Efficacy and Tolerability of Once-Daily 5-Fluorouracil 5% Cream for Treatment of Actinic Keratoses

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Twice-daily topical application of 5-fluorouracil 5% cream has been widely used to effectively treat actinic keratoses (AKs). In this study, once-daily application of 5-fluorouracil 5% cream for 4 weeks was evaluated in 12 patients, and monitoring of lesions continued for an additional 8 weeks. Complete clearance of AKs was achieved at 12 weeks in 92% (11 of 12) of patients. The total count of AK lesions initially increased more than 2-fold from baseline during weeks 2 and 3 of treatment, as subclinical lesions became evident. By 12 weeks, the total count of lesions had been reduced by more than 99% from baseline. Once-daily 5-fluorouracil 5% cream was well tolerated. On average, patients reported that it was "slightly painful" at week 2 and "not painful at all" at weeks 4 and 8. Once-daily application of 5-fluorouracil 5% cream appears to be an effective and useful alternative to the traditional twice-daily regimen for treatment of AKs.

Actinic keratoses (AKs) are prevalent, occurring in an estimated 5 million Americans.[1] Risk factors include an individual's cumulative lifetime sun or UV exposure, sensitivity to UV exposure (fair skin), immune status, and age.[2] Although the prevalence of AKs increases dramatically with age, a substantial number of patients younger than 40 years present with the condition.[3]

Treatment options for AKs include cryosurgery, curettage, photodynamic therapy, and topically applied creams. Cryosurgery has been the gold standard for treating visible AK lesions. Topically applied therapies have the advantage of treating not only visible AK lesions but also subclinical lesions. Diclofenac sodium 3% gel and imiquimod 5% cream are 2 of the topical AK therapies available.[4,5] They are administered twice daily for 60 to 90 days and twice weekly for 16 weeks, respectively. Imiquimod 5% cream demonstrated complete clearance of AKs in 44% (48 of 108) and 46% (49 of 107) of patients in 2 pivotal trials.[5] A recent study of diclofenac sodium 3% gel applied twice daily in 28 patients demonstrated clearance of 89% (111 of 125) of AK lesions from baseline. In the same comparison trial, twice-daily treatment with 5-fluorouracil 5% cream resulted in clearance of 98% (124 of 126) of AK lesions.[6]

The compound 5-fluorouracil, the active ingredient in several topical therapeutics for AKs, induces an inflammatory response in and around AKs that is believed to be associated with successful clearance of the lesions.[7] The 5-fluorouracil creams are typically administered for

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2 to 4 weeks, shorter treatment regimens than those of diclofenac sodium 3% gel and imiquimod 5% cream. In a study conducted by Weiss et al,[8] treatment with 5-fluorouracil 0.5% cream, administered once daily for 4 weeks, achieved total clearance of AK lesions in 47.5% of patients. In another study, by Jorizzo et al,[9] 5-fluorouracil 0.5% cream, administered once daily for 4 weeks, achieved total clearance of AK lesions in 57.8% of patients. The 5-fluorouracil 5% cream, administered twice daily for 2 to 4 weeks, achieved complete clearance of AKs in 75% to 86.5% of patients.[7] In a comparative trial, treatment with 5-fluorouracil 5% cream twice daily for 4 weeks resulted in a 94% mean reduction in total AK lesion counts when measured 2 months posttreatment, whereas imiquimod 5% cream resulted in a 66% reduction when measured 2 months after completion of a 16-week treatment course.[10] In addition, 5-fluorouracil 5% cream achieved complete clearance of AKs in 63% (12 of 19) of patients in this study compared with 24% (4 of 17) of patients treated with imiquimod 5% cream, when measured 8 weeks posttherapy.[10]

Twice-daily treatment with 5-fluorouracil 5% cream for 2 to 4 weeks has shown the best efficacy, along with the shortest treatment period, of any topically applied treatment for AKs. The purpose of this study was to examine the efficacy of 5-fluorouracil 5% cream when administered once daily to patients with AKs.

METHODS

This was an open-label, single-center pilot study, conducted in accordance with the Declaration of Helsinki and approved by an institutional review board; written informed consent was obtained from all participants.

