Background: Imiquimod 5% cream may provide an effective nonsurgical treatment for superficial basal cell carcinoma (sBCC) based on results of previous studies.

Objective: The objective of this phase II dose-response study was to explore various dosing regimens using imiquimod 5% cream for sBCC to find the most effective frequency of dosing with tolerable side effects.

Methods: Patients ($n = 128$) were dosed twice daily, once daily, 5 times a week, or 3 times a week in this 12-week, randomized, double-blind, vehicle-controlled study. At 6 weeks after treatment, the entire tumor area was clinically evaluated, excised, and examined exhaustively for histologic evidence of residual sBCC.

Results: Complete response rates were 100% (10/10), 87.1% (27/31), 80.8% (21/26), and 51.7% (15/29) for patients in the twice daily, once daily, 5 times a week, and 3 times a week imiquimod groups, respectively, and 18.8% (6/32) in the vehicle group.

Conclusion: Imiquimod 5% cream was effective in the treatment of sBCC. Daily or 5 times a week dosing for 12 weeks demonstrated high efficacy results with acceptable safety profiles. (J Am Acad Dermatol 2002; 47:390-8.)

B asal cell carcinoma (BCC) is the most common cancer in the United States, with approximately 1 million new cases estimated annually. An increasing incidence has been observed in the past several years in the United States and other parts of the world.1,2 There are several histologic subtypes of BCC with significant differences in site distribution and clinical outcome between subtypes.3-5 Although nodular BCC (nBCC) is the dominant subtype for all anatomic sites, superficial BCCs (sBCCs) are commonly seen on the trunk and limbs, and appear at an earlier age.6

Surgical excision and curettage-electrodesiccation are the most common treatments for primary, nonaggressive BCC. These procedures are effective and have low recurrence rates when used to treat primary BCC on low-risk anatomic sites (neck, trunk, and extremities).7,8 A total of 36% of patients who have 1 BCC have additional primary BCCs, and many of these patients experience multiple new BCCs.9 Imiquimod may offer an alternative to repeated surgical or ablative treatments.

Imiquimod cream, 5%, a drug approved in the United States under the trade name Aldara for the topical treatment of external genital/perianal warts, is a novel immune response modifier that induces interferon production by monocytes/macrophages. Imiquimod has induced immunologic activity in human skin infected with human papillomavirus (HPV), stimulating significant increases in mRNA for interferon-$\alpha$ (IFN-$\alpha$), 2'5'-oligoadenylate synthetase (2'5'-AS) and IFN-$\gamma$.10 Increases in mRNA for CD4,
CD8, and tumor necrosis factor-α (TNF-α) were also observed, suggesting activation of a helper T-cell type 1-mediated response. IFN alone has significant activity against BCC, but requires multiple intralesional injections that can be difficult to administer, and the treatment can result in unpleasant but usually transient side effects.

Imiquimod has a unique mechanism of action, and, because it is applied by the patient, imiquimod 5% cream may be more convenient and well tolerated for BCC than many current treatments. In a pilot study, imiquimod 5% cream demonstrated clinical efficacy in the treatment of BCC. The objective of the present study was to establish a safe and effective treatment regimen using topical imiquimod 5% cream in a larger series of patients for the treatment of sBCC.

PATIENTS AND METHODS

Patients

Male or female patients, 18 years of age or older, who had a histologically confirmed diagnosis of sBCC, were eligible for study participation. The target tumor site excluded areas within 1 cm of the hairline, eyes, nose, mouth, or ears; the anogenital area; and hands and feet. The target tumors were primary, noninfected, measured between 0.5 and 2.0 cm², and could not have been previously treated, recurrent, or within 5 cm of another BCC tumor.

Methods

This phase II, randomized, double-blind, vehicle-controlled, dose-response study was conducted in 13 study centers in the United States, consisting of a pretreatment screening visit, a 12-week treatment period with regularly scheduled interval visits, and a 6-week posttreatment visit for surgical excision of the target tumor area. At the screening visit, patients were informed of study procedures and of their rights and responsibilities as study participants; all patients signed an institutional review board approved, written, informed consent document.

