Original Investigation

Long-term Efficacy of Topical Fluorouracil Cream, 5%, for Treating Actinic Keratosis
A Randomized Clinical Trial

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IMPORTANCE Topical fluorouracil was demonstrated to be effective in reducing the number of actinic keratoses (AKs) for up to 6 months, but no randomized trials studied its long-term efficacy.

OBJECTIVE To evaluate the long-term efficacy of a single course of fluorouracil cream, 5%, for AK treatment.

DESIGN, SETTING, AND PARTICIPANTS The Veterans Affairs Keratinocyte Carcinoma Chemoprevention (VAKCC) trial was a randomized, double-blinded, placebo-controlled trial with patients from dermatology clinics at 12 VA medical centers recruited from 2009 to 2011 and followed up until 2013. Our study population comprised 932 veterans with 2 or more keratinocyte carcinomas in the 5 years prior to enrollment. The mean follow-up duration was 2.6 years in both treatment and control groups.

INTERVENTIONS Participants applied either topical fluorouracil cream, 5% (n = 468), or vehicle control cream (n = 464) to the face and ears twice daily for up to 4 weeks.

MAIN OUTCOMES AND MEASURES This study reports on AK counts and treatments, which were secondary outcomes of the VAKCC trial. Actinic keratoses on the face and ears were counted by study dermatologists at enrollment and at study visits every 6 months. The number of spot treatments for AKs on the face and ears at semiannual study visits and in between study visits was recorded.

RESULTS The number of AKs on the face and ears per participant was not different between the fluorouracil and control groups at randomization (11.1 vs 10.6, $P > .10$). After randomization, the fluorouracil group had fewer AKs compared with the control group at 6 months (3.0 vs 8.1, $P < .001$) and for the overall study duration ($P < .001$). The fluorouracil group also had higher complete AK clearance rates (38% vs 17% at 6 months) and fewer spot treatments at 6-month intervals, at study visits, and in between study visits during the trial ($P < .01$ for all). The fluorouracil group took longer to require the first spot AK treatment (6.2 months) compared with the control group (6.0 months) (hazard ratio, 0.69; 95% CI, 0.60-0.79). The number of hypertrophic AKs was not different between the 2 groups overall ($P = .60$), although there were fewer hypertrophic AKs in the fluorouracil group at 6 months (0.23 vs 0.41) ($P = .05$).

CONCLUSIONS AND RELEVANCE Our results indicate that a single course of fluorouracil cream, 5%, effectively reduces AK counts and the need for spot treatments for longer than 2 years.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00847912

⊞ **Supplemental content** at jamadermatology.com

⊞ **CME Quiz** at jamanetworkcme.com and **CME Questions** page 1043

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The morbidity and cost associated with actinic keratoses (AKs) is notable in our aging population. Actinic keratoses are not malignant in themselves, but have malignant potential.[1] The rate of AK transformation to squamous cell carcinoma has been observed to be 0.1% to 0.6% per lesion-year.[1,2] In addition, AKs directly affect quality of life. The number of AKs on the face and ears has been shown to be a key correlate of a worse quality of life, independent of demographic factors or the number of prior keratinocyte carcinomas (KCs [basal cell and squamous cell carcinomas]).[3]

Actinic keratoses are treated to avoid morbidity and mortality associated with possible progression to KCs.[4] Direct cost for AK treatment was reported to be $1.2 billion in the United States in the year of 2004 alone,[5] and it has been projected to increase with time.[6,7] Actinic keratoses are commonly treated by spot treatment such as liquid nitrogen or electrosurgery, but field treatment with topical medications (eg, fluorouracil, imiquimod, diclofenac, and ingenol mebutate) is used for multiple lesions in an area and/or evidence of the background photodamaged skin.[6,8,9] Topical fluorouracil has been demonstrated to be effective in reducing the number of AKs and increasing the complete AK clearance rates compared with placebo. However, these randomized trials followed up the study participants no longer than 6 months after a course of topical fluorouracil application.[10-13] We studied the long-term efficacy of a single course of topical fluorouracil cream, 5%, in reducing the number of AKs and the need for spot treatment of AKs.

Methods

Study Population

Participants were recruited from 12 Veterans Affairs (VA) medical centers. All were at high-risk for KC, defined as at least 2 KCs in the 5 years prior to enrollment, at least 1 of which was on the face or ears. The KCs did not count toward the inclusion criteria if they occurred in the area of previous radiation therapy or on genital or perianal skin. Inclusion criteria included the following: (1) ability to comply with protocol requirements and to provide consent and (2) no skin cancer on full-body skin examination at randomization. Presence of an AK on the face or ears was not required for inclusion. Exclusion criteria were (1) current or prior field therapy for AKs on the face or ears in the past 3 years; (2) current or prior use of systemic fluorouracil or oral capecitabine within the past 3 years; (3) known allergy to sunscreen, triamcinolone, or fluorouracil; (4) solid organ transplant; (5) genetic disorders associated with high skin cancer risk (eg, basal cell nevus syndrome, erythrodysplasia verruciformis, xeroderma pigmentosum); (6) arsenic exposure; (7) psoralen plus UV-A treatment; (8) cutaneous T-cell lymphoma; (9) current or prior radiation therapy to the face or ears; (10) those with very high mortality risk at randomization (estimated <50% chance of surviving in 4 years); (11) women of childbearing potential not willing to use birth control; (12) dihydropyrimidine dehydrogenase enzyme deficiency; and (13) concurrent treatment with methotrexate.

This study was conducted in accordance with the Declaration of Helsinki Principles, and all participants gave written informed consent. The study was approved by the VA Central Institutional Review Board. The trial protocol is reproduced in Supplement 1.

Study Design and Treatment

The VA Keratinocyte Carcinoma Chemoprevention (VAKCC) trial (Cooperative Studies Program [CSP] 562) was a randomized, double-blind, parallel group, 2-arm trial comparing the efficacy of topical fluorouracil cream, 5%, vs vehicle control cream in a high-risk population for reducing KC risk. This article reports results of a secondary outcome of the CSP 562: long-term efficacy of a single course of fluorouracil in treating AKs.

Enrollment occurred from June 2009 through September 2011, and the follow-up was concluded in June 2013. Using a permuted block randomization stratified by study site, an electronic data system assigned participants in a 1:1 ratio to receive topical fluorouracil cream, 5%, or vehicle control cream. **Figure 1** shows the randomization, stratification, and follow-up of study participants. The vehicle control cream was a vanishing cream base consisting of the same inactive ingredients as the fluorouracil cream: white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60, and parabens. Participants and study dermatologists responsible for counting AKs at follow-up study visits were blinded to the study cream assignment. Separate unblinded dermatologists and study nurses monitored adverse effects of the study medication during the active treatment period.

The participants were instructed to apply the study cream twice daily on the face and ears for a total of 56 doses (a 4-week course of treatment). They had telephone interviews or follow-up visits in alternating weeks to monitor for adverse effects during the active treatment period. The adverse effects monitored included erythema, pruritus, burning, soreness and/or tenderness, crusting and/or erosions, scaling and/or flaking, and swelling.[14] Severity of the symptoms was graded weekly at telephone interviews and follow-up visits. If a participant could not tolerate the twice daily dosing because of adverse effects, the study medication was discontinued and triamcinolone cream, 0.1%, was applied twice daily for 5 days. If and only if the participant did not apply at least 28 doses, then the participant resumed the study medication once daily at 3 weeks after stopping the study medication to complete 56 doses. If the participant could not tolerate the study medication again, the study medication was discontinued and was not resumed. Additional field treatment on the face or ears with any topical medication or photodynamic therapy was not permitted during the follow-up period, but spot treatment (treatment of an individual AK without treating the surrounding area) was allowed at clinical discretion.

All participants received education about skin cancer, sun protection, and the use of sunscreen. Sunscreen (sun protection factor 30) was provided to all participants for the duration of the study. Participants were shown photographs of moderate to severe reactions to topical fluorouracil and counseled to contact the study nurse if they develop similar reactions.

Figure 1. Randomization, Stratification, and Follow-up of Study Participants
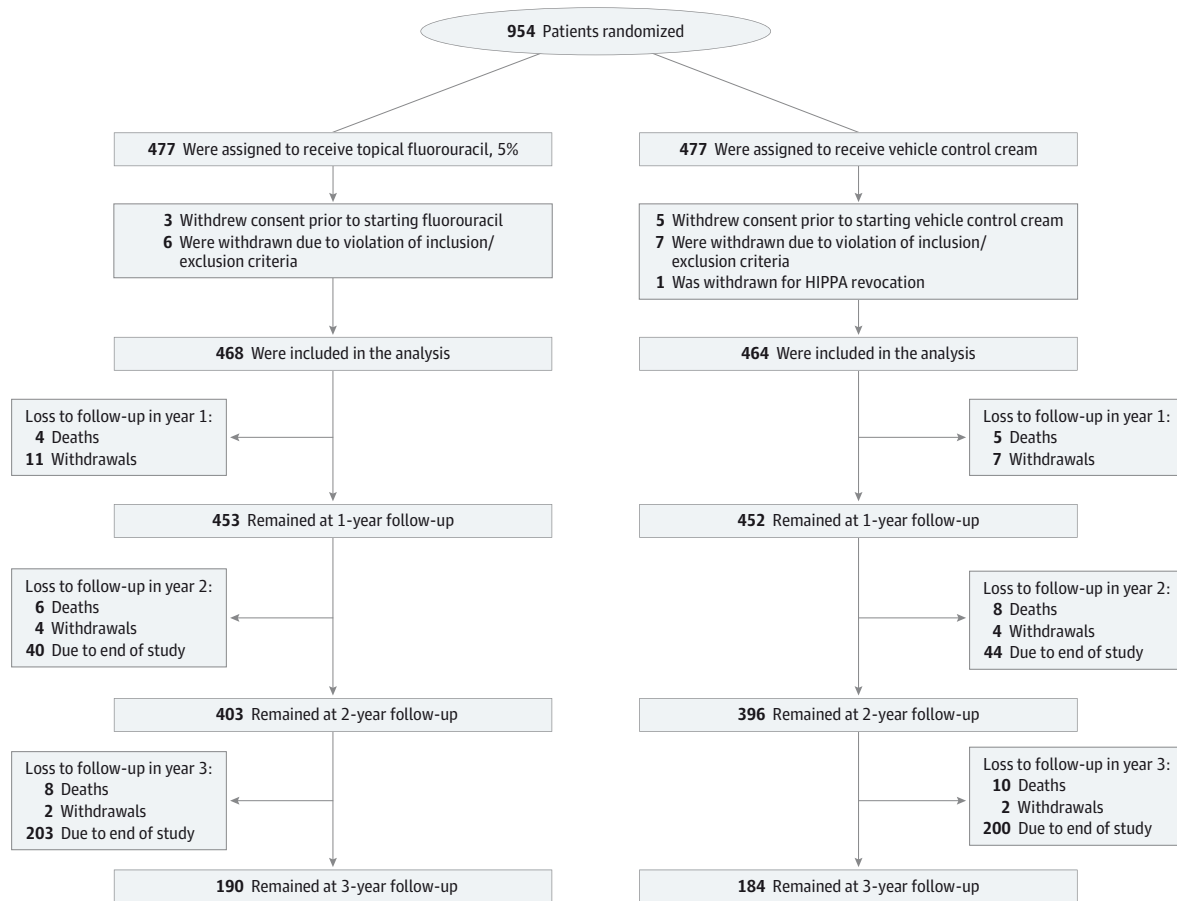
Owing to the nature of the recruitment process, an exact number of the screened individuals could not be identified. The recruitment was done in several steps (ie, identifying patients scheduled for dermatology clinic visit, reviewing these patients' medical records for possible eligibility, obtaining informed consent, performing full-body skin examination for keratinocyte carcinomas, obtaining comprehensive medical records in the prior 5 years).

Study Variables

Participants visited the blinded study dermatologist every 6 months for skin examination and AK counting after randomization. The dermatologist performed full-body skin examination including counting all AKs in predefined anatomical regions on the face and ears. They also recorded the number of hypertrophic and nonhypertrophic AKs. Once AKs on the face and ears were counted, individual lesions could be treated according to the study dermatologists' clinical judgment. The number of AK treated at the study visit was recorded. If a participant had a treatment for an AK in between study visits, the number of the treatments, the area treated, and the method of spot treatment were documented from the medical record. Study dermatologists participated in annual meetings that included training and consensus development in AK counting.[15]

Statistical Analysis

The study sample size was powered to the primary outcome of KC development treated surgically. The baseline characteristics of the fluorouracil and the control groups were compared by a 2-tailed t test or χ^2 test. We carried out a cross-

sectional time-series regression with a generalized least squares estimator and first-order autoregressive covariance model to account for random effects and correlations within the repeated measures to compare the fluorouracil and the control groups for the overall study duration. The parameters compared in this model were the number of total AKs; the number of hypertrophic AKs; the percentage of participants without AKs; and the number of spot AK treatments at every 6-month interval, at the time of 6-month study visits, and in between study visits. Linear contrasts compared the number of AKs and AK treatments in the 2 groups at 6 months. We used the Kaplan-Meier method to compare the time to the first AK treatment in the fluorouracil group with the time in the control group. Statistical analyses were conducted with STATA SE version 8 (StataCorp).

Results

Of 932 participants, 468 were randomized to topical fluorouracil cream, 5%, and 464 to vehicle control cream (Figure 1).

Table 1. Baseline Characteristics of Participants[a]

Characteristic	Participants, No. (%)	
	Topical Fluorouracil Cream, 5% (n = 468)	Control (n = 464)
Age, mean (SD), y	71 (9)	71 (9)
Male sex	457 (98)	459 (99)
Race		
White	455 (97)	457 (98)
Other	11 (2)	5 (1)
Unknown/not stated	2 (0.4)	2 (0.4)
Ethnicity		
Not Spanish, Hispanic, or Latino	464 (99)	459 (99)
Spanish, Hispanic, or Latino	4 (1)	5 (1)
Highest level of education		
Grade school	16 (3)	13 (3)
High school	133 (28)	118 (25)
College/graduate school	319 (68)	333 (72)
Currently married	269 (57)	266 (57)
History of AK treatment		
Yes	398 (85)	393 (85)
No	59 (13)	65 (14)
Do not remember	11 (2)	6 (1)
History of topical fluorouracil treatment on face and/or ears	92 (20)	74 (16)

Abbreviation: AK, actinic keratosis.

