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A real-world, community-based cohort study comparing the effectiveness of topical fluoruracil vs. topical imiquimod for the treatment of actinic keratosis

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Abstract

Background—The most widely used topical agents for the field-based treatment of multiple actinic keratoses (AKs) are 5-fluorouracil and imiquimod, but their comparative effectiveness has not been assessed in a real-world setting.

Objective—We compared the effectiveness of 5-fluorouracil and imiquimod in reducing risk of subsequent AKs in a large, integrated healthcare delivery system in Northern California.

Methods—In this cohort study, we identified adult health plan members that had an AK diagnosed in 2007 and subsequently filled a prescription for 5-fluorouracil or imiquimod (n=5,700). We followed subjects for subsequent AKs identified by International Classification of Diseases codes and estimated the 2-year (“short-term”) and 5-year (“long-term”) differences in cumulative risk while controlling for potential confounding by pre-treatment variables.

Results—5-Fluorouracil reduced the short-term incidence of subsequent AKs (cumulative risk difference –4.54% [95% CI: –7.91% to –1.17%]), but there was no statistically significant evidence of a long-term decreased risk (cumulative risk difference –1.43% [95% CI: –3.43% to 0.05%]) compared to imiquimod.

Limitations—This is a retrospective study. Generalizability to other healthcare settings may be limited.

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Attachments: research protocol/statistical analysis plan

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Conclusion—We found that 5-fluorouracil appeared to be significantly more effective than imiquimod in the short-term, but not long-term, prevention of subsequent AKs.

Keywords

Actinic keratosis; Skin cancer; Squamous cell carcinoma; Basal cell carcinoma; Keratinocyte carcinoma; Comparative effectiveness

INTRODUCTION

Actinic keratoses (AKs) are keratinocyte-derived precancerous neoplasms that arise on chronically sun-exposed skin.¹ AKs arise in nearly 40 million Americans per year,^{2–4} and treatment costs over a billion dollars annually.⁴ AKs can be treated with destructive therapies (cryotherapy, curettage, chemical peels), topical chemotherapeutic agents (such as 5-fluorouracil [5-FU], imiquimod [imq], diclofenac, tretinoin, ingenol mebutate), and light-based treatments (lasers, photodynamic treatment). Treatment selection depends on a variety of factors including patient characteristics and patient and provider preferences. Focally destructive treatments (“lesion-directed”) are suitable for treating a few discrete lesions. When a patient has numerous AKs in an anatomic unit, treatment of the broader field of disease (“field-treatment”) with medications such as 5-FU or imq are employed. In contrast to focally applied destructive modalities, field treatments can attack subclinical AKs, which may decrease the risk of future AKs and keratinocyte carcinomas (KCs) in the treated area.

There are no clearly established guidelines for the field-treatment of AKs. There are several different types of field-treatments, and there is considerable variation in how each field-treatment is deployed. A Cochrane review on interventions for AKs concluded that “more direct comparisons...are needed to determine the best therapeutic approach,”⁵ and a recent review on AKs noted that “more head-to-head comparisons of alternative treatment strategies for AK are needed to determine the best treatment.”⁶ There is little real-world data comparing the effectiveness of 5-FU to imq for field-treatment of AKs. The translation of efficacy to effectiveness is especially urgent where disease prevalence is high and variations in cost and efficacy can have large impacts.

MATERIALS AND METHODS

We performed a retrospective longitudinal cohort study of all Kaiser Permanente Northern California (KPNC) members who were diagnosed with AKs and filled prescriptions for 5-FU (n=5,062) or imq (n=638) in 2007. Cohort members were followed for subsequent AK diagnosis.

Study Setting

KPNC is a pre-paid, comprehensive, integrated care organization that serves 4 million members. KPNC’s computerized record system provides a comprehensive record of members’ demographic characteristics, pathology results, pharmacy use, and utilization benefits.