Participants were 21 years of age or older and had 4 or more AKs in each of 1 or 2 facial cosmetic units (eg, cheeks, forehead, central face, or scalp). Patients had not undergone facial resurfacing procedures such as chemical peel, laser resurfacing, or dermabrasion in the previous 6 months, and had not been treated with liquid nitrogen within the previous 60 days. Those who were immunosuppressed or women who were pregnant, lactating, or planning to become pregnant were excluded. Participants had not used any other investigational product in the previous month and did not apply any other medications during the study.

Participants applied 5-fluorouracil 5% cream once daily (overnight) for 4 weeks to 1 or 2 cosmetic units, each containing at least 4 AKs. The primary end point was the percentage of patients showing complete clearance of AKs at the 12-week visit. Secondary end points included the mean percentage reduction in total counts of AKs and evaluations of patients' tolerability, erythema, and overall improvement. Adverse events were assessed at each study visit by the investigating physician and graded on a scale of 0 to 3 (0=none, 1=mild, 2=moderate, 3=severe).

RESULTS

Fifteen patients were enrolled, and 12 completed the study; the remaining 3 patients were lost to follow-up shortly after beginning therapy. The mean age of the 12 patients who completed the study was 59 years (range, 37–85 years).

A total of 143 AKs identified at baseline were treated in the study with once-daily application of 5-fluorouracil 5% cream (Figure 1). The mean number of AKs per patient at baseline was 11.9. The total count of AKs increased markedly from baseline to weeks 2 to 4 during treatment as subclinical lesions became apparent (Figure 1). A greater than 2-fold increase in total AK lesions was found in weeks 2 and 3 of treatment. After 4 weeks, treatment ended, and total counts of AKs decreased to 48 lesions at 8 weeks and 1 lesion at 12 weeks (Figure 1). Complete clearance of AKs at 12 weeks was achieved in 92% (11 of 12) of patients. The mean percentage of reduction from baseline in AKs at 12 weeks was greater than 99%.

The physician assessment of overall efficacy for once-daily 5-fluorouracil 5% cream therapy was scored on a 4-point scale (1=very effective, 2=moderately effective, 3=slightly effective, and 4=not effective). The mean efficacy score at 2 weeks was 1.5 and improved to 1 at 8 weeks (Table).

Physician assessments of erythema in 5-fluorouracil 5% cream–treated areas averaged 1.8 after 2 weeks, near the "moderate" rating (2) on the scoring scale (Figure 2). By the end of treatment at 4 weeks, the mean erythema

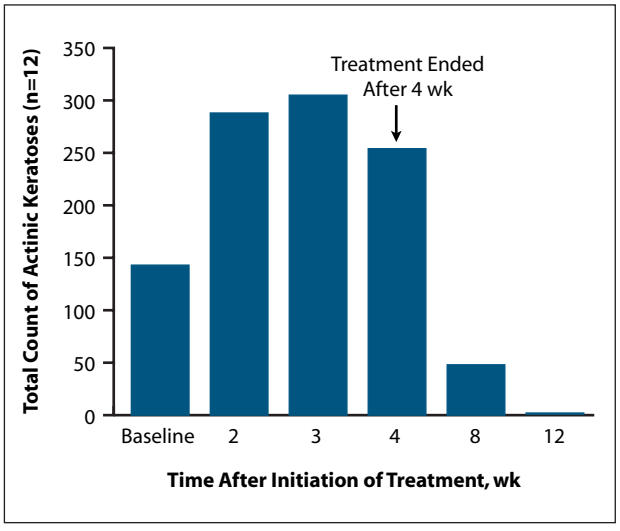

Figure 1. Total count of actinic keratoses during and after treatment with 5-fluorouracil 5% cream for 12 participants treated once daily. Note that the counts for weeks 2 to 4 include subclinical lesions. Treatment ended at week 4. Complete clearance of actinic keratoses was achieved for 92% (11 of 12) of patients.

Overall Efficacy of 5-Fluorouracil 5% Cream Treatment in 12 Patients Treated Once Daily

Weeks After Initiation of Treatment	Mean Efficacy Score*
2	1.5
3	1.2
4	1.1
8	1.0

*Scale: 1=very effective, 2=moderately effective, 3=slightly effective, 4=not effective.