[a] $P > .10$ for all baseline characteristic comparisons between the fluorouracil and the control groups.

The mean follow-up durations were 2.62 and 2.61 years in the fluorouracil and the control groups, respectively. There was no significant difference in the baseline characteristics between the 2 groups, including the history of AK treatment and history of topical fluorouracil application on the face and/or ears (**Table 1**).

Skin Examination at Enrollment

The mean total AK count on the face and ears at enrollment was 11.1 in the fluorouracil group and 10.7 in the control group (**Figure 2**A and **Table 2**). The number of hypertrophic AKs was 0.7 per person (6% of all AKs) in the fluorouracil group and 0.8 per person (7% of all AKs) in the control group (Figure 2B and Table 2). Fifteen percent of the participants in the fluorouracil group and 12% in the control group had no AKs on the face and ears (Figure 2C and Table 2). At the time of enrollment, the fluorouracil and control groups were not different in the numbers of total and hypertrophic AKs and the proportion of the participants without AKs on the face and ears ($P > .10$ for all 3 comparisons).

AK Counts

The number of AKs on the face or ears in the fluorouracil group was reduced to 3.0 per participant (73% reduction) by 6 months after randomization ($P < .001$ in paired t test comparing the AK number at baseline with the number at 6 months in the fluorouracil group). The number of AKs in the control group was reduced to 8.1 per participant (24% reduction) for the same time

Figure 2. Number of Actinic Keratoses (AKs) on the Face or Ears
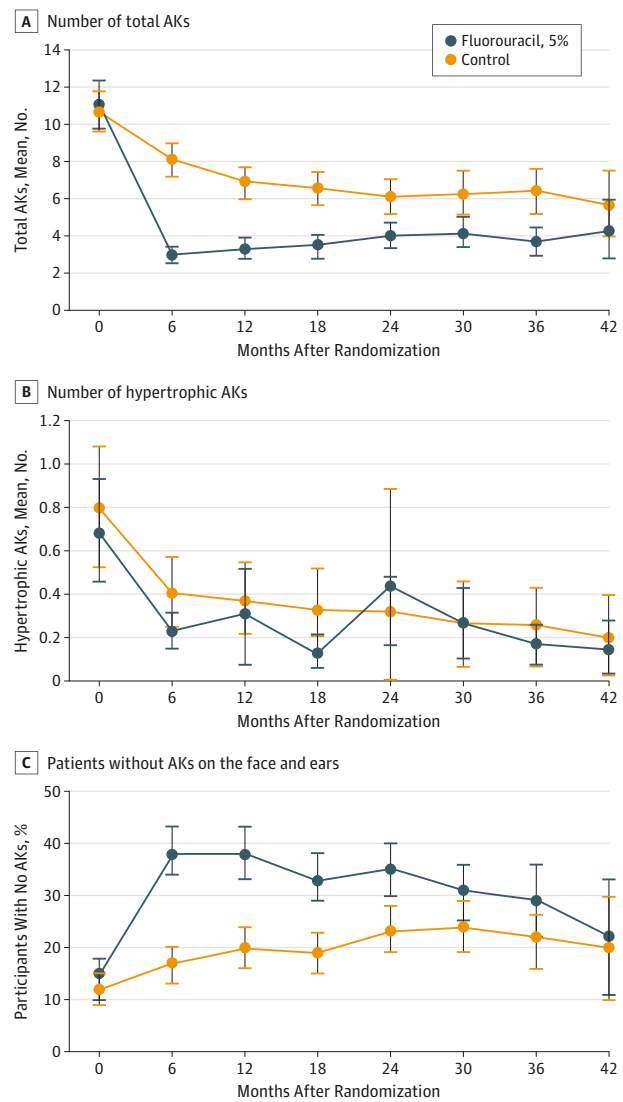
Error bars indicate SE.

interval ($P < .001$ in paired t test) (Figure 2A and Table 2). The fluorouracil group had fewer AKs on the face or ears compared with the control group at 6 months ($P < .001$ in linear contrast). The fluorouracil group also had fewer AKs compared with the control group over the 42-month period, when the AK numbers from baseline to 42 months were modeled by a generalized estimation model that accounted for random effects and correlations within repeated measures ($P < .001$) (Figure 2A).

