. [32]	≥ 18 y/o, 5–9 AKs in 25 cm^2 area on face or balding scalp	259	DB, VC	20 weeks	AKCLEAR100	5% IMIQ Vehicle	Once daily 3 times per week for 4 weeks, 4 week washout, repeat 4-week cycle if no clearance Once daily 3 times per week for 4 weeks, 4 week washout, repeat 4-week cycle if no clearance	55%*# 2.3%	Erythema, flaking/scaling/dryness, scabbing/crusting, edema#, vesicles#, erosion/ulceration#, weeping/exudate# Erythema, flaking/scaling/dryness, scabbing/crusting, edema, vesicles, erosion/ulceration, weeping/exudate
Korman et al. [11]	≥ 18 y/o, 4–8 AKs in 25 cm^2 area on face or balding scalp	492	DB, VC	24 weeks	AKCLEAR100	5% IMIQ Vehicle	Once daily 3 times per week for 16 weeks Once daily 3 times per week for 16 weeks	48.3%*# 7.2%	Itching#, burning#, pain#, tenderness, infection, stinging, swelling Itching, burning, tenderness, stinging
Szeimies et al. [33]	≥ 18 y/o, 5–9 AKs in 25 cm^2 area on face or balding scalp	286	DB, VC	24 weeks	AKCLEAR100	5% IMIQ Vehicle	Once daily 3 times per week for 16 weeks Once daily, 3 times per week for 16 weeks	57.1%# 2.2%	46.3% ASR Burning#, erythema#, itching#, pain#, scabbing#, soreness#, discharge, irritation, pimples, stinging, swelling, tenderness, tightness, warmth 11.5% ASR Burning, irritation, itching, warmth

Table 2 (continued)

Author	Patient population	# of patients	Study design	Follow-up	Primary outcome	Treatment	Treatment regimen	Results	Adverse effects
Alvares et al. [37]	60–90 y/o, 3–10 AKs on each forearm	40	PB	8 weeks	AKCLEAR100	99 SPF sunscreen 99 SPF sunscreen/ antioxidants 99 SPF sunscreen/photolyase 99 SPF sunscreen/photolyase/antioxidants	Twice daily for 8 weeks Twice daily for 8 weeks Twice daily for 8 weeks Twice daily for 8 weeks	5% 10% 0% 5%	Itching Itching, 1 case of squamous cell carcinoma Itching 1 case of basal cell carcinoma
Carducci et al. [35]	≥ 65 y/o, 4–10 AKs on face or scalp area, Caucasian	28	OL	6 months	Field cancerization measured by fluorescence diagnostics using methylaminolevulinate	50 SPF sunscreen 50 SPF sunscreen/1% photolyase/1% endonuclease	Twice a day for 6 months Twice a day for 6 months	141 ± 15* 117 ± 11*#	No significant reported No significant reported
Bobyr et al. [36]	≥ 61 y/o, ≤ 6 AKs on face or scalp area	50	OL	12 weeks	Field cancerization measured by fluorescence diagnostics using methylaminolevulinate	50 SPF sunscreen/0.8% piroxicam 50 SPF sunscreen	Twice daily for 12 weeks Twice daily for 12 weeks	101 ± 12*# 131 ± 16*	No significant reported No significant reported
Blauvelt et al. [40]	≥ 18 y/o, 4–8 AKs in 25 cm^2 area	702	DB, VC	57 days	AKCLEAR100	1% Tirbanibulin Vehicle	Once daily for 5 days Once daily for 5 days	49.3%# 8.6%	Erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, erosion/ulceration Erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, erosion/ulceration

DB double blind, *VC* vehicle control, *PB* partially blind, *y/o* years old, *RUE* right upper extremity, *LUE* left upper extremity, *EB* evaluator blind, *OL* open label, *ASR* application site reaction, *SAE* severe adverse reaction, *HA* hyaluronic acid, *SA* salicylic acid, *IMIQ* imiquimod, *5-FU* 5-fluorouracil, *AKCLEAR100* 100% clearance of AK lesions, *AK* actinic keratosis, *LSR* localized skin reaction

*$p < 0.05$ vs baseline

#$p < 0.05$ p vs vehicle

14 weeks, there was 75% clearance of solar keratoses in 72% and 30% of patients who received IMIQ or vehicle cream, respectively [29].

In one RCT, 479 patients received 3.75% IMIQ, 2.5% IMIQ, or placebo for cutaneous field therapy. The treatment protocol entailed patients applying the study drug once daily for 2 weeks, followed by a 2-week break, and then another 2 weeks of daily application. At 14 weeks, 35.6%, 30.6%, and 6.3% of patients achieved AKCLEAR100 in the 3.75% IMIQ, 2.5% IMIQ, and placebo groups, respectively [30].

Two 20-week RCTs showed significant improvement of cutaneous field cancerization in patients who received 5% IMIQ once daily three times per week for four weeks, a 4-week washout period, followed by a repeat 4-week cycle if patients had no clearance of AKs compared to placebo [31, 32]. In two other well-designed 24-week RCTs, patients received 5% IMIQ daily three times per week for 16 weeks and showed significant improvements in AKCLEAR100 compared to placebo [11, 33]. One study reported patients who experienced more erythema with treatment had better clearance of AKs [11].

One RCT treated varied the frequency of IMIQ administration for field therapy in 149 patients. Patients were instructed to apply 5% IMIQ once daily, two, three, five, or seven times a week for 8 weeks. After 16 weeks, AKCLEAR100 was 3.2%, 6.9%, 3.3%, and 6.7% in treatment arms, respectively. None of the patients who received vehicle gel achieved AKCLEAR100. Adverse effects increased as the frequency of IMIQ increased, and all treatment arms had significantly more adverse effects compared to placebo [34].

Grade of recommendation: C for imiquimod for cutaneous field therapy based on 7 level 1b studies and 1 level 2b study (see Table 2).

Sunscreen combination therapies

While sunscreen is known to prevent the progression of AKs, it has also been recently been investigated as the base for combination therapy for the treatment of cutaneous field cancerization [35–37]. One RCT involving 28 elderly patients treated cutaneous field cancerization with 50 SPF sunscreen or 50 SPF sunscreen, 1% photolyase, and 1% endonuclease twice a day for 6 months. Photolyase and endonuclease are DNA-repair enzymes hypothesized to assist in DNA-repair due to sun damage [38]. Field cancerization was measured with fluorescence diagnostics using methylaminolevulinate. Field cancerization decreased 29% in the enzyme group and 10% in sunscreen only group [35]. Another study involving 50 patients found cutaneous field cancerization decreased 36% in patients using 50 SPF sunscreen and piroxicam 0.8% and 11% in patients using 50 SPF sunscreen after 12 weeks [36].

One partially blinded RCT treated patients with 99 SPF sunscreen, 99 SPF sunscreen and topical antioxidants, 99 SPF sunscreen and photolyase, or 99 SPF sunscreen, photolyase, and topical antioxidants. Total AK clearance on the forearms improved significantly from baseline in all treatment groups by the end of the trial. There was no significant difference in AK clearance between treatment groups and only the antioxidant group had significantly decreased total AKs compared to sunscreen only [37].

Grade of recommendation: C for sunscreen combination therapies for cutaneous field therapy based on 3 level 2b studies (see Table 2).

Tirbanibulin

Tirbanibulin is a novel topical treatment of AKs that inhibits tubulin polymerization and disrupts microtubule formation [39]. In one RCT involving 702 patients, 53.7% of patients who received 1% tirbanibulin once a day for 5 days achieved AKCLEAR100 after 57 days, while 8.6% of placebo patients had AKCLEAR100. Among the patients who had AKCLEAR100 with 1% tirbanibulin treatment, 47% of patients had recurrent lesions, and 42% had new lesions after one year. Both treatment arms reported similar instances of mild localized skin reactions, that mostly resolved by the end of the study [40].

Grade of recommendation: C for tirbanibulin for cutaneous field therapy based on 1 level 1b study. (See Table 2).

Clinical recommendations

We strongly recommend 0.5% 5-FU/10% SA once daily for 12 weeks or 0.5% 5-FU once daily for 4 weeks as topical agents for cutaneous field therapy. 85% of patients that applied 0.5% 5-FU on one side of the face and 5% 5-FU on the other reported they preferred treatment with 0.5% 5-FU, endorsing less irritation and easier application [20]. 5% 5-FU is the most efficacious and cost-effective treatment for cutaneous field cancerization with comparison to Ingenol Mebutate, IMIQ, and MAL-PDT [14]. Life-threatening reactions associated with topical 5-FU have been reported in patients deficient in dihydropyrimidine dehydrogenase (DPD), the enzyme responsible for the catabolism of 5-FU [41, 42]. While such cases are uncommon, DPD deficiency is present in 3–5% of the population [43]. A lower dose of 5-FU may demonstrate fewer side effects, but clinicians should discuss side effects with patients and avoid prescribing in patients with DPD deficiency. Due to superior efficacy, mild side effect profile, and low-risk for severe adverse reactions, 0.5% 5-FU/10% SA and 0.5% 5-FU receives the strongest recommendation.