A biopsy specimen of no more than 25% of the tumor area was taken for histologic confirmation of sBCC. Biopsy specimens were processed at one center but read by 2 independent, blinded dermatopathologists. Superficial BCC was defined as tumor confined in the specimen to the superficial reticular and papillary dermis arranged as small tumor nests at the undersurface of the epidermis.

If a BCC contained nodular or micronodular components, or if the basaloid cells extended deep into the reticular dermis, the tumor was not classified as sBCC and was not eligible for the study. A consensus of the 2 dermatopathologists’ histologic diagnoses was required for patient enrollment.

A baseline area of the target tumor was determined at the treatment initiation visit by measuring and multiplying the 2 largest perpendicular dimensions of the target tumor. The target tumor site and appropriate surrounding anatomic landmarks were mapped using a clear, flexible polypropylene sheet as a template so that the correct site could be found for excision at the end of the study.

Treatment. Patients were randomized to receive either imiquimod or vehicle in 1 of 4 dosing regimens: twice daily, once daily, 5 times a week, or 3 times a week according to a computer-generated randomization schedule. Upon randomization, patients were assigned a unique identification number in numerical sequence. Imiquimod 5% cream and vehicle cream were in identical packaging as 250 mg single-use sachets. Both patients and investigators were blinded to the content of the treatment cream (active or vehicle) dispensed.

Patients applied imiquimod 5% or vehicle cream to the target tumor until 12 weeks of treatment were completed. Patients were prescribed rest periods as needed up to a total of 14 days, for local skin reactions, or for treatment site adverse events. Rest periods were counted as part of the 12-week treatment period.

The estimated amount of study cream applied at each dose was determined by the larger diameter of the target tumor. Tumors up to 1 cm² in size were dosed with a cream droplet approximately 4 mm in diameter (0.5 mg imiquimod). Tumors ranging from 1 cm² to <1.5 cm² were covered with 5 mm (1.25 mg imiquimod) and tumors ≥1.5 cm² were covered with 7 mm (2 mg imiquimod).

Safety evaluations. To assess safety, patients returned to the clinic for designated visits for evaluation, photographs and documentation of tumor appearance, local skin reactions, vital sign measurements, adverse events, and concomitant medications.

Local skin reactions. A visual assessment of the target tumor area was performed by the investigator at each clinic visit. Local skin reaction categories were erythema, edema, induration, vesicles, erosion, ulceration, excoriation/flaking, and scabbing. A 4-point scale was used where: 0 = none, 1 = mild, 2 = moderate, 3 = severe.

Patient-reported signs or symptoms corresponding to the above local skin reactions and other adverse events were recorded separately at each visit.

Efficacy evaluations. At the 6-week posttreatment visit, the investigator made a clinical assessment to determine whether BCC was visible at the target tumor site. All patients then had the entire target tumor area and a 3-mm margin surgically excised and histopathologically examined for evidence of residual tumor. A patient was considered a
complete responder if there was no histologic evidence of BCC in the excised posttreatment target tumor tissue.

The excision specimen was bread-loaf sectioned from tip to tip in 2- to 4-mm thick slices, which were then paraffin embedded. The specimens were step-sectioned at least every millimeter in the center of the specimen and at least every 3 mm through the tips. Sections were stained with hematoxylin and eosin and histologically examined for residual BCC using light microscopy. All sections were examined by two independent, blinded dermatopathologists for evidence of any residual BCC and to ensure that the excisional margins were free of tumor. At least 6 and up to 20 or more slides were examined per case, depending upon the size of the ellipse that was excised.

Statistical evaluations. Sample size calculations were based on the ability to detect differences in complete response rates. Eighteen patients in each of the 3 imiquimod dose groups and 18 patients in the combined vehicle group gave this study at least 80% power to detect a difference in complete response rates of 20% for vehicle patients versus 80% for any of the imiquimod dose groups, assuming that each imiquimod-versus-vehicle comparison was carried out at an alpha level of 0.05/3; this Bonferroni adjustment was made to preserve the overall alpha level at 0.05. The response rate of the twice-daily imiquimod group was not compared to vehicle because of the small sample size for this group.

A secondary analysis was completed to compare the investigator’s clinical assessment of target tumor clearance at the 6-week posttreatment visit to the histologic evaluation.

RESULTS

A total of 128 patients, including 82 men and 46 women, were enrolled and randomized beginning July 22, 1998. The mean age was 59 years (range, 35 to 85 years). All patients were white with Fitzpatrick skin types I-IV: 13% had skin type I, 46% had skin type II, 34% had skin type III, and 7% had skin type IV.15

Of the 128 patients, 92 (71.9%) had undergone at least 1 previous excision for BCC and 68 (53.1%) had nontarget BCC tumors present at study initiation (Table I). A total of 96 patients were randomized to imiquimod treatment groups and 32 patients to the vehicle treatment group. Although 10 patients were randomized to the twice-daily regimen, no additional patients were enrolled into this treatment group because of the incidence and severity of reported local reactions in this regimen.

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Of the 128 randomized patients, 24 (18.8%) withdrew from the treatment portion of the study. Overall, 13 (10.2%) patients discontinued treatment because of local skin reactions, including 3 from the twice-daily group, 7 from the once-daily group, and 3 from the 5-times-a-week group. Four (3.1%) patients discontinued because of application site adverse events, including 1 from the twice-daily group, 2 from the once-daily group and 1 from the 5-times-

Table I. Patient demographics and target tumor characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Combined vehicle n = 32</th>
<th>3 times a week n = 29</th>
<th>5 times a week n = 26</th>
<th>Once daily n = 31</th>
<th>Twice daily n = 10</th>
<th>All patients n = 128</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>13</td>
<td>8</td>
<td>11</td>
<td>2</td>
<td>46</td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
<td>16</td>
<td>18</td>
<td>20</td>
<td>8</td>
<td>82</td>
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<tr>
<td>Age — mean years (range)</td>
<td>58 (38-85)</td>
<td>62 (36-85)</td>
<td>55 (38-84)</td>
<td>56 (35-85)</td>
<td>69 (51-85)</td>
<td>59 (35-85)</td>
</tr>
<tr>
<td>Patients with history of BCC excision</td>
<td>24</td>
<td>20</td>
<td>19</td>
<td>21</td>
<td>8</td>
<td>92</td>
</tr>
<tr>
<td>Patients with nontarget tumors</td>
<td>15</td>
<td>18</td>
<td>12</td>
<td>19</td>
<td>4</td>
<td>68</td>
</tr>
<tr>
<td>Target tumor location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck/face/forehead</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Upper extremity (not hand)</td>
<td>11</td>
<td>7</td>
<td>6</td>
<td>9</td>
<td>4</td>
<td>37</td>
</tr>
<tr>
<td>Trunk: anterior</td>
<td>7</td>
<td>7</td>
<td>11</td>
<td>12</td>
<td>2</td>
<td>39</td>
</tr>
<tr>
<td>Trunk: posterior</td>
<td>8</td>
<td>12</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>Lower extremity/thigh (not foot)</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Median target tumor size</td>
<td>0.8 cm²</td>
<td>1.0 cm²</td>
<td>0.6 cm²</td>
<td>0.7 cm²</td>
<td>1.0 cm²</td>
<td>0.8 cm²</td>
</tr>
</tbody>
</table>
a-week group. Some of these discontinuations were not the choice of the patient, but were imposed by the investigator because the maximum 14-day rest from dosing allowed by the protocol had been exceeded. Also, 2 (1.6%) discontinued because of non-compliance, 2 (1.6%) were lost to follow-up, and 1 (0.8%) was discontinued for a laboratory abnormality identified at initiation. Despite the fact that nearly 20% of patients discontinued treatment before the end of the 12-week treatment period, only 3 (2%) patients were not followed to completion. Of the 128 patients randomized, 125 completed the end of study procedures and histologic evaluations by January 19, 2000.