Study Population

The cohort was comprised of adult KPNC members diagnosed with an AK (International Statistical Classification of Diseases and Related Health Problems, 9th revision [ICD-9] code 702.0) in 2007 who received subsequent topical field-based treatment in 2007 with 5-FU or imq (n=8,556). The year 2007 was chosen because imq was not available before 2007, and it allowed for all outpatient ambulatory notes to be reviewed electronically, facilitating abstraction of information on indication. To maximize uniformity in the cohort and minimize confounding by sun exposure, skin type, and other unmeasured potential risk factors, we limited eligibility to members who were prescribed a topical field-based treatment for their actinic damage. We did not include members who had AKs that were spot-treated or untreated so that we could a priori make AK severity as similar as possible across the treatment groups. Subjects were followed from the date of first AK treatment dispensed (cohort entry date) until the earliest of health plan disenrollment (defined as a membership gap >90 days), death, a subsequent AK diagnosis, or the end of the study period on December 31, 2012. Subjects were excluded if 5-FU or imq was prescribed for any indication other than AK (such as warts or skin cancer) as determined by chart review, or if they had a history of any of the following ever recorded in the KPNC database: (1) UV light treatment; (2) infection with human immunodeficiency virus (HIV); (3) chronic lymphocytic leukemia (CLL); (4) solid organ transplant; (5) bone marrow transplant (Figure 1). Patients with a history of UV light treatment were excluded due to the increased risk of skin cancer associated with these therapies.⁷ Patients with a history of HIV infection, CLL, solid organ transplant, and bone marrow transplant were excluded due to the increased risk of skin cancer associated with immunosuppression.^{8–11}

Exposure

Exposure was defined as pharmacy dispensation of 5-FU or imq following an AK diagnosis in 2007.

Outcome

The outcome was time to subsequent AK diagnosis after cohort entry, defined as the first date after the start of follow-up when AK was recorded (ICD-9 code 702.0). Follow-up was right-censored by the earliest of health plan disenrollment, death, or the end of the study period. We examined both short-term (within 2 years) and long-term (within 5 years) subsequent AK cumulative incidence. The Veterans Affairs Keratinocyte Carcinoma Chemoprevention (VAKCC) trial, a randomized, double-blind, placebo-controlled trial of the long-term efficacy of 5-FU, found that a single course of 5-FU reduced AK counts and the need for spot treatments for longer than 2 years;¹² we therefore selected 2 years as the first time point for follow-up. Given that we had up to six years of follow-up for cohort members, we chose 5 years for long-term follow-up.

Covariates

Information on potential confounders was obtained from KPNC's databases for patient demographics including age (date of birth), sex (male, female, transgender, other), and race/ethnicity (white-non-Hispanic, white-Hispanic, black, Asian, Native-American). Data on

risk factors for AKs including cigarette use (current/former, never, unknown), body mass index (< 24.9 [normal], 25–29.9 [overweight], ≥ 30 [obese]), comorbidities (Charlson score 0, 1, 2, and 3+), healthcare utilization (average annual number of any healthcare provider emergency department or outpatient visits per year in the 2 years prior to baseline), surveillance measure (average annual number of dermatology visits per year in the 2 years prior to baseline), prior KC (yes/no within 5 years prior to baseline), prior AK (yes/no within 5 years prior to baseline), 5-FU treatment prior to cohort entry (yes/no), and photosensitizing medication use within two years prior to baseline were also ascertained. Photosensitizing medications were identified through literature review.¹³

Statistical Analysis

The comparative effectiveness of 5-FU versus imq was evaluated with an intention-to-treat (ITT) propensity score (PS)-based analytic approach known as inverse probability weighting (IPW) estimation to adjust for potential confounding by baseline variables (i.e., variables measured prior to the start of follow-up, including past surveillance intensity and history of prior 5-FU treatment).¹⁴ Differential non-compliance or surveillance between the agents was not expected because their directions for use, duration, and side-effect profile are quite similar.¹⁵ This rationale supported the ITT analytic approach comparing the outcomes between exposure groups defined by the type of medication dispensed rather than the medication used and the duration of use.

The PS was estimated by logistic regression with main terms for all baseline variables. The short- and long-term cumulative risk differences were estimated by linear regression using stabilized IP weights calculated based on these PS estimates.¹⁶ Outcomes from patients with no new AK diagnosis and with less than 2 years of follow-up were treated as missing in the regression and missingness was assumed to occur randomly. Conservative 95% CIs were derived based on the robust variance estimator (sandwich estimator implemented in the SAS GENMOD procedure with the option “repeated” and an independence working correlation matrix).¹⁷ We examined the distribution of the stabilized IPW weights to detect extreme weight values. The maximum IPW weight value did not warrant weight truncation.¹⁶ Results from the IPW estimation approach above were compared to results from 1) crude (unadjusted) estimation of the short-term cumulative risk differences derived by unweighted linear regressions, 2) a crude (unadjusted) analysis based on the Kaplan Meier estimator of the survival curves for the two exposure groups, and 3) an IPW estimation of the hazard ratio from a Cox proportional hazard marginal structural model for a single-time point intervention.¹⁷ All analyses were conducted using SAS, version 9.3. This study was approved by the Institutional Review Board, Kaiser Foundation Research Institute.

