

COMPARISON OF 5% 5-FLUOROURACIL CREAM AND 5% IMIQUIMOD CREAM IN THE MANAGEMENT OF ACTINIC KERATOSES ON THE FACE AND SCALP

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Abstract

It is timely to compare the efficacy and tolerability of 2 actinic keratosis (AK) therapies—5% 5-fluorouracil (5-FU) cream and imiquimod cream. Thirty-six patients with 4 or more AKs were randomly assigned to receive 5% 5-FU cream twice daily for 2 to 4 weeks or 5% imiquimod cream twice weekly for 16 weeks. Five percent 5-FU was more effective than imiquimod in exposing what were presumed to be subclinical AKs, reducing the final AK count (total AK count declined during the 24-week study by 94% vs. 66%, $P < .05$), achieving complete clearance (incidence of 84% vs. 24% by week 24, $P < .01$), and achieving clearance rapidly. Tolerability was similar except for erythema, which was initially significantly higher with 5-FU than imiquimod but resolved rapidly and was significantly lower than imiquimod by week 16. Five percent 5-FU remains the gold standard field therapy for AKs.

Introduction

Actinic keratoses (AKs) are dysplastic epidermal lesions that have the potential to develop into invasive squamous cell carcinomas. Occurring with a prevalence of 11% to 25% in the northern hemisphere,¹ they develop most commonly in fair-skinned individuals who have had prolonged exposure to ultraviolet radiation.² AKs are probably an early stage in a biologic continuum that culminates in squamous cell carcinomas^{2,3} and, although it is known that up to 16% of untreated AKs will progress to squamous cell carcinomas each year,⁴ it is difficult to predict which lesions will undergo malignant transformation. As a result, it is advisable to treat all AKs before they have a chance to progress to invasive cancer.

AKs can be treated using ablative options (including liquid nitrogen cryosurgery and curettage) and topical approaches (eg, 5-fluorouracil [5-FU], diclofenac sodium, photodynamic therapy with aminolevulinic acid hydrochloride, and imiquimod). Ablative options are optimal for hypertrophic and clearly delineated lesions but are not effective in resolving subclinical lesions and can be associated with a risk of scarring, infection, and dyspigmentation.⁵ Topical medications are better suited than ablative spot treatments for treating larger areas of skin and have the significant advantage of treating subclinical AKs as well as clinically apparent AKs. This is important as patients may have 10 times as many subclinical lesions as visible lesions.⁶

Imiquimod was approved by the US FDA for the treatment of AKs in 2004. Therefore, there are few data directly comparing it with other topical treatments for AKs. As a result, it is timely to compare its efficacy and tolerability with 5-FU, which has been the gold standard field therapy for AKs since its approval in 1970.

Methods

Patients

Adult patients at least 21 years of age were eligible to enroll in this 2-center, physician-blinded, randomized study if they had at least 4 AKs in one 25-cm² area (ie, one cosmetic unit) on the face, forehead, or scalp. Cosmetic units were defined as the forehead, left cheek including the ear, right cheek including the ear, central face (nose, upper lip, lower lip, and chin), or scalp. In each patient, each cosmetic unit containing at least 4 AKs was treated.

Patients were ineligible for the study if their target AKs had been treated in the preceding 2 months. They were also ineligible if they had received other specified treatments during any of the following time periods before study entry: one month prior for any investigational product or for liquid nitrogen on the face or neck area; 2 months prior for aminolevulinic acid hydrochloride, systemic or topical chemotherapy, systemic or topical immunotherapy, systemic or topical steroids, oral or topical retinoids, diclofenac, topical 5-FU, or any other treatment that could affect AKs; or 6 months prior for facial resurfacing procedures.

Patients were excluded from the study if they were pregnant, lactating, or of childbearing potential; were immunosuppressed; had scheduled elective surgery within 30 days of the study; had any clinical laboratory value outside the normal range, or any organic or psychological disease that could interfere with the outcome or interpretation of the study results; or had an active herpes infection in the 30 days preceding study entry. Patients were required to be willing to refrain from using topical products on the affected area during the treatment period. In addition, they were requested to attend the study visits without makeup on their face or neck.