Target tumor characteristics

Out of 128 patients, 116 (90.6%) had biopsy-confirmed prestudy diagnoses of sBCC. Twelve patients had confirmed prestudy histologic diagnoses of nBCC after being randomized with a preliminary diagnosis of sBCC; if even a small nodular component was evident histologically, the biopsy was classified as nBCC for study purposes. These 12 patients were included in the analysis. The median target tumor size after biopsy at the initiation visit for each treatment group is presented in Table I. Locations of the target tumors were primarily on the upper body. The most frequently reported target tumor location was upper extremities (excluding the hand), reported by 37 (28.9%) of 128 patients.

Amount of imiquimod applied

There was substantial variability in the amount of study drug applied from week to week in each imiquimod dose group because of patient discontinuations and rest periods. A total of 41 patients took rests from study cream application during the treatment period. In general, a decreasing percentage of patients took rests as the dosing frequency of imiquimod decreased and the median number of doses rested was lower with less frequent dosing (Table II). No vehicle patients took rests. Over the 12-week course of treatment, the mean total amounts of imiquimod applied were 146 mg for the twice-daily group, 69 mg for the once-daily group, and 43 mg for both the 5-times-a-week and the 3-times-a-week groups.

Treatment response

Of the 128 patients included in the intent-to-treat data set, 125 (97.7%) had posttreatment excisions. Depending on the size of the tumor treated, an average of 125 histologic sections were examined for each excision specimen, with over 100 sections for most. The 3 patients who did not complete the posttreatment excision were lost to follow-up (one on vehicle and one on 5 times a week imiquimod dosing) or noncompliant (one on once daily imiquimod dosing). These 3 were counted as treatment failures in the statistical analysis. There was a positive association between dosing frequency and complete response rate; higher response rates were associated with more frequent dosing (Fig 1). Fisher’s exact tests comparing the 3 imiquimod dosing groups (once daily, 5 times a week, and 3 times a week) to the vehicle group in a pairwise manner found statistically significant differences between groups with respect to complete response rates (all \( P \) values \(< .05/3 \)) (Figs 2-6).

Although the number of patients with mixed superficial and nodular histology enrolled into each treatment group was too small to analyze separately, 9 of the 12 patients (including all 6 of those treated once daily or 5 times a week) were complete responders to treatment. Similarly, the number of patients enrolled into the twice-daily, once-daily, and 5-times-a-week treatment groups who discontinued treatment before completing 12 weeks of dosing were small and not analyzed separately for efficacy. However, 5 of 5 patients treated twice daily, 8 of 10 treated once daily, and 4 of 6 treated 5 times a week who discontinued treatment early were complete responders. For these responders who discontinued early, the length of treatment varied, ranging from 4 to 11 weeks for the once-daily and 5-times-a-week treatment groups.

Investigator assessment versus excision results

The ability of the investigators to correctly assess the target site for tumor evidence was analyzed by com-

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**Table II. Rest periods taken by patients in the imiquimod dosing groups**

<table>
<thead>
<tr>
<th>Rest period data</th>
<th>3 times a week n = 29</th>
<th>5 times a week n = 26</th>
<th>Once daily n = 31</th>
<th>Twice daily n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients taking rest periods from dosing</td>
<td>6 (21%)</td>
<td>7 (27%)</td>
<td>21 (68%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Median number of doses rested (range)</td>
<td>3 (3-6)</td>
<td>10 (5-11)</td>
<td>13 (1-19)</td>
<td>14 (11-30)</td>
</tr>
<tr>
<td>First week that rests were taken: median (range)</td>
<td>Week 7 (3-9)</td>
<td>Week 5 (2-9)</td>
<td>Week 5 (2-9)</td>
<td>Week 5 (2-7)</td>
</tr>
</tbody>
</table>

**Table II. Rest periods taken by patients in the imiquimod dosing groups**
paring the investigator assessment of the target tumor site at the 6-week posttreatment excisional visit with the histologic results (Table III). For all imiquimod groups combined, the negative predictive value for the investigator assessment was 100% (38/38). Therefore, all patients clinically assessed as negative (no target tumor visually evident) by the investigators were confirmed to be negative by the histologic results. The positive predictive value was 39.2% (20/51). Thus, only 39.2% of the patients assessed as positive by the investigators (target tumor clinically evident) were confirmed to be positive by the histologic results. The sensitivity of the investigator assessment of positive sites was 100% (20/20). This indicated that the investigators correctly identified as positive all of the patients who were confirmed to be positive by the histology. In some cases, clinical clearance was not determined.