In the same model, the number of hypertrophic AKs on the face or ears was not significantly different between the 2 groups in the entire follow-up period of 42 months ($P = .60$), but there were fewer hypertrophic AKs in the fluorouracil group than the control group at 6 months ($P = .05$) (Figure 2B, Table 2). The number of nonhypertrophic AKs in the fluorouracil and the control groups followed the similar pattern as those of the total AKs; significantly fewer nonhypertrophic AKs on the face or

Table 2. Number of Actinic Keratoses (AKs) on the Face or Ears and Percentage of Participants With No AKs on the Face or Ears

Months After Randomization	Participants Who Completed Physical Examination, No.		Mean of Total AKs, No. (SE)[a]		Mean of Hypertrophic AKs, No. (SE)[b]		Complete AK Clearance, %[a]	
	Fluorouracil Cream, 5%	Control	Fluorouracil Cream, 5%	Control	Fluorouracil Cream, 5%	Control	Fluorouracil Cream, 5%	Control
Enrollment	468	464	11.1 (0.6)	10.7 (0.6)	0.69 (0.12)	0.80 (0.14)	15	12
6	434	431	3.0 (0.2)	8.1 (0.5)	0.23 (0.04)	0.41 (0.08)	38	17
12	423	410	3.3 (0.3)	6.9 (0.4)	0.31 (0.12)	0.37 (0.08)	38	20
18	382	409	3.5 (0.3)	6.6 (0.4)	0.13 (0.04)	0.33 (0.10)	33	19
24	349	359	4.0 (0.4)	6.1 (0.4)	0.44 (0.23)	0.32 (0.08)	35	23
30	251	249	4.2 (0.4)	6.3 (0.6)	0.27 (0.08)	0.27 (0.10)	31	24
36	162	166	3.7 (0.4)	6.4 (0.6)	0.17 (0.05)	0.26 (0.09)	29	22
42	59	66	4.3 (0.8)	5.7 (0.9)	0.15 (0.06)	0.20 (0.10)	22	20

[a] $P < .001$ comparing the fluorouracil, 5%, and the control groups at 6 months and for the overall study duration.

[b] $P = .05$ comparing the fluorouracil, 5%, and the control groups at 6 months and $P = .60$ for the overall study duration.

ears were counted in the fluorouracil group than in the control group at 6 months and for the entire 42-month follow-up period ($P < .001$ in linear contrast and $P < .001$ in generalized estimation model, respectively).

Complete Clearance of AKs

The proportion of the participants with no AKs on the face or ears in the fluorouracil group increased from 15% at enrollment to 38% at 6 months ($P < .001$). The proportion in the control group increased from 12% to 17% ($P = .01$) (Figure 2C and Table 2). At 6 months, the proportion of participants who were clear of AKs in the fluorouracil group was more than double the proportion in the control group ($P < .001$ in linear contrast). The generalized estimation model showed that the fluorouracil group overall had a significantly larger proportion of the participants without any AKs on the face and ears compared with the control group for the entire 42-month follow-up period ($P < .001$) (Figure 2C).

AK Treatment

The total number of each individual spot AK treatment for up to 42 months after randomization was 6491 in the fluorouracil group and 12 204 in the control group. Among these AK treatments, 5610 (86%) in the fluorouracil group and 10 589 (87%) in the control group occurred at the study visit every 6 months. The rest of the treatments were performed in between study visits. Ninety-eight percent of AK treatments during follow-up in this trial were cryotherapy.

The fluorouracil group had 2.0 (95% CI, 1.9-2.2) spot AK treatments per visit per participant, and the control group had 3.9 (95% CI, 3.7-4.2) treatments per visit per participant ($P < .001$).

The fluorouracil group received fewer spot treatments for AKs on the face or ears compared with the control group in the first 6 months after randomization ($P < .001$ in linear contrast) (Figure 3A and Table 3). The fluorouracil group also received fewer AK treatments compared with the control group for the entire study duration, when the total number of AK treatments at 6-month intervals in the 2 groups was compared in a generalized estimation model accounting for random effects ($P < .001$) (Figure 3A and Table 3). The number of

Figure 3. Number of Actinic Keratosis (AK) Treatments on the Face and Ears
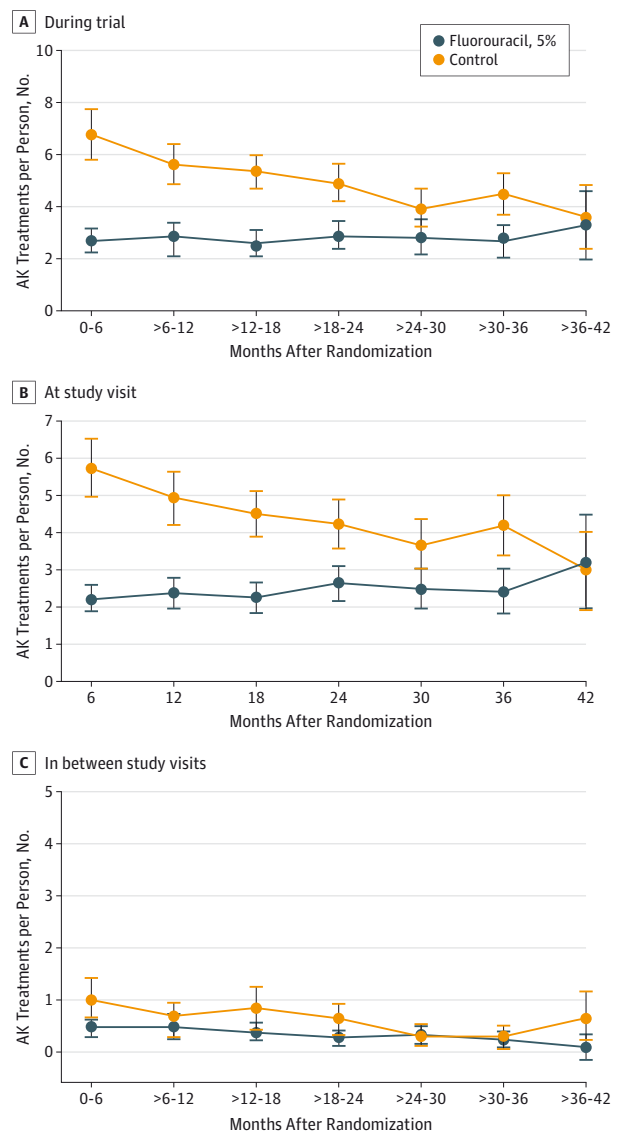
Error bars indicate SE.