We recommend 3% diclofenac sodium in 2.5% hyaluronic acid gel twice a day for 60 days as a topical agent

for cutaneous field therapy. The included studies utilizing diclofenac sodium reported mild side effects and high efficacy [21, 22, 24]. Patients report preference of topical treatments that require few administrations and due to the frequent applications of diclofenac sodium, a stronger recommendation cannot be made [13].

Calcipotriol and 5% 5-FU may be used as a topical agent for cutaneous field therapy. The study investigating this combination compared the efficacy of calcipotriol and 5% 5-FU with petroleum jelly and 5% 5-FU [26]. It is unclear whether petroleum jelly affected the absorption of 5-FU. The study reported more side effects and greater efficacy associated with calcipotriol [26]. Clinicians should discuss the side effect profile associated with calcipotriol and 5% 5-FU therapy with patients and monitor side effects. Further RCTs must be conducted before a stronger recommendation can be made, however, due to the same active ingredient as 5% 5-FU, clinicians should only consider calcipotriol and 5% 5-FU as topical treatment for patients without DPD deficiency.

Imiquimod (5%) three times a week for 4 weeks may serve as a topical agent for cutaneous field therapy. All the included RCTs reported LSRs, while two of the trials reported systemic AEs such as headache, fatigue, nausea, and leukopenia [11, 28–34]. Clinicians should discuss adverse effects associated with IMIQ with patients and can adjust dosing and frequency. Given the varying efficacy and safety profile, further RCTs comparing IMIQ to other treatments must be conducted before a stronger recommendation can be given.

Sunscreen combination therapy may serve as a treatment option for cutaneous field therapy. Sunscreen with DNA repair enzymes or piroxicam can provide benefit in treating field cancerization; however, the benefit is miniscule and not comparable to the efficacy of 5% 5-FU [35–37]. Sunscreen combination therapies may be used as initial treatment for mild cases or as an adjuvant therapy with 5% 5-FU. Sunscreen has recently been investigated for its endocrine-disrupting properties; however, AEs are extremely rare and still up for debate [44]. Furthermore, the limited patient populations and inconsistent drug formulations in the included studies restrict the robustness of their conclusions. While the protective benefits of sunscreen are well established, its role in field cancerization treatment is yet to be solidly established, meriting only a weak recommendation at this stage.

Tirbanibulin (1%) once a day for 5 days may serve as a topical agent for cutaneous field therapy. The included RCT reported mild LSR associated with treatment; however, patients had high relapse of lesions [40]. RCTs with comparisons to standard treatments and more long-term safety data must be conducted before a higher recommendation can be made.

Conclusion

As it is not possible to identify AKs that may transform into SCC; it is important to treat all AKs and the surrounding field [3]. We performed a systematic review on the topical treatments for cutaneous field therapy. We strongly recommend 0.5% 5-FU/SA and 0.5% 5-FU as topical treatment options for cutaneous field therapy. We recommend diclofenac sodium as a topical treatment option for cutaneous field therapy. Calcipotriol/5% 5-FU, IMIQ, sunscreen combination therapy, and 1% tirbanibulin may be considered as treatment options, but risks and benefits should be considered prior to prescribing. More research must be conducted for long-term efficacy and potential adverse events.

Our findings are in line with previous research that identified 5-FU as the most effective treatment option for cutaneous field cancerization [14]. Imiquimod serves as an alternative therapy to 5-FU with a lower recommendation, which is supported by our results [14]. This review supports previous research while also incorporating alternative topical treatment options.

The limitations of this systematic review include that some RCTs have small patient populations ($n < 50$) and varied drug treatment formulations and clinical parameters. Differences in treatment formulations and dosing may have a significant impact on efficacy, limiting the universality of the findings. Also, many of the studies determined efficacy by AKCLEAR100, which can favor studies that treated a smaller number of AKs. The number of AKs treated, listed in Table 2, may impact the reliability of efficacy measurements. Non-English articles that may have contributed to this study were not included. A strength of this study is that we included mostly double-blind, placebo controlled RCTs. Also, this study utilized PRISMA guidelines and highlighted key parameters to provide evidence-based recommendations, delivering clinically relevant information to clinicians.

Many of the studies determined efficacy of treatment by clinical assessment of AK lesions. Only two studies included utilized more objective, accurate methods of determining the extent of field cancerization and sub-clinical lesions such as cross polarized light photography or fluorescence diagnosis [35, 36, 45]. A novel scoring system specifically for extensive field cancerization has recently been developed and is more accurate than the Actinic Keratosis Field Assessment Scale (AK-FAS) [46]. Future studies should utilize these updated methods to better assess outcomes and provide more robust recommendations. Future RCTs examining effects of topical medication on cutaneous field cancerization should also focus on varied patient populations, including patients with darker skin and patients who are immunocompromised.

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Declarations

Competing interests The authors declare no competing interests.

Conflict of interests None.

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