RESULTS

Of the 5,700 patients in the cohort, 5,062 were exposed to 5-FU and 638 were exposed to imq. The majority (n=4,946) were diagnosed with a subsequent AK during follow-up. Of the 754 patients with no subsequent AK diagnosis, 289, 100, and 365 patients were lost to follow-up due to a membership gap >3 months, death, and administrative end of study, respectively. In total, 281 patients were lost to follow-up with no subsequent AK diagnosis

before 2 years, and 441 were lost to follow-up with no subsequent AK diagnosis before 5 years.

Table I describes the distribution of baseline covariates by exposure groups. The Kaplan-Meier estimators of the two survival curves indicate a statistically significant reduction in subsequent AK risk for 5-FU compared to imq at 2 years but not at 5 years (Figure 2). The crude (unweighted) estimate of the cumulative risk difference was -4.78% ($p=0.006$) at 2 years and -1.11% ($p=0.27$) at 5 years, while the adjusted estimate based on IPW estimation was -4.54% (95% CI: -7.91% to -1.17%) at 2 years and -1.43% (95% CI: -3.43% to 0.05%) at 5 years. The opposite values of these risk differences can be interpreted as the excess risks of subsequent AK if all patients in the cohort were treated with imq versus if all patients were treated with 5-FU. The hazard ratio from the Cox proportional hazard model fitted with IP weights was 0.929 (95% CI: 0.851 to 1.015], while that fitted without IP weights was 0.945 (95% CI: 0.866 to 1.032). The maximum value for the IP weights was 2.55, suggesting that extreme weighting and strong observed confounding were not concerns.¹⁶

DISCUSSION

In this large cohort study based in a real-world HMO setting with comprehensive integrated healthcare delivery, we show that 5-FU may be more effective than imq in preventing subsequent AKs in the short-term, but we did not find statistically significant evidence of a difference in the long-term.

To our knowledge, this is the first study to compare the effectiveness of 5-FU and imq in preventing subsequent AKs in a real-world setting. Only two small randomized trials have directly compared the efficacy of 5-FU and imq for the treatment of AKs: one trial ($n=36$, duration=24 weeks) found that 5-FU was more effective than imq in reducing final AK count, and achieving complete AK clearance;¹⁸ whereas the other ($n=50$, duration=12 months) found that imq resulted in superior sustained clearance compared with 5-FU.¹⁵ Previous studies have shown that both 5-FU and imq provide a sustained clinical benefit at two years.^{12,19} Our direct comparison of 5-FU and imq in a real-world clinical setting suggests that 5-FU may be superior to imq in the short-term, though there are no statistically significant long-term differences. Our results are in agreement with a recent meta-analysis that ranked 5-FU above imq in determining the relative efficacy of eight AK treatments based on complete clearance,²⁰ leading the authors to conclude that 5-FU should be the treatment of choice for AKs to prevent progression to KC.²⁰

The observed differences in duration of effect may be related to 5-FU and imq's distinct mechanisms of action. 5-FU decreases cellular proliferation and induces cell death by interfering with DNA and RNA synthesis through inhibition of thymidylate synthetase.⁵ In contrast, imq acts as an immune modulator through the activation of toll-like receptors, which ultimately induces the production of cytokines and enhances innate and acquire immune responses with antitumor activity.⁵ The immune response that imq induces may be more short-lived than 5-FU's inhibitory effect on DNA and RNA synthesis. A randomized placebo-controlled trial evaluating the long-term efficacy of 5-FU for AK treatment in 954

patients found that a single course of 5-FU reduced AK counts and the need for spot treatments for longer than two years,¹² providing further support for its efficacy at two years post-treatment.