Table 3. Face and Ear Actinic Keratosis (AK) Treatments

Months After Randomization	Participants Who Remained in the Study, No.[a]		Mean of AK Treatments, No. (SE)	
	Fluorouracil Cream, 5%	Control	Fluorouracil Cream, 5%	Control
AK Treatments During Trial[b]				
>0-6	459	454	2.7 (0.2)	6.8 (0.5)
>6-12	453	452	2.8 (0.3)	5.6 (0.4)
>12-18	447	443	2.6 (0.3)	5.4 (0.4)
>18-24	403	396	2.9 (0.3)	4.9 (0.4)
>24-30	302	292	2.8 (0.3)	4.0 (0.4)
>30-36	190	184	2.7 (0.3)	4.5 (0.4)
>36-42	74	78	3.3 (0.7)	3.6 (0.6)
AK Treatments at Study Visits[c]				
6	459	454	2.2 (0.2)	5.7 (0.4)
12	453	452	2.4 (0.2)	4.9 (0.4)
18	447	443	2.2 (0.2)	4.5 (0.3)
24	403	396	2.6 (0.2)	4.2 (0.3)
30	302	292	2.5 (0.3)	3.7 (0.3)
36	190	184	2.4 (0.3)	4.2 (0.4)
42	74	78	3.2 (0.7)	3.0 (0.5)
AK Treatments in Between Study Visits[d]				
0-6	459	454	0.5 (0.1)	1.0 (0.2)
6-12	453	452	0.5 (0.1)	0.7 (0.1)
12-18	447	443	0.4 (0.1)	0.9 (0.2)
18-24	403	396	0.3 (0.1)	0.6 (0.1)
24-30	302	292	0.4 (0.1)	0.3 (0.1)
30-36	190	184	0.2 (0.1)	0.3 (0.1)
36-42	74	78	0.1 (0.1)	0.7 (0.3)

[a] The number of participants enrolled in the study at the end of the 6-month interval.

[b] Actinic keratoses counted at study visit on the ending month of each 6-month period, but not on the beginning month, were included. $P < .001$ comparing the fluorouracil cream, 5%, and the control groups in the first 6 months and for the overall study duration.

[c] $P < .001$ comparing the fluorouracil cream, 5%, and the control groups at 6 months and for the overall study duration.

[d] Actinic keratoses counted at study visits were not included. $P < .001$ comparing the fluorouracil cream, 5%, and the control groups in the first 6 months and $P = .008$ for the overall study duration.

Figure 4. Cumulative Sum of Actinic Keratosis (AK) Treatments per Person

spot treatment after randomization later than the control group (median time to the first spot treatment, 6.2 months in fluorouracil group [95% CI, 6.0-6.3 months] and 6.0 months in control group [95% CI, 5.97-6.03 months]; $P = .003$ in median test).

The cumulative sum of the number of AK treatments on the face or ears at 6 months was 2.7 per person in the fluorouracil group and 6.8 per person in the control group ($P < .001$) (Figure 4). By 42 months, the fluorouracil group had 19.8 treatments per person, while the control group had 34.8 treatments per person (Figure 4).

spot treatments for AKs at the time of the 6-monthly study visits was fewer in the fluorouracil group compared with the control group ($P < .001$) (Figure 3B and Table 3). The fluorouracil group also had fewer spot AK treatments in between study visits compared with the control group ($P = .008$) (Figure 3C and Table 3).

A total of 382 participants in the fluorouracil group (82%), compared with 413 in the control group (89%), received at least 1 spot treatment for AKs on the face or ears after randomization. The fluorouracil group was less likely to receive any spot treatment for AKs compared with the control group (hazard ratio, 0.70; 95% CI, 0.60-0.80) (eFigure in the Supplement 2). Furthermore, the fluorouracil group experienced the first AK

Discussion

The VAKCC trial provides data on long-term efficacy of twice-daily application of topical fluorouracil cream, 5%, compared with vehicle control cream in treating AKs on the face and ears in a patient population at high risk for KCs. The participants who were treated with a course of fluorouracil cream had fewer total AKs and received fewer spot treatments for AKs for longer than 2 years.

Literature searches that aimed to identify all randomized clinical trials comparing topical fluorouracil cream with placebo in the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed/MEDLINE, and the US Food and Drug Administration (FDA) website found none comparing fluorouracil cream, 5%, with placebo. Two randomized clinical trials

compared topical fluorouracil cream, 0.5%, in treating AKs with placebo, and 1 trial compared topical fluorouracil cream, 0.5%, cream and cryotherapy with vehicle cream and cryotherapy (eTable in the Supplement 2).[10-13] Jorizzo et al[10] and Weiss et al[11] randomized the participants to fluorouracil cream, 0.5%, or vehicle control cream for 1, 2, or 4 weeks for treatment of AKs on the face or frontal scalp. Both studies reported more reduction of AK counts in the fluorouracil group than in the control group at 4 weeks after completion of the assigned treatment. Jorizzo et al[10] reported 22% reduction in AK counts in the control group, whereas fluorouracil given for 2 weeks resulted in 86% reduction in AK counts and for 4 weeks, 92% reduction. Similarly, in the study by Weiss et al,[11] the control group had 34% reduction in AK counts, whereas the fluorouracil group had 84% reduction of AK counts at 2 weeks and 89% at 4 weeks.

A trial that randomized participants to either a 1-week course of fluorouracil cream, 0.5%, or 1-week course of vehicle cream compared AK counts in the 2 groups at 4 weeks after randomization (eTable in the Supplement 2).[12,13] Cryotherapy was used in both groups at 4 weeks, and AKs were counted again at 6 months.[12] Participants in this study underwent 2 additional cycles of study cream and cryotherapy.[13] Even after cryotherapy was used to treat all the persistent AKs after topical treatment in both groups, the fluorouracil group had a significantly larger reduction of AKs compared with the vehicle cream group (21% mean difference in reduction rate) at 6 months after starting the first cycle. The fluorouracil group had the mean of 2 more lesions reduced from the baseline count compared with the control group at 6 months after starting the third cycle, but the difference was not statistically significant.[13,16] Our study showed a 73% AK count reduction in the fluorouracil group and a 26% reduction in the vehicle control cream group at 6 months after randomization. A large part of the reduction in the control group was presumably due to spot treatments, which could be performed in both groups. Our results cannot be directly compared with the previous randomized trials because we used fluorouracil cream, 5%, not 0.5%, although a randomized trial of fluorouracil cream, 0.5%, vs fluorouracil cream, 5%, in treating AKs showed no difference in their efficacies.[17] To our knowledge, our study is the only randomized clinical trial to date that showed superior efficacy of fluorouracil cream, 5%, compared with vehicle control cream in AK treatment.

Our results were notable for the larger decrease in total AKs and the larger increase in complete AK clearance rates in the fluorouracil group than in the control group at study visits, even when the fluorouracil group received fewer spot treatments.

The consistently fewer AK counts and fewer spot AK treatments in the fluorouracil group indicate that field treatment with fluorouracil prevents occurrence and/or recurrence of AKs in the treated area. The preventive role of fluorouracil is also indicated by the delayed time to the first AK treatment after randomization; over 80% of the participants in both groups eventually received at least 1 spot treatment for a lesion during the follow-up period, but it took longer for the fluorouracil group to receive the first spot treatment than it did for the control group. In addition, we found that a single course of the topical fluorouracil cream, 5%, treatment may be effective in reducing the number of hypertrophic AKs in the first 6 months, but we could not demonstrate its effectiveness for the overall study duration. It should be noted that there were only a few hypertrophic AKs in the study, and the power to detect the differences in the number of hypertrophic AKs between the 2 groups was low.

A limitation of our trial is that AKs were diagnosed clinically without histological information. A previous study reported that the dermatologists in the CSP 562 trial had disagreement in AK diagnoses.[18] They met annually to compare and review AK diagnoses among themselves, and the discrepancies decreased over time.[15] Spot AK treatment was left to the study dermatologists' clinical judgment with substantial potential variations. However, this study design may have an advantage of being more generalizable to the actual clinical practice, where AKs are treated according to clinical judgment rather than strict guidelines. Topical fluorouracil can cause severe cutaneous reactions and possibly reveal a participant's treatment assignment, but our blinding method (see "Study Design and Treatment" in the Methods section) ensured that dermatologist counting AKs could remain blinded to each participant's treatment assignment as much as possible because their first visit with the participant after randomization was at 6 months.

Conclusions

Our findings highlight the long-term efficacy of topical fluorouracil cream in treating and preventing AKs. A single course of topical fluorouracil cream, 5%, treatment led to a sustained reduction of the number of AKs and subsequent AK treatments in the population at high risk for KC. These findings indicate that treating a patient with a single course of fluorouracil would reduce the subsequent number of spot treatments and benefit care of patients with multiple AKs for longer than 2 years.

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NOTABLE NOTES

Of Steinbeck and Sunburn

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John Steinbeck's literary work is known for depictions of Depression-era rural California and for portraying the condition of exploited farm laborers. In his fiction, protagonists often have scraped hands and sunburnt skin, which serve as physical testimony to their honest, hard work. While dermatologists agree that sunburns are related to skin cancer, Steinbeck used sunburned skin to signify hard-working, straight-living characters.

Sunburn is an unsurprising descriptor for Steinbeck's protagonists, who often drift from farm to farm across California's arid, cloudless Central and Salinas Valleys. Of interest, however, is the context where Steinbeck uses sunburn to convey integrity, moral strength, and other favorable attributes.

In *East of Eden*, Steinbeck describes the strong, widely admired Samuel Hamilton as "a big man, bearded like a patriarch...his cheeks above his beard were pink where the sun had burned his Irish skin."[1(p139)] Of Samuel's son, Tom Hamilton, Steinbeck writes, "You could feel [his] strength and warmth and an iron integrity...his skin, perhaps from sun, was a black red."[1(p275)]

In *The Grapes of Wrath* (**Figure**), Mr Thomas, a landowner more interested in honest earnings than dishonorable wealth, refuses to take advantage of vulnerable migrant workers. His "sunburned eyebrows were drawn down in a scowl. His cheeks were sunburned a beef red."[2(p345)] Steinbeck uses sunburn when describing the hardworking tenants of the land, "their sunburned faces were dark, and their sun-whipped eyes were light."[2(p40)] The antagonists in this work, however, never work outdoors where they can become sunburnt.

Why does Steinbeck link the condition of painful inflamed skin due to sun overexposure to positive virtues? Historically, pallor has often indicated lofty social status but to Steinbeck, pallor indicated the indoor machinations of exploitative capitalism. Only laborers and members of the working class, those who produce true goods and services, had tanned or sunburned skin. Thus, while pale upper classes suppressed the commonweal, sunburned laborers shouldered the work necessary to bring luxury to the upper class. Steinbeck explored such injustices and depicted his admiration for those who work outdoors by giving them the truest mark of outdoor work—the sunburn.

Throughout Steinbeck's work, sunburns signify virtue and hard work—and that challenges dermatology's perception of sunburns as simply a medical issue. Steinbeck might argue that similar divisions of labor continue to exist today; migrant workers are often oppressed, overworked, and yet wholly dedicated to the American dream, while captains of finance still hold outsized influence on our society, an influence unrelated to intrinsic virtue, worth, or integrity. These examples demonstrate how Steinbeck used sunburn to characterize virtuous yet marginalized populations, and compel us to think more deeply about the relationship between medical issues and social concerns. Medical professionals should not forget that. Steinbeck certainly never did.

Figure. Dust Jacket From the First Edition of *The Grapes of Wrath* by John Steinbeck
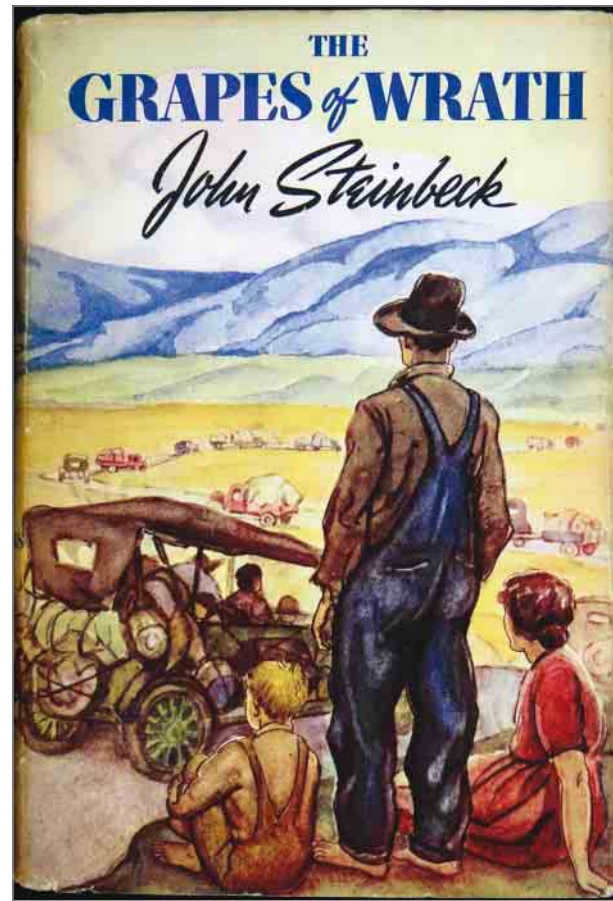
Cover art by Elmer Hader. New York, NY: The Viking Press; 1939.

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