

Comparison of 5-Fluorouracil 5% and Imiquimod 5% for Actinic Keratoses

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A prime treatment option for field therapy of actinic keratoses (AKs) has long been 5-fluorouracil (5-FU) 5% cream because of its efficacy, safety, ease of application, and affordability. The author reports on an interim trial comparing 5-FU 5% cream (Efudex®) with the novel biologic agent imiquimod 5% cream for treating AKs. In preliminary results, although both agents appear to have efficacy, 5-FU 5% cream cleared more lesions, was easier to control, and cost less.

Dermatologists already have a generous number of strategies with which to treat actinic keratoses (AKs) and other manifestations of photodamaged skin. Recently, the topical immune modifier imiquimod 5% cream was introduced to treat AKs. This article reviews interim results from a study comparing the efficacy and tolerability of 5-fluorouracil (5-FU) 5% cream (Efudex®) and imiquimod 5% cream in patients with facial and scalp AKs.

FORMULATIONS CONTAINING 5-FU

Formulations containing 5-FU have been widely used for over 30 years and well accepted for their efficacy

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and ease of application. The 5-FU 5% formulation has been the gold standard for field therapy of AKs. Complete response rates (defined as complete clearing of AKs at the end of study) for this therapy range from 75% to 86.5% for 5-FU 5%¹ and from 40% to 87.5% for imiquimod 5%.¹

5-FU 5% also has a short treatment time, 2 to 4 weeks, and it detects, brings out, and treats sub-clinical AKs. Moreover, 5-FU 5% cream produces facial rejuvenation as a result of its cosmetic peel effect. It has a low recurrence rate and is cost-effective.

The most frequently reported adverse events of 5-FU 5% include erythema, crusting, and superficial ulceration that reliably occur and are based on a 2- to 4-week, twice-a-day course of treatment. During treatment it is important to evaluate the extent of side effects and to taper off therapy when appropriate. Posttreatment wound care is important, with emollients and gentle washing suggested. Most patients are back to normal 1 to 3 weeks after cessation of therapy.

IMIQUIMOD

Imiquimod is an immunomodulator in cream form recently approved by the FDA for the treatment of AKs. However, it has not been approved for full-face use. Dosing is twice a week for 16 weeks. Clinical trials have evaluated the effects of imiquimod on 1 cosmetic unit, that is, an area 25 cm² (5×5 cm), such as the forehead or a cheek. Its efficacy on larger areas has not been formally studied. In phase 3 trials, a complete clearance rate of approximately 45% was reported.² (Complete clearance was defined as the proportion of subjects at the 8-week posttreatment visit with no clinically visible AK lesions in the treatment area.) A partial clearance rate (defined as the percentage of patients in whom 75% or more baseline AK lesions were cleared) of approximately 59% was reported.²

The most frequently reported local skin reactions to imiquimod include erythema; flaking, scaling, and

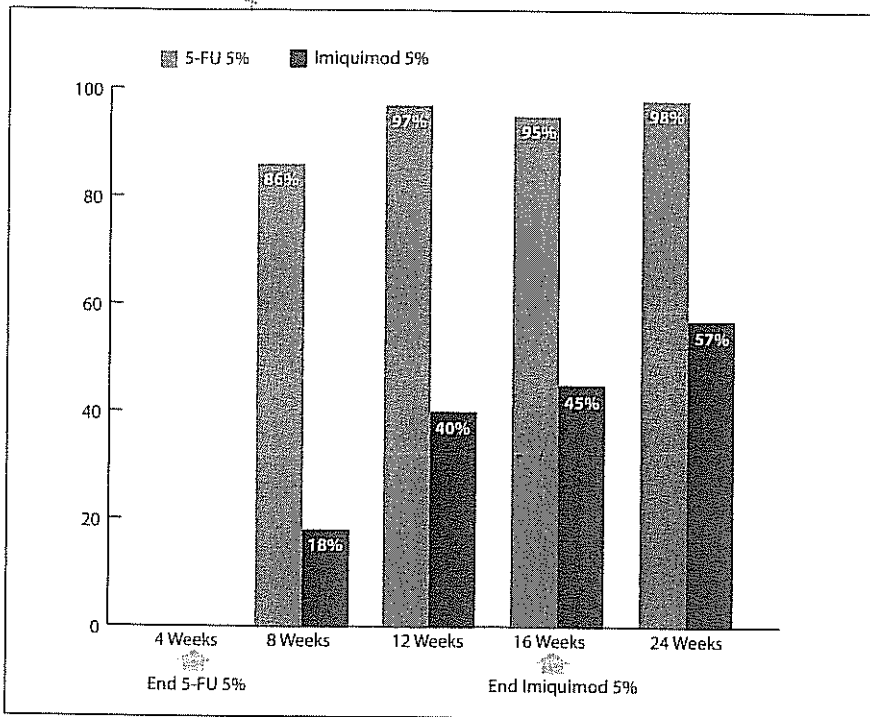


Figure 1. Percentage reduction in actinic keratosis lesions over time in both groups (N=31). 5-FU indicates 5-fluorouracil.⁶

dryness; scabbing and crusting; erosion and ulceration; and edema. These effects are highly dependent on the dosing method used and there appears to be significant variability between individual patients. A 97% incidence of erythema in patients thus treated has also been reported.²

While standard dosing for imiquimod is for 16 weeks, alternate dosing regimens have been published. Salasche and coworkers³ applied imiquimod to 25 patients in once-daily doses 3 times a week for 4 weeks, followed by a rest period of 4 weeks. They repeated the cycle on each cosmetic unit if they found residual lesions. Most patients had 2 cycles, only a few had a third, the maximum allowed in the study. Complete clearance was noted in 82% of patients, with 50% clear after the first cycle. Twenty-five percent of the patients in this trial experienced an intense inflammatory reaction.³

Stockfleth et al⁴ evaluated the efficacy of imiquimod in a randomized, double-blind, vehicle-controlled study. They applied cream or vehicle to AK lesions 3 times a week for 12 weeks or until lesions had resolved. In the event of an adverse reaction, imiquimod 5% cream was applied 1 or 2 times per week followed by rest periods when needed. The number and appearance of lesions were evaluated before, during, and after treatment. Thirty-six patients were enrolled, aged 45 to 85. The 3-times-weekly dosing was tolerated by 40% of patients; 48% had

to reduce the dosing to twice a week because of an intense inflammatory response. Patients in the 3-times-a-week group had their lesions cleared by 60%, but 100% of them had a prominent inflammatory reaction, with 80% experiencing significant erythema that lasted an average of 6 weeks. No reduction in size or number of lesions was observed in vehicle-treated patients. The results of this study suggest that efficacy may correlate with irritation.⁴

Persaud and Lebwohl⁵ treated 3 patients with imiquimod. One patient was treated 3 times a week for 4 weeks. Two subsequent patients were treated in a bilateral paired comparison study. Both patients had the same number of AK lesions on symmetric areas, but only 1 side was treated with imiquimod cream 2 to 3 times a week with frequent rest periods to avoid local inflammation. After 8 weeks, both patients applied the cream twice a week for 9 months, with continued reduction in AKs on both sides. The mean reduction in AK lesions was from 10.1 lesions to 6.2 (39%) at the end of the study.⁵

ONGOING TRIAL WITH 5-FU 5% VERSUS IMIQUIMOD 5%

Given the novelty of imiquimod and its clinical behavior, my colleague, Wm. Philip Werschler, MD, and I conducted a prospective study comparing the efficacy of imiquimod with that of 5-FU 5% cream in

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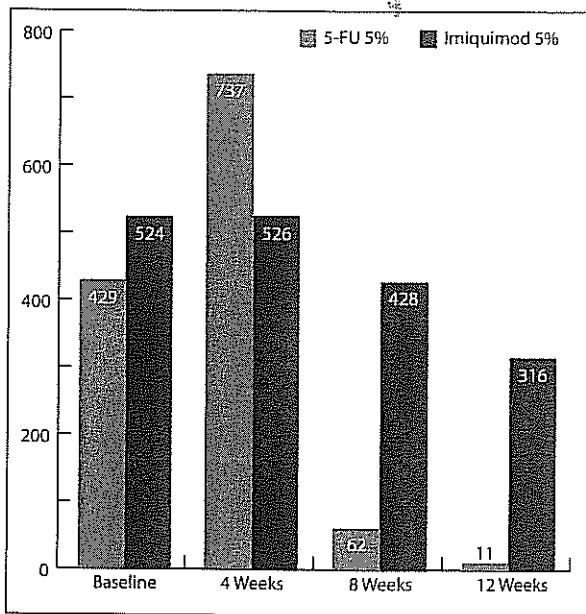


Figure 2. Total number of actinic keratosis lesions in each group during the first 12 weeks of the study (N=31). 5-FU indicates 5-fluorouracil.⁶

treating AKs on the face and scalp in subjects from our dermatology practice outpatient population.⁶

We enlisted 31 adults, aged 21 to 64 years, in good health and with a minimum of 4 AKs (no maximum). Patients who were immunocompromised, pregnant, had a known allergy to the study medications, had used topical medications for AK within the previous 2 months, had facial laser treatments within the previous 6 months, or liquid nitrogen treatment within the previous 30 days were excluded from the study. Of the 31 patients enrolled, 13 (group 1) have thus far been treated with 5-FU 5% cream from 2 to 4 weeks and 18 (group 2) with imiquimod 5% cream twice a week for 16 weeks.⁶

All patients were photographed, clinically evaluated, and had AK lesions counted at baseline, on a monthly basis during therapy, and at month 2 after completing therapy. The number of lesions was evaluated and adverse events were recorded at each visit. Photographs of AKs were obtained at baseline and at all follow-up visits.⁶

Mean reductions in AK lesion counts were compared between group 1 and group 2 throughout the study and at 2 months after completion of therapy (Figure 1). At the 8-week visit (4 weeks posttherapy), patients treated with 5-FU 5% experienced a mean reduction in AK lesions counts of 86%, and a reduction of 97% at the 12-week visit (n=13). We saw a complete clearance of all keratoses in 69% (9 of 13) of the subjects treated with 5-FU 5%. An additional 15% (2 of 13) had a near-complete response with

5-FU 5% cream, with only 1 AK remaining at the 8-week follow-up visit.⁶

Percentage Reductions

Patients treated with 5-FU 5%, showed a mean reduction in AK counts of 97% at week 12.⁶ Those treated with 5% imiquimod showed a mean reduction in AK counts of 45% at week 16. When we compared the results of both treatments at week 24, we observed a 98% reduction of AK lesions in those treated with 5-FU 5%, whereas those treated with imiquimod 5% showed a 57% reduction (Figure 1).⁶

These results are consistent with the published literature. Furthermore, 5-FU 5% highlighted a larger number of subclinical lesions that also resolved during the treatment period. In contrast, imiquimod did not reveal subclinical AKs during treatment, suggesting little efficacy in the treatment of subclinical AKs (Figure 2).⁶

Physician's Global Assessment of Patients Treated With 5-FU 5% Versus Imiquimod 5%

Looking at different points in the study, the physicians' consensus is that patients do better with 5-FU 5% than with imiquimod 5%, based on a 4-point rating scale (1=very effective, 2=moderately effective, 3=slightly effective, 4=not effective at all)(Figure 3). 5-FU 5% was assessed as more effective than imiquimod 5% cream throughout the study ($P<.05$ at each time point).⁶ This assessment is consistent with the results that we have observed among our patients.

The study is in progress, so the remaining subjects in Group 2 are still undergoing therapy.

Tolerability of Both Regimens

Both regimens have been well tolerated by our patients. We saw erythema, crusting, and erosion in some patients, but these conditions were all transient.⁶ Patients were told beforehand of possible side effects to expect during and after treatment. Initially, there may have been more discomfort among the patients treated with the 5-FU 5% cream, but, ultimately, they were satisfied with the end results.

Preliminary Results

Patients treated with 5-FU 5% experienced a brisk inflammatory response at the beginning of therapy. The inflammation typically begins to resolve over a number of days and is gone by week 4 posttreatment (Figure 4). With imiquimod 5%, the inflammation worsens during the first 2 to 4 weeks and can persist during the full 16-week course of therapy. It appears that 5-FU 5% works quicker, and clears

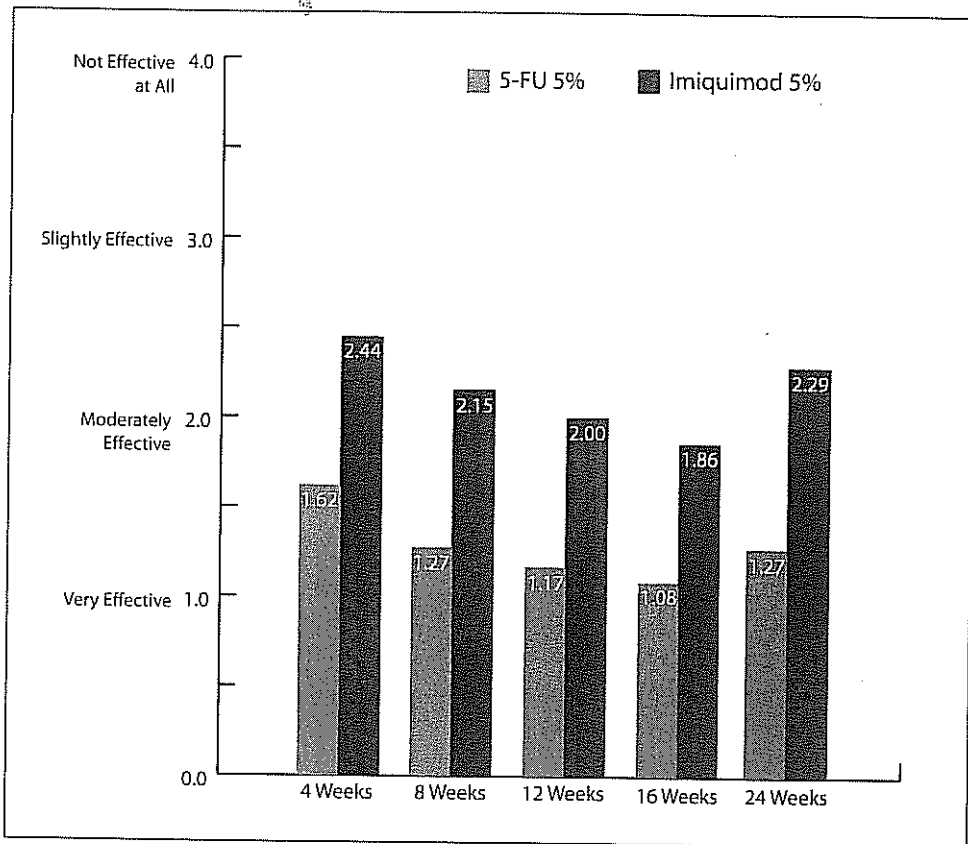


Figure 3. Physician's global assessment of patients (N=31). Difference between the 2 groups was significant at each time point ($P < .05$). 5-FU indicates 5-fluorouracil.⁶

faster than imiquimod 5%, 2 weeks versus 16 weeks. It also appears that 5-FU 5% is more effective, uncovering subclinical lesions during treatment and hence achieving a more thorough clearing of AKs at the end of therapy. The 2 agents behave differently, with 5-FU 5% having a predictable response, whereas imiquimod 5% requires close monitoring. In fact, this unpredictability would be a concern were this agent used in a primary care setting. The interim results of this study suggest that topical 5-FU 5% cream applied for 2 to 4 weeks leads to greater and more rapid improvement in AK lesion counts compared with imiquimod 5% cream applied for 16 weeks.⁶

COST COMPARISON

Cost of therapy is an important consideration when it comes to choosing a drug, even among patients who are insured. The 5-FU 5% cream formulation is now available as a 40-g tube, and is sufficient to treat the entire face. The present average wholesale price is \$166.94 per tube, or \$4.17/g. Imiquimod 5% cream is packaged in small sachets, and each sachet is

effective on only a 25 cm² area of skin. Three boxes of 12 sachets are recommended for a 16-week course of therapy. The average wholesale price is \$174.66 per box of 12 sachets (3 g), or \$58.22/g.⁷ Therefore, one needs to reflect on the total disbursement per patient. With 5-FU 5% cream, treating the entire face and scalp will cost \$166.94. Although imiquimod 5% cream is approved only for treating small areas of skin, one can calculate the potential costs of treating larger areas of the body. For example, treating one part of the face would require 3 boxes and cost \$523.98. A full-face treatment (3 cosmetic units) would cost \$1571.94. Treating the face and a small area of scalp (4 cosmetic units) would cost close to \$2100.

CONCLUSION

Despite the efficacy of the 2 agents studied, there are differences in their modes of action and affordability. 5-FU 5% cream appears to be the more effective of the 2 agents: more lesions become apparent during therapy and, because of this, the clearance seen after therapy is more thorough.

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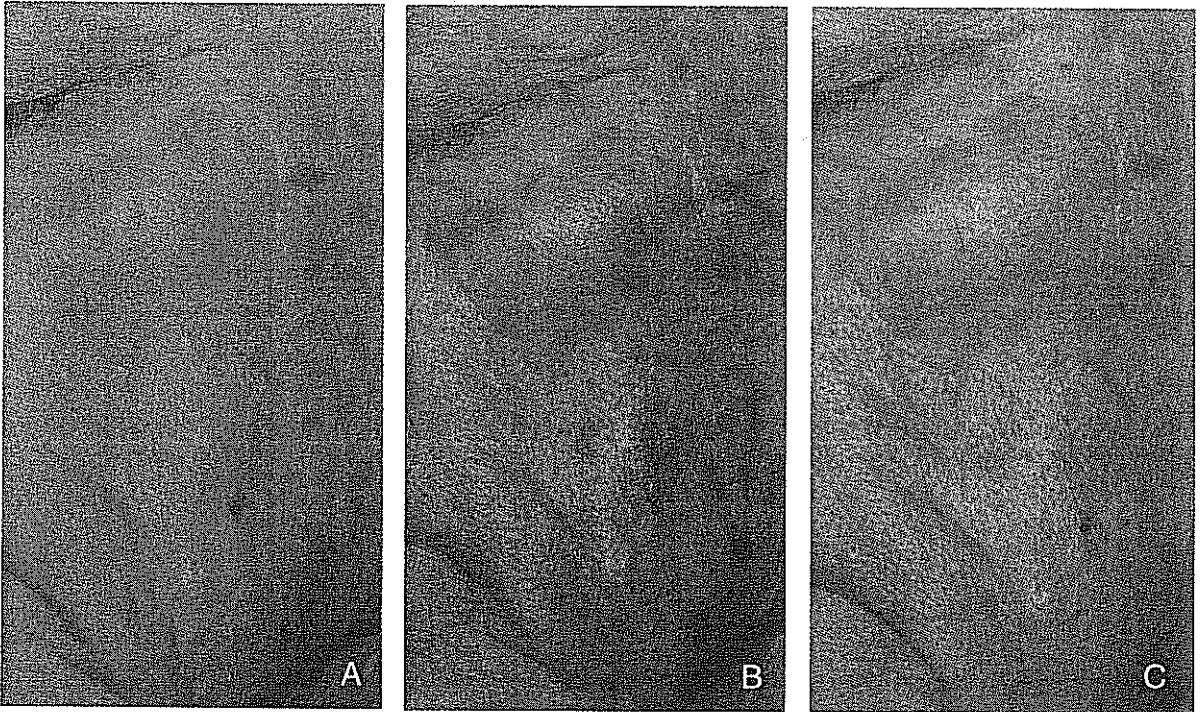


Figure 4. Patient at baseline (A), after 26 days of twice-daily treatment with 5-fluorouracil 5% cream (B), and at follow-up 6 months after baseline with complete clearing of actinic keratoses (C).

5-FU 5% cream has a predictable response, whereas imiquimod 5% cream requires careful monitoring. Both drugs induce a brisk inflammatory response that is therapeutically beneficial. 5-FU 5% cream is a low-cost, safe treatment option. Imiquimod 5% cream is more expensive and patients should be closely monitored for those who experience an unusually brisk inflammatory response.

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