The study protocol was approved by the relevant institutional review boards and was conducted in accordance with the Declaration of Helsinki, including amendments up to and including the Hong Kong revision (1989). All patients provided signed informed consent.

Treatment Regimen

Patients were randomly assigned to receive one of the following treatments to be applied in a thin layer to completely cover each affected cosmetic unit: 5% 5-FU cream twice daily for 2 to 4 weeks or 5% imiquimod cream overnight twice each week for 16 weeks. No other medications were allowed to be applied to the face or neck area during the study although moisturizers could be applied, as necessary, at least one hour after the study medication. Other medications prohibited during the study were isotretinoin, tretinoin, adapalene, tazarotene, topical and systemic steroids, 5-FU (other than on the target AKs), systemic cancer chemotherapy, immunotherapy, and investigational products.

Outcome Measures

Patients were evaluated at baseline and weeks 4, 8, 12, 16, and 24 and the outcome was assessed in terms of AK count, percent change in AK count, incidence of complete clearance, physician's global assessment, patient perception of efficacy, physician's assessment of erythema, and patient perception of discomfort associated with the treatment. The physician's global assessment and the patients' perception of efficacy were assessed using a scale of 1 = very effective, 2 = moderately effective, 3 = slightly effective, and 4 = not effective at all. The physician's assessment of erythema was assessed using a scale of 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Finally, the patients' perception of discomfort was assessed using a scale of 1 = very painful, 2 = moderately painful, 3 = slightly painful, and 4 = not painful at all.

Statistical Analyses

Between-group differences in AK count, percent change in total AK count, incidence of complete clearance, and mean scores for the physician's global assessment and physician's assessment of erythema were analyzed using the paired student t test. For all analyses, a 2-sided *P*-value of .05 or less was considered to be statistically significant.

Results

Patients

Of 39 patients enrolled in the study, 36 (92%) completed the study (19 treated with 5% 5-FU, 17 treated with imiquimod). Two patients in the imiquimod group and one patient in the 5-FU group were lost to follow-up shortly after randomization.

Efficacy

At baseline, the total AK count (the sum of all AKs in all patients) was 646 in the 5% 5-FU group and 490 in the imiquimod group. In the 5% 5-FU group, the total AK count almost doubled at week 4 (presumably due to exposure of subclinical lesions) and then fell dramatically to 80 at week 8 and to 40 or less from week 12 onward (Figure 1).

Figure 1. Total actinic keratosis count across all completing patients (n = 19 in 5% 5-FU group, n = 17 in imiquimod group).

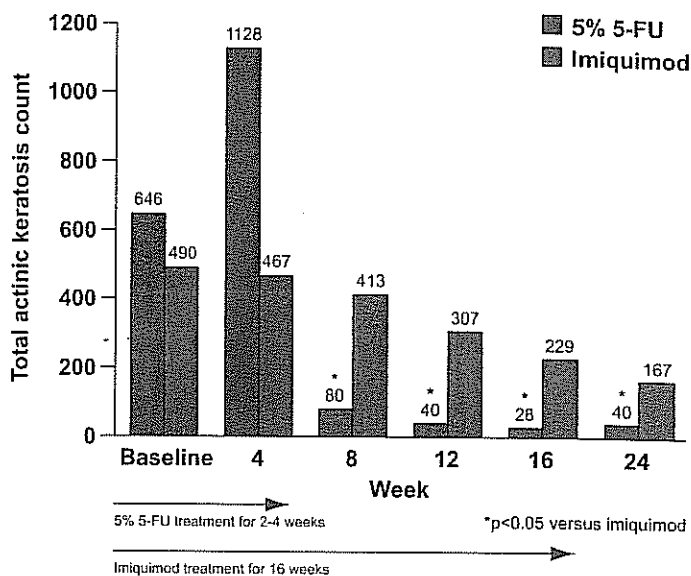
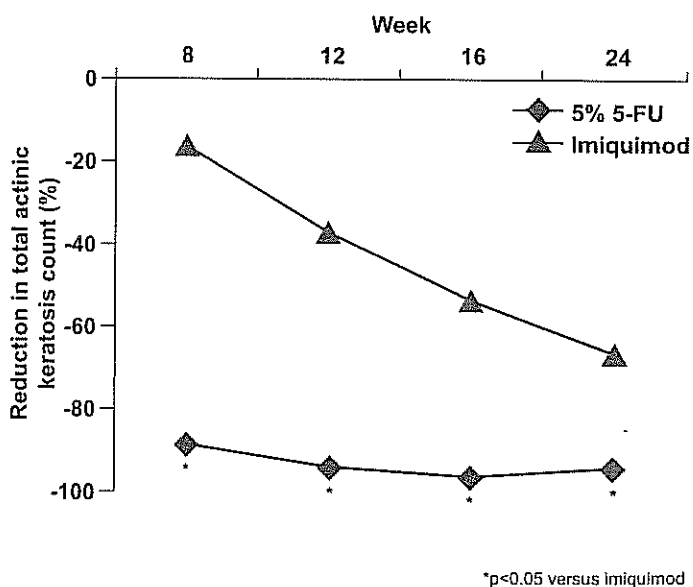


Figure 2. Mean reduction in total actinic keratosis count from baseline.



By contrast, in the imiquimod group, the total AK count decreased gradually at each successive visit to a low of 167 at week 24. Despite the initially higher level in the 5% 5-FU group, the total AK count decreased more in this group so that counts were significantly lower in the 5% 5-FU group than the imiquimod group from weeks 8 through 24. Consequently, the percent reductions in the total AK count were also significantly greater with 5% 5-FU than imiquimod from week 8 onward. At week 24, the total AK count was reduced by 94% from baseline with 5% 5-FU compared to 66% with imiquimod (Figure 2).

The incidence of patients with at least a two-thirds reduction in their AK count at week 24 was 100% in the 5% 5-FU group compared with 53% in the imiquimod group. In individual patients, the reduction in AK count at week 24 ranged from 69% to 100% of the baseline level in the 5% 5-FU group and was more variable—ranging from 0% to 100%—in the imiquimod group. Complete clearance of AKs was attained in a significantly greater proportion of patients in the 5% 5-FU group than the imiquimod group by week 24 (84% vs. 24%, $P < .01$). Complete clearance was also attained more rapidly with 5% 5-FU than with imiquimod. At week 12, 63% of patients had achieved complete clearance with 5% 5-FU.

Mean scores for the physician's global assessment showed that 5% 5-FU resulted in significantly greater efficacy than imiquimod from week 4 through week 24 (Figure 3).

Figure 3. Mean scores for the physician's global assessment.

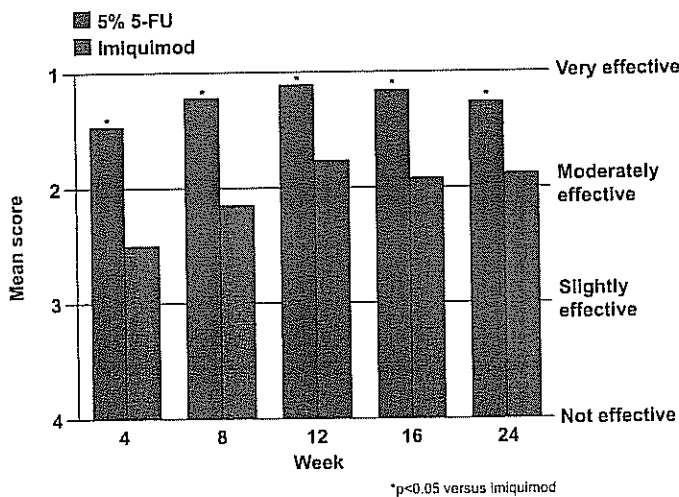
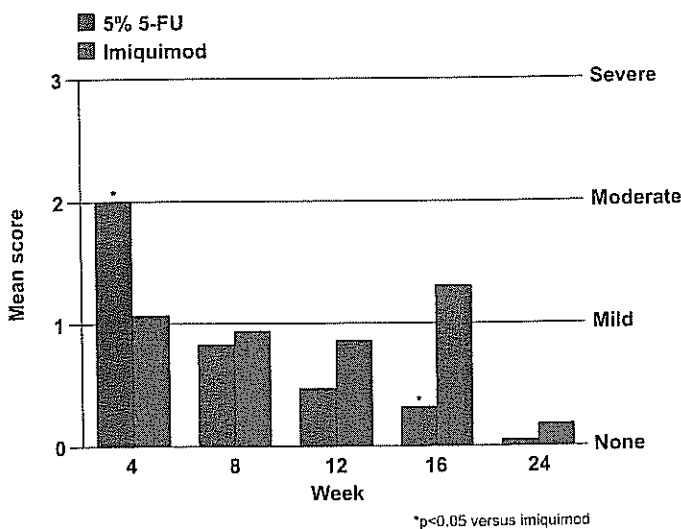


Figure 4. Mean scores for the physician's assessment of erythema.



Patient ratings were similar and revealed consistently greater efficacy with 5% 5-FU than with imiquimod.

Tolerability

The types of local skin reactions experienced by patients were similar with both therapies. In both groups, the majority of patients experienced erythema, crusting, erosion, and edema (consistent with the therapeutic effects of these agents).

Although erythema was transient in all patients, it persisted longer in those receiving imiquimod than in those receiving 5% 5-FU. Physician assessments of erythema showed that mean levels were moderate in the 5% 5-FU group at week 4 and then decreased steadily post-treatment to less than mild from week 8 onward and to virtually none by week 24 (Figure 4). In contrast, mean levels of erythema in the imiquimod group remained at mild levels throughout the 16-week duration of treatment and did not decrease substantially until week 24. The patients' mean ratings of discomfort associated with treatment were less than "slightly painful" in both groups throughout the study (Table 1).

Discussion

The results of this trial demonstrate that twice-daily 5% 5-FU cream for 2 to 4 weeks offers significantly greater efficacy, as well as more rapid improvement, than twice-weekly 5% imiquimod cream for 16 weeks. Between baseline and week 24, the total AK count was reduced by 94% with 5% 5-FU versus 66% with imiquimod. In addition, the incidence of complete clearance by week 24 was 84% versus 24%, respectively. Five percent 5-FU cream has previously demonstrated complete clearance rates of approximately 85%, as reported in the original New Drug Application for

Table 1. Mean scores for the patients' perception of discomfort associated with their treatment.

Week	Mean score \pm standard deviation	
	5-FU	Imiquimod
4	3.1 \pm 1.02	3.9 \pm 0.26
8	3.8 \pm 0.54	3.7 \pm 0.48
12	4.0 \pm 0.23	3.7 \pm 0.47
16	4.0 \pm 0.00	3.9 \pm 0.34
24	3.7 \pm 0.81	3.9 \pm 0.33

Scale used: 1 = very painful, 2 = moderately painful, 3 = slightly painful, and 4 = not painful at all.

this agent.⁷ In addition, although the approved regimen for 5% 5-FU cream is twice-daily dosing, once-daily applications have been reported to result in a comparable clinical cure rate (92%) and a faster resolution of erythema.⁸ Moreover, with even less frequent dosing (4 applications in the first week and 2 to 4 applications per week thereafter), a healing rate of 89% has been reported with 5% 5-FU.⁹ In comparison, phase III studies evaluating the use of imiquimod 5% cream, twice weekly for 16 weeks, reported complete clearance in 45% of patients and a median reduction in AK count of 83%.¹⁰

Compared with imiquimod, 5% 5-FU treatment was more likely to result in an increase in the number of AKs visible at some point during therapy (a sign that subclinical AKs were likely being exposed, although confirmatory biopsies were not performed). This suggests that 5% 5-FU was more effective in exposing subclinical AKs than imiquimod.