Three patients were not assessed by the investigator for tumor clearance. In 4 patients, the investigator could not determine whether tumor was present; in all 4 of these cases, there was no histologic evidence of residual tumor.

**Adverse events**

Adverse events occurred in all treatment groups, with 118 (92.2%) of 128 patients reporting at least one adverse event. Application site reactions, including itching, pain, and tenderness at the target tumor site, were the most frequently reported adverse events (Fig 7). Thirty-two severe adverse events (ie, events that substantially interfered with daily activities) were reported by 25 patients; 6 were considered to be probably or possibly related to
study drug (all 6 were application site reactions in the once daily treatment group). Six serious adverse events (Shy Drager syndrome [postural hypotension], fever and lobar pneumonia, *Staphylococcus* infection of the right elbow [unrelated to treatment site on left side of chest], transient ischemic attack, and a prostate biopsy) were reported by 5 patients and resulted in hospitalizations. These hospitalizations were related to intercurrent illnesses or events and were not considered to be related to study drug; all affected patients recovered and completed the study. Four patients discontinued dosing with study drug early because of treatment-related adverse events (3 because of pain at the treatment site, 1 of which was severe, and 1 because of bleeding at the treatment site).

**Local skin reactions**

Local skin reactions, identified by type as erythema, scabbing, erosion, excoriation/flaking, induration, edema, ulceration, and vesicles occurred in all treatment groups (Fig 8). In the twice-daily group, severe erythema and severe scabbing were each recorded by investigators for 3 (30%) of the 10 patients, and severe erosion and severe excoriation/flaking were each recorded for 1 (10%) of the 10 patients. In the other treatment groups, erythema was noted most often among severe reactions. Of the 13 patients discontinued from treatment because of local skin reactions (listed as the primary reason), 6 patients had local skin reactions considered severe (Fig 9).

**DISCUSSION**

This study demonstrated that 87.1% and 80.8% of patients who treated a single, primary, nonaggressive sBCC with imiquimod 5% cream once daily or 5 times a week for 12 weeks were histologically free of tumor 6 weeks after treatment. Of the patients who treated similar tumors 3 times a week for 12 weeks, 51.7% were histologically free of tumor. An acceptable safety profile was seen in 3 of the 4 imiquimod dosing regimens. Only the most frequent dosing regimen, twice daily for 12 weeks, presented a safety profile that was judged not acceptable because of severe local skin reactions at the treatment site. A clearance rate of 18.8% was also noted in the vehicle treatment group and was remarkably consistent with the tumor cure rate previously reported for a controlled study using intralesional interferon for the treatment of small BCC tumors that were similarly diagnosed. An acceptable safety profile was seen in 3 of the 4 imiquimod dosing regimens. Only the most frequent dosing regimen, twice daily for 12 weeks, presented a safety profile that was judged not acceptable because of severe local skin reactions at the treatment site. A clearance rate of 18.8% was also noted in the vehicle treatment group and was remarkably consistent with the tumor cure rate previously reported for the placebo-treated group of a controlled study using intralesional interferon for the treatment of small BCC tumors that were similarly diagnosed. As expected, the vehicle response rate in this study, in which the size of the diagnostic biopsy was limited, was lower than a recently reported histologic cure rate of 33% observed approximately 1 to 6 months after standard diagnostic punch or shave biopsies of 42 small, primary BCC tumors. Superficial BCC was confirmed with a small, pre-
study biopsy (<25% of the clinically evident tumor) before treatment, in accordance with standard dermatologic practice. Only those tumors with superficial BCC (with no nodular or aggressive features) were intended for treatment in this study. Because of the small size of the specimen, the prestudy biopsy may not have been representative of the histology of the entire tumor, and 12 patients with mixed superficial and nodular histology were included in the study. Although the number of patients with mixed histology enrolled into each treatment group was not analyzed separately, 9 of the 12 patients (including all 6 of those treated once daily or 5 times a week) were complete responders to treatment, indicating that the response of superficial tumors with some nodular histologic components may be comparable to the response of tumors with purely superficial histology on biopsy.

A posttreatment excision of the entire target tumor area was performed, and the excised tissue sample was examined for any histologic evidence of residual tumor. The step-sectioning procedure was much more thorough than standard sectioning, and it is unlikely that any residual tumor was missed. The inclusion of a posttreatment excision was considered appropriate for this stage of clinical development because the efficacy of imiquimod for BCC has not been fully defined. The posttreatment excision of the tumor area allowed patients to have their tumors surgically removed if the study drug was not effective, as well as providing definitive evidence of tumor clearance. The posttreatment excision and its thorough histologic evaluation served as the endpoint for the treatment effect of imiquimod cream, rather than the clinical assessment of tumor clearance or persistence.
The clinical assessment for persistent tumor done by investigators 6 weeks after treatment, however, was illuminating. When the investigators recorded no clinical evidence of BCC 6 weeks after treatment, histology confirmed the clinical impressions in all 38 cases (100% negative predictive value). Of 51 cases in which the investigators had recorded clinical evidence of BCC at the treated target tumor site, only 20 had BCC confirmed histologically (39% positive predictive value). These 20 represented all of the histologically positive cases in the study, indicating that the investigators were successfully able to identify residual BCC by clinical evaluation in all of the treatment failures. In 31 cases, the investigators recorded evidence of BCC, which was not supported by the histology. This indicated that investigators had some difficulty determining that the tumor was gone in a percentage of cases that were actually clear. It is assumed that this difficulty is related to the persistence of some low-grade erythema in a percentage of cases at 6 weeks after treatment when the assessments were done.

Consistent with past studies using imiquimod 5% cream for the treatment of BCC, the most commonly reported adverse event was itching at the target site. Pain and tenderness at the target site were the next most frequently reported symptoms.

Despite the fact that nearly 20% of patients discontinued their treatment before the end of the planned 12-week treatment period, several of these patients in the twice-daily, once-daily, and 5-times-a-week treatment groups were completely clear of BCC on histologic examination. In another study evaluating 33 patients, dosing once daily with imiquimod for 6 weeks (rather than the 12-week treatment in this study) the complete response rate was 87.9%. This suggests that additional clinical studies are needed to determine the appropriate duration of treatment for this novel and effective therapy.

Mohs micrographic surgery offers the best cure rates for the treatment of BCC. The recurrence rates with surgical excision for primary BCCs vary based upon the characteristics and location of the tumor treated and the size of the surgical margin, but in general range from 3.2% to 8%, so that the cure rates are 92% to 96.8%. The 5-year cure rates are similar for curettage and cautery. The complete response
rate of 87.1% seen in the once-daily imiquimod group is lower than the response rate seen in these commonly used modalities for primary BCC. However, with the incidence of BCC increasing, imiquimod may still offer an alternative treatment that avoids surgical or ablative treatment.19

Recurrent BCC after incomplete resection and the presence of residual BCC in excisional margins continue to present a treatment challenge.21 Although curettage before excision decreased margin positivity after excision by 24%, this procedure still results in a failure rate with positive histologic margin in 13% of such excisions.22 The potential use of imiquimod as an adjuvant treatment to surgery may warrant consideration. It may be beneficial to determine whether imiquimod could reduce the size of larger tumors before surgery, and to see whether the immune system could induce a specific Th1 immune response that would perhaps decrease the risk for recurrence of high-risk and recurrent tumors. Clearly, with larger studies, imiquimod may be proven as a viable alternative to surgery for low-risk sBCC tumors.

In conclusion, imiquimod 5% cream was effective in the treatment of sBCC in all dosing regimens used in this study. The once-daily or 5-times-a-week dosage groups had the highest efficacy results with acceptable safety profiles. This novel therapy offers a potential nonsurgical option for a disease traditionally treated by surgery and may be important in our management of an increasingly common cutaneous malignancy.

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