Objective: To evaluate the long-term efficacy of systemic retinoids in reducing the incidence of cutaneous squamous cell carcinomas (SCCs) in organ transplant recipients (OTRs), who are at greatly increased risk of SCCs.

Design: A retrospective before-after study of OTRs who had received low-dose systemic retinoids during 1 to 16 years for prevention of SCCs.


Patients: Thirty-two OTRs with at least 1 histologically proved SCC.

Interventions: Continuous systemic retinoids at dosages of 0.2 to 0.4 mg/kg per day for a minimum of 12 months.

Main Outcome Measures: The mean difference between the number of SCCs developing annually during retinoid treatment and the number during the 12-month pretreatment interval.

Results: In 28 continuously treated individuals, the mean number of SCCs in the 12-month pretreatment interval was 2.9. The number of SCCs was significantly reduced, with a mean difference of 1.46 in the first year of treatment ($P = .006$), 2.20 in the second ($P < .001$), and 2.14 in the third ($P = .02$). The numbers of SCCs were also reduced in subsequent years, but this effect was no longer significant because of smaller patient numbers. Six patients in whom retinoid treatment was interrupted subsequently had a significant increase in SCCs.

Conclusions: Low-dose systemic retinoids significantly reduce SCC development in OTRs for the first 3 years of treatment, and this effect may be sustained for at least 8 years, with a generally well-tolerated side-effect profile. Studies are now required to further optimize their use as a chemopreventive strategy in high-risk OTRs.

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ence transcription of specific genes, with a consequent wide range of biological activities. Possible mechanisms by which they prevent or reduce development of skin cancer include induction of growth arrest or apoptosis of tumor cells with resultant inhibition of tumor differentiