Adherence to a Topical Regimen of 5-Fluorouracil, 0.5%, Cream for the Treatment of Actinic Keratoses

Several different methods can be used to treat actinic keratoses (AKs), including cryosurgery, curettage and electrodessication, phototherapy with amnioluvulinic acid, chemical peels, and various topical medications. Many topical medications either produce hypopigmentation or are irritating to the skin. One would expect adherence to a treatment regimen of irritating and unpleasant topical medications to be worse than that demonstrated with a regimen of nonirritating topical agents for atopic dermatitis and psoriasis. In many cases, nonadherence rather than nonresponse underlies treatment failure.

While studies of topical 5-fluorouracil have demonstrated good efficacy for AK treatment, few data are available on patients’ compliance with therapy. Since most patients overestimate their actual use of medication, electronic monitors are more reliable assessment tools than patients’ self-reports of usage. This study assesses patient compliance with a regimen of topical 5-fluorouracil, 0.5%, cream for the treatment of AKs by using electronic monitors hidden in the caps of the medication.

Methods. After institutional review board approval, 20 patients, 50 years or older, with moderate to severe AKs of the face and scalp were enrolled in this prospective study. Each participant was given fluorouracil, 0.5%, cream (Carac; Dermik Laboratories, Berwyn, Pennsylvania, a subsidiary of Sanofi-Aventis) with an attached Medication Event Monitoring System cap (MEMS; Ardex Corp, Geneva, Switzerland). Subjects were directed to apply the medication at bedtime each day for 4 weeks. They were assessed at baseline and at weeks 2, 4, and 8 for skin quality, local skin reaction, and number of AKs.

Table: Sensitivity and specificity of self-reports of skin-pigmentation conditions compared with findings of physical examination. PIH indicates postinflammatory hyperpigmentation. Sensitivity and specificity are reported as mean (SD) percentages.

<table>
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<tr>
<th></th>
<th>Self-report</th>
<th>Yes</th>
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<th>Total</th>
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<th>Yes</th>
<th>No</th>
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<td>42</td>
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<td>31</td>
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<tr>
<td></td>
<td>Sensitivity</td>
<td>41/44 = 93.2 (3.8)</td>
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<td></td>
<td>31/31 = 100.0</td>
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<td></td>
<td>9/11 = 81.8 (11.6)</td>
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<td></td>
<td>35/38 = 92.1 (4.4)</td>
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<td><strong>Melasma</strong></td>
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Figure 2. Sensitivity and specificity of self-reports of skin-pigmentation conditions compared with findings of physical examination. PIH indicates postinflammatory hyperpigmentation. Sensitivity and specificity are reported as mean (SD) percentages.
lesions. The patients were instructed to report any adverse events associated with the use of medication at each follow-up appointment.

Subjects were unaware of the monitoring by MEMS cap until consent to use the recorded data at the completion of treatment was obtained. Clinical evaluators were blinded to the adherence data. MEMS cap overall adherence was defined as the proportion of days during the 4-week active treatment phase of the trial that the cap recorded at least 1 event or opening of the medication. Weekly adherence per patient was similarly defined as the proportion of days during the week that the cap recorded at least 1 event.

Descriptive statistics, including frequencies and proportions for categorical data and means, standard deviations, and medians for continuous data, were calculated. Paired t tests were used to compare the number of AK lesions observed at baseline with the number observed on week 8. Baseline severity of AK was divided into moderate and severe based on where the patient had fewer than 10 or 10 or more lesions. A mixed model was then fit to the data to test for a significant difference in adherence between severity levels.

Results. Nineteen of the 20 enrolled subjects completed the study; 1 was lost to follow-up. Most were white men (18 of 19), mean age 67 years. Based on electronic monitoring, adherence ranged from 54% to 100%, with 14 of the subjects having a mean adherence greater than 80%. Mean MEMS cap overall adherence to the once-daily application regimen was 86%. Mean weekly adherence to once-daily application of topical 5-fluorouracil, 0.5%, dropped over the 4 weeks of active treatment from 92% during the first week to 82% by the end of the active treatment period (Figure). Adherence was not affected by baseline disease severity.

The total number of AKs at baseline ranged from 4 to 45, with a mean of 9.1 and 5.6 AKs on the face and anterior scalp, respectively. The number of lesions initially increased but ultimately dropped to a mean of 2.2 and 0.9, respectively, on the face and scalp by week 8. Median improvement in the total number of lesions was 80% by week 8 (P < .001) (Table). Fifty-three percent of subjects (n=10) achieved success (100% clearance) or partial clearance (75% clearance) by week 8 (32% [n=6] and 21% [n=4], respectively).

Treatment was well tolerated. Most subjects (79%; n=15) reported at least 1 adverse effect such as tenderness (n=9), burning (n=8), redness (n=4), or blistering (n=1), with some subjects reporting a combination thereof. No serious adverse events were reported, nor did any subject discontinue treatment secondary to adverse events.