Although both regimens resulted in erythema, the duration of erythema was shorter with the 5% 5-FU regimen than the imiquimod regimen. With 5% 5-FU, patients experienced an initial brisk inflammatory reaction that generally resolved within a few weeks. In contrast, although the erythema arising with imiquimod was generally not as marked as with 5% 5-FU, it tended to persist for 16 weeks.

Five percent 5-FU has additional clinical benefits relative to imiquimod. For example, it can be used on multiple areas of the body (eg, face, scalp, trunk, and limbs) whereas imiquimod is approved by the FDA for use only on the face or scalp (not both concurrently), and is not approved for full-face application during a single treatment session.¹¹ In addition, imiquimod is an immune response modifier and, unlike 5-FU, is approved for use only in immunocompetent adults.¹¹ Five percent 5-FU cream also has significant cost advantages over imiquimod.

Conclusions

Twice-daily topical 5% 5-FU cream for 2 to 4 weeks offered greater efficacy than twice-weekly imiquimod 5% cream for 16 weeks. Five percent 5-FU was more effective than imiquimod in exposing what were presumed to be subclinical AKs, reducing the final AK count, and achieving complete clearance. Five percent 5-FU also achieved complete clearance more rapidly than imiquimod. The response to 5% 5-FU was generally predictable but the response to imiquimod was more variable, suggesting that imiquimod requires closer monitoring than 5% 5-FU in clinical practice. The tolerability profile of the 2 regimens was generally similar with one exception—erythema levels were initially significantly higher with 5% 5-FU than with imiquimod but resolved more rapidly and were significantly lower with 5% 5-FU than imiquimod by week 16. Five percent 5-FU remains the gold standard field therapy for AKs.

Disclosure

Valeant Pharmaceuticals International provided a grant for the study. Neither author has any other relevant financial disclosures.

References

1. Frost CA, Green AC. Epidemiology of solar keratoses. *Br J Dermatol.* 1994;131:455-464.
2. Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. *J Am Acad Dermatol.* 2000;42:4-7.
3. Cockerell CJ, Wharton JR. New histopathological classification of actinic keratosis (incipient intraepidermal squamous cell carcinoma). *J Drugs Dermatol.* 2005;4:462-467.
4. Glogau RG. The risk of progression to invasive disease. *J Am Acad Dermatol.* 2000;42:23-24.
5. Jorizzo JL, Carney PS, Ko WT, Robins P, Weinkle SH, Werschler WP. Treatment options in the management of actinic keratosis. *Cutis.* 2004;74(suppl):9-17.
6. Actinic keratosis: What you should know about this common precancer. Available at: <http://www.skincancer.org/ak/index.php>. Accessed April 7, 2006.
7. Jeffes EWB III, Chen JT. New approaches to the treatment of actinic keratosis. *Am J Cancer.* 2003;2:151-168.
8. Woodson J. Efficacy and tolerability of 5% 5-fluorouracil cream applied once-daily as an alternative to twice-daily for the treatment of actinic keratoses on the face and scalp. Poster presented at: 63rd Annual Meeting of the American Academy of Dermatology; February 18-22, 2005; New Orleans, LA.
9. Labandeira J, Pereiro M Jr, Valdes F, Toribio J. Intermittent topical 5-fluorouracil is effective without significant irritation in the treatment of actinic keratoses but prolongs treatment duration. *Dermatol Surg.* 2004;30:517-520.
10. Lebwohl M, Dinehart S, Whiting D, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *J Am Acad Dermatol.* 2004;50:714-721.
11. Aldara [package insert]. St Paul, MN: 3M Pharmaceuticals; 2004.

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