Strengths of this study include the closed KPNC healthcare system, which enables a community-based comparison of the efficacy of 5-FU and imq. The comprehensive care patients receive at KPNC is captured by a computerized health record, allowing us to accurately assess AKs and potential pre-treatment confounders. Unlike a clinical trial, this study included patients with a variety of characteristics, and not just those that fit specific eligibility criteria. Limitations of this retrospective study include the inability to control for disease severity and the potential for unmeasured pre-treatment variables that affect subsequent AK risk and may have been associated with differential prescribing of 5-FU and imq, such as prior treatment failure. However, we maximized uniformity in the cohort and minimized confounding by unmeasured risk factors by limiting eligibility to members who had sufficient sun damage to have had an AK diagnosed and a topical field-based treatment prescribed. A formal causal analytic approach was used to adjust effect estimates for the potential confounding bias by measured pre-treatment covariates, such as prior KC, which may suggest higher disease severity. Prior 5-FU exposure may have affected patients' overall AK burden and influenced subsequent treatment selection given familiarity with the drug, its efficacy, and its side effect profile. Given the potential impact of prior 5-FU exposure on treatment selection and subsequent AK risk, we adjusted for it in our multivariate analysis. Although our analyses did not account for potential bias from differential clinical monitoring during follow-up between the two exposure groups (informative interval-censoring), differential surveillance is not expected.¹⁵ We relied on prescriptions filled at KPNC pharmacies as a surrogate for medication use, which may not reflect patients' true exposure. However, this reflects a true practice setting and enables measurement of effectiveness, rather than efficacy like in a clinical trial. Treatment with 5-FU and imq spans several weeks, leading to many opportunities for non-compliance. However, differential non-compliance between the two agents was not expected because their directions for use, duration of application, and side-effect profiles are quite similar,¹⁵ though a recent Cochrane review did suggest that 5-FU may cause higher rates of irritation than imq.⁵ However, if irritation were to cause decreased compliance among those treated with 5-FU, we would expect to see decreased efficacy in preventing subsequent AKs. We saw a lower risk of AKs among those treated with 5-FU at two years, and we might expect to see an even stronger effect were irritation not a confounder. We did not examine subsequent treatment with additional field-based therapies during the study period. Although we did not account for potential informative interval-censoring, we adjusted for differential surveillance prior to baseline. We ascertained subsequent AK diagnoses through ICD-9 codes, which are not site-specific; we were therefore unable to confirm whether subsequent AKs arose in the treated field. However, it is unlikely that there are differential effects on subsequent AKs arising outside of the treated field by exposure category (i.e., that patients treated with imq would have fewer or more AKs arising outside of the treated area than patients treated with 5-FU). Finally, our study was conducted among insured adults in Northern California. Our results may not be completely generalizable to uninsured persons and other healthcare or geographic settings.

In summary, our findings suggest that between 5-FU and imq, the two most common topical agents for field-based treatment of AKs, 5-FU may be more effective in preventing subsequent AKs in the short-term. We found no statistically significant differences in the long-term. Though there remains no agreement on the most efficacious AK treatment,⁶ this direct comparison performed in a real-world clinical setting suggests that 5-FU should be considered over imq for short-term reduction in subsequent AK risk.

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Abbreviations

AK	actinic keratosis
KC	keratinocyte carcinoma
SCC	squamous cell carcinoma
5-FU	fluorouracil
Imq	imiquimod
KPNC	Kaiser Permanent Northern California
CI	confidence interval
ICD-9	International Statistical Classification of Diseases and Related Health Problems, 9 th revision
HIV	human immunodeficiency virus
CLL	chronic lymphocytic leukemia
UV	ultraviolet
ITT	intention-to-treat
IPW	inverse probability weighting
PS	propensity score

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Figure 1.
Study flow diagram
Flow diagram depicting the derivation of the study cohort.

Figure 2.

Kaplan-Meier estimators (crude)

Kaplan-Meier estimators showing the probability of subsequent actinic keratosis (AK) based on treatment type. The Kaplan-Meier estimators indicate a statistically significant reduction in risk of subsequent AK for 5-FU compared to imiquimod at 2 years but not at 5 years.