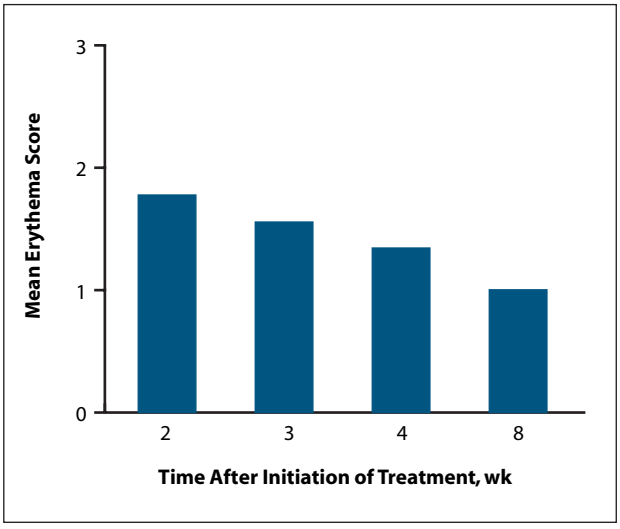

Figure 2. Mean erythema scores of 12 patients during and after once-daily treatment with 5-fluorouracil 5% cream. Erythema was assessed by the physician on a scale of 0 to 3 (0=none, 1=mild, 2=moderate, 3=severe). Treatment ended at week 4.

score had declined to 1.3, and by 8 weeks it had declined further to 1 (Figure 2).

The 5-fluorouracil 5% cream administered once daily was well tolerated. Mean tolerability of the treatment as reported by patients at 2 weeks was 3.1 on a scale of 1 to 4 (1=very painful, 2=moderately painful, 3=slightly painful, 4=not painful at all). At 4 weeks and 8 weeks, mean tolerability was 4. One hundred percent of patients reported that they would undergo once-daily 5-fluorouracil 5% cream therapy in the future. No serious adverse events occurred during the study.

DISCUSSION

Traditionally, 5-fluorouracil 5% cream is applied twice daily to areas of skin with AKs. This study was designed to evaluate the efficacy and tolerability of once-daily administration of 5-fluorouracil 5% cream for 4 weeks.

Of the 12 patients in the study, 11 (92%) had complete clearance of AK lesions at 12 weeks. The other patient had only a single remaining lesion. Importantly, subclinical AK lesions that were not evident at baseline became apparent during weeks 2 to 4 of treatment, with a greater than 2-fold increase in total counts of AK lesions found during weeks 2 and 3. At 12 weeks the mean AK lesion count per patient decreased by greater than 99% from baseline. Treatment provided the additional benefit of a cosmetic peel effect, as most patients experienced a visible improvement in their overall photodamage, and the physician's overall assessment of the treatment at week 8 was "very effective."

These results demonstrate that once-daily application of 5-fluorouracil 5% cream is as efficacious as a twice-daily regimen.

Once-daily 5-fluorouracil 5% cream was well tolerated. On average, patients reported that it was "slightly painful" at week 2 and "not painful at all" by weeks 4 and 8. The erythema typically accompanying 5-fluorouracil 5% cream treatment peaked at week 2 and was reduced to "mild" by week 8. The degree of erythema was less than that typically seen with twice-daily application. However, once-daily application did not compromise the efficacy of the treatment. No serious adverse events were reported during the study. As another measure of favorable tolerability, all patients were willing to repeat the once-daily treatment should their physicians find it necessary to prescribe it again in the future.

Once-daily administration of 5-fluorouracil 5% cream provides benefits in convenience for the patient compared with twice-daily administration. Additionally, a number of studies have demonstrated improved compliance with therapeutic regimens that employ a reduced dosing frequency,[11] and improved compliance should provide better clinical results.

This study's limitations include the small number of patients who participated, the open-label design, the absence of biopsies, and the lack of long-term follow-up for recurrence. Owing to the limitations of this study, additional long-term follow-up and direct blinded comparison studies are needed to confirm the equivalence of 5-fluorouracil 5% cream once daily with the twice-daily regimen.

CONCLUSION

Administration of 5-fluorouracil 5% cream once daily effectively treated AKs and was well tolerated by patients.

Complete clearance of AKs was achieved in 92% of patients. Once-daily application of 5-fluorouracil 5% cream appears to be a useful alternative to the traditional twice-daily application regimen.

***Acknowledgment*—**This study was supported by an unrestricted educational grant from Valeant Pharmaceuticals International, Aliso Viejo, Calif.

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