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Actinic Keratosis

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JAMA DERMATOLOGY

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.

JAMA Dermatol. 2015;151(9):952-960.
doi:10.1001/jamadermatol.2015.0502

Actinic keratosis (AK) is a very common skin lesion. Although AKs are not malignant, about 0.1% to 0.6% will transform to squamous cell carcinomas,[1] which are troublesome to treat. What is not known is whether all AKs should be treated and, if so, which of all the available treatments for AKs should be used.

There is ample evidence that AKs are premalignant, and p53 and p16 tumor suppressor mutations are found in both AKs and squamous cell carcinomas.[2] In one study, AKs were contiguous to primary lesions in 44% of 22 cases of metastatic squamous cell carcinoma.[3] Other studies of the relationship between AK and squamous cell carcinoma found that 82.4% of 165 squamous cell carcinomas occurred with concomitant AKs; 26.7% arose within AKs, and 55.7% arose in close proximity to AKs.[4]

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Given the availability of numerous treatments for AKs, how is the optimal treatment selected? Although there are head-to-head trials of some topical therapies for AKs, these trials had limitations. Randomized clinical trials for treatment of AKs cannot be blinded because all of the agents used to treat these lesions cause skin irritation and therefore are usually easily distinguished from placebo. Many studies are limited because they did not confirm the histology of the AK diagnosis. In some cases, AKs may be confused with superficial squamous cell carcinomas.

A clinical trial published in the September 2015 issue of *JAMA Dermatology*[1] overcame some of these limitations. Pomerantz and colleagues[1] randomized 932 veterans who had 2 or more keratinocyte carcinomas in the 5 years before enrollment into groups that received either topical 5% fluorouracil cream (n = 468) or vehicle control cream (n = 464) applied to their face and ears twice daily for up to 4 weeks. After 6 months, patients treated with topical

fluorouracil had fewer AKs (3.0 vs 8.1 per patient, $P < .001$). Fewer AKs were found among patients in the active treatment group throughout the study duration with a mean follow-up of 2.6 years, and these patients also required fewer spot treatments, such as cryotherapy, compared with patients who received placebo. This trial overcame some of the limitations of previous studies of AK treatment by ensuring that patients without AKs at baseline were included, by using a vehicle control cream, and by allowing cryotherapy follow-up visits.

There are 2 major approaches for treating AK: destruction of isolated lesions or treating large areas of skin (ie, "field therapy"). Isolated lesions can be treated with destructive therapies like cryotherapy, trichloroacetic acid, or curettage and electrodessication. Field therapy, the approach investigated by Pomerantz et al,[1] in which large areas of skin are treated, can be accomplished by several approaches, including topical fluorouracil, diclofenac sodium, imiquimod, ingenol mebutate, and photodynamic therapy. Drug cost may guide which of these agents is preferred. For instance, there is a 10-fold difference in the cost of generic topical 5% fluorouracil ($103.42 for 40 g) compared with brand-name drugs ($743.68-$1141.81).[5] Another generic drug, 5% imiquimod cream, was also relatively inexpensive ($63.00 for 12 packets).[5]

Field therapy of AK may be limited by the irritation caused by the drugs used for this treatment. In a single-blind bilateral study comparing 0.5% fluorouracil cream on one side of the face once daily in 21 patients with 5% fluorouracil cream twice daily on the other side, fewer patients reported symptoms of irritation with the 0.5% cream, but the efficacy between the 2 dosing strategies was similar.[6] Another bilateral trial comparing diclofenac gel with topical 5% fluorouracil in 30 patients showed that diclofenac gel was less irritating. Only 27% developed moderate or severe erythema on the diclofenac-treated side of the face compared with 83% on the fluorouracil-treated side.[7]

Some patients have difficulty tolerating the long duration needed for some AK treatments. This is particularly difficult when inflammation, oozing, and crusting of the facial skin occur during the treatments. Ingenol mebutate can overcome this problem because this agent is applied for only 3 days and local facial skin reactions usually resolve in 2 weeks or less.[8] Photodynamic therapy and other destructive modalities like laser resurfacing and acid peels are administered as single treatments, and recovery periods vary from days to weeks.

Well-executed clinical trials have shown some agents to be more effective than others in treating AK. In the pivotal trials for 5% imiquimod cream, complete clearance occurred in 45.1% (of 215 patients) compared with 3.2% (of 221 patients) for vehicle.[9] Similar complete clearance rates occurred with ingenol mebutate (42.2% [of 277 patients] vs 3.7% [of 270 patients] for placebo) on the face and scalp.[8]

The study by Pomerantz et al[1] confirms the efficacy of 5% fluorouracil cream. Application of 5% fluorouracil twice daily for up to 4 weeks resulted in greater reductions in AKs at 6 months and in less need for spot treatments than placebo vehicle treatment. The reductions in AKs and need for treatments persisted for more than 2 years. This is a useful first step in achieving the ultimate goal of managing patients with AK, ie, reducing squamous cell carcinomas of the skin. Longer follow-up of patients would help answer the critical question: does a single 2- to 4-week course of fluorouracil treatment of AKs reduce the future development of squamous cell carcinoma?

ARTICLE INFORMATION

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Lebwohl reported having served as an investigator, consultant, or both for LEO Pharmaceuticals, Valeant, AbGenomics, Amgen, Can-Fite Biopharma, Coronado Biosciences, Dermipsor, Forward Pharma, Janssen Biotech, Lilly, Meda Pharmaceuticals, Merck, Novartis, Pfizer, Taro Pharmaceuticals, and UCB Pharma.

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