Table I

Characteristics of KPNC members treated with 5-FU or imiquimod for actinic keratosis in 2007

VARIABLES	Full Cohort (n=5,700)	5-FU (n=5,062)	Imiquimod (n=638)	P values
Demographics				
Age, years, mean (SD)	66.6 (11.6)	66.6 (10.6)	66.6 (12.3)	0.9619
Age years, n (%)				
18–49	427 (7.5%)	379 (7.5%)	48 (7.5%)	0.0222
50–65	2,232 (39.2%)	1,968 (38.9%)	264 (41.4%)	
66–80	2,322 (40.7%)	2,094 (41.4%)	228 (35.7%)	
>80	719 (12.6%)	621 (12.3%)	98 (15.4%)	
Gender, n (%)				
Male	3,383 (59.3%)	3,042 (60.1%)	341 (53.5%)	0.0013
Female	2,317 (40.7%)	2,020 (39.9%)	297 (46.5%)	
Race and Ethnicity, n (%)				
Non-Hispanic White	5,283 (92.7%)	4,688 (92.6%)	595 (93.3%)	0.5533
Other	417 (7.3%)	374 (7.4%)	43 (6.7%)	
Risk Factors for AK/KC				
Cigarette use, n (%)				
Never	3,534 (62.0%)	3,131 (61.9%)	403 (63.2%)	0.9254
Former	1,809 (31.7%)	1,614 (31.9%)	195 (30.6%)	
Current	258 (4.5%)	229 (4.5%)	29 (4.6%)	
Unknown/Not Asked/Second Hand	99 (1.7%)	88 (1.7%)	11 (1.7%)	
Body mass index, n (%)				
24.9 (normal)	1,850 (32.5%)	1,622 (32.0%)	228 (35.7%)	0.0633
25–29.9 (overweight)	2,263 (39.7%)	2,014 (39.8%)	249 (39.0%)	
30 (obese)	1,409 (24.7%)	1,273 (25.2%)	136 (21.3%)	
Unknown/missing	178 (3.1%)	153 (3.0%)	25 (3.9%)	
Photosensitizing drug exposure,^{1,2} n (%)				
No	1,300 (22.8%)	1,155 (23.6%)	148 (23.2%)	0.8354
Yes	4,400 (77.2%)	3,869 (76.4%)	490 (76.8%)	
Prior AK,¹ n (%)				
No	1,270 (22.3%)	1,155 (22.8%)	145 (22.7%)	0.9594
Yes	4,430 (77.7%)	3,907 (77.2%)	493 (77.3%)	
Prior KC,¹ n (%)				
No	3,298 (57.9%)	2,993 (59.1%)	305 (47.8%)	<.0001
Yes	2,402 (42.1%)	2,069 (40.9%)	333 (52.2%)	

VARIABLES	Full Cohort (n=5,700)	5-FU (n=5,062)	Imiquimod (n=638)	P values
Prior 5-FU treatment,^{1,3} n (%)				
No	3,144 (55.2%)	2,755 (54.4%)	389 (61.0%)	0.0017
Yes	2,556 (44.8%)	2,307 (45.6%)	249 (39.0%)	
Baseline Healthcare Utilization				
Charlson comorbidity score				
0	3,543 (62.2%)	3,139 (62.0%)	404 (63.3%)	0.5400
1–2	1,549 (27.2%)	1,375 (27.2%)	174 (27.3%)	
3+	608 (10.7%)	548 (10.8%)	60 (9.4%)	
Outpatient Utilization: Mean (SD) outpatient visits ¹	10.9 (9.6)	10.9 (9.8)	11.4 (10.1)	0.2290
Surveillance: Mean (SD) dermatology visits ¹	1.6 (1.8)	1.6 (1.8)	1.9 (1.8)	<.0001
Prescriber Type				
Dermatologist	5,386 (94.5%)	4,770 (94.2%)	616 (96.6%)	0.0155
Non-Dermatologist	314 (5.5%)	292 (5.8%)	22 (3.4%)	

¹ Average annual number in two years prior to cohort entry.

² Photosensitizing drugs included tetracyclines, sulfonamide antibiotics, fluoroquinolones, thiazide diuretics, loop diuretics, calcium channel blockers, potassium-sparing diuretics, alpha-adrenergic agonists, antiarrhythmics, sulfonyleureas, antimetabolites, antiestrogens, salicylic acid derivatives, propionic acid derivatives, acetic acid derivatives, enolic acid derivatives, benzodiazepines, tricyclic antidepressants, and oral retinoids.¹³

³ There is no prior imiquimod exposure in the cohort because imiquimod was not available prior to 2007.

KPNC: Kaiser Permanente Northern California; 5-FU: 5-fluorouracil; KC: keratinocyte carcinoma; AK: actinic keratosis