Comment. Because adherence to topical therapy regimens is generally poor, we anticipated that the adverse effects associated with topical 5-fluorouracil would be associated with poor adherence. Surprisingly, despite the high rate of adverse effects, adherence to a regimen of once-daily topical application of 5-fluorouracil, 0.5%, cream was excellent. This high adherence rate might be owing to several factors. First, the adverse events were mild to moderate in severity and were not bothersome enough to affect adherence. However, the adverse effects of the treatment might actually have increased adherence because the patient felt that something was happening and was therefore encouraged to continue using the treatment. It may be that a visible or tactile effect from medication application “proves” to the patient that the medication is effective. This may lead to strategies for improving adherence, such as incorporating menthol for sensation or developing color-changing topical treatments.

A second possibility is that older patients may be more adherent to treatment regimens than younger patients, and AKs generally occur in older patients, as they did in the present study. Additionally, the premalignant nature of AKs may be associated with heightened concern, and fear of developing cancer may be a potent inducer of adherence. Another possibility for the good adherence to the regimen of topical 5-fluorouracil, 0.5%, cream is that fixed-duration treatment provides a “light at the end of the tun-

<table>
<thead>
<tr>
<th>Location</th>
<th>Baseline (n=19)</th>
<th>Week 2 (n=19)</th>
<th>Week 4 (n=19)</th>
<th>Week 8b (n=17)</th>
<th>P Valuec</th>
</tr>
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<tbody>
<tr>
<td>Face</td>
<td>9.1 (11.4)</td>
<td>13.8 (10.9)</td>
<td>10.1 (9.8)</td>
<td>2.2 (3.3)</td>
<td>&lt;.01</td>
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<tr>
<td>Sculp</td>
<td>5.6 (8.9)</td>
<td>8.1 (8.8)</td>
<td>5.0 (5.5)</td>
<td>0.9 (1.9)</td>
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<tr>
<td>Total</td>
<td>14.7 (12.7)</td>
<td>21.9 (14.7)</td>
<td>15.1 (8.7)</td>
<td>3.1 (3.7)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

a Unless otherwise noted, data are presented as mean (SD) number of lesions.

b The total percentage change in number of lesions through the week 8 examination ranged from −100% to +50% (median, −80%) (n=17). Two subjects missed their week 8 visit and lesion count.

c Paired t test comparing week 8 number of lesions with number of lesions at baseline.
nel” effect that encourages better adherence. Diseases such as psoriasis are lifelong, often requiring an indefinite length of continuous therapy. Unfortunately, long-term topical treatments are difficult to sustain. Moreover, previous studies of patients with chronic skin diseases such as psoriasis and atopic dermatitis may have included subjects who had already tried topical treatment and become frustrated with it. The resulting dissatisfaction might have led to poor adherence. In contrast, in the present study, subjects might not have been predisposed to expect treatment failure and therefore might have been more motivated to use the treatment.

With continued treatment, the lesion counts decreased, and most improvements are seen after the active treatment was completed. In the first few weeks after treatment was initiated, an increase in the number of AKs was observed. This suggests that treatment with 5-fluorouracil, 0.5%, cream can cause subclinical AKs to become detectable, and this may be useful to help identify lesions for cryosurgical treatment. The clearing of the affected field of AKs—rather than only treating lesions that are clinically detectable—can reduce recurrence rates.10-11

A limitation of this study was that the sample size and variability in adherence were too small to assess a relationship between adherence to a topical regimen of 5-fluorouracil, 0.5%, cream and treatment outcomes. There is some evidence to indicate that the treatment is somewhat forgiving of poor adherence in that good treatment responses were observed even in the 2 subjects whose adherence rates were less than 80%. This is congruous with the efficacy of intermittent or pulse treatment of AKs with 5-fluorouracil. In summary, topical treatment with 5-fluorouracil, 0.5%, cream in the AK population appears to be well tolerated (despite the related adverse reactions) and associated with good adherence to treatment.

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Role of the Sponsors: The sponsors had no role in the design and conduct of the study, in the collection, analysis, and interpretation of data, or in the preparation of the manuscript, review, or approval of the manuscript.


5. Jorizzo J, Carney PS, Ko WT, Robins P, Worschler WH. Fluorouracil 5% and 0.5% creams for the treatment of actinic keratosis: equivalency of efficacy with a lower concentration and more convenient dosing schedule. Catis. 2004;74(6(suppl)):18-23.

Molecular Identification of Mycologic Correlation in Patients With Concomitant Tinae Pedis and Tinae Manuum Infection

Tinea manuum is usually combined with tinea pedis or toenail onychomycosis. In 2 feet–1 hand syndrome, tinea manuum has a tendency to develop on the hand used to excoriate the infected feet.1 Therefore, it has been postulated that the infected feet may be the sites from which the fungal infections spread to other body areas.2 However, there have been few reports clarifying the mycologic correlation in the coexistence of tinea manuum and tinea pedis, although many epidemiologic studies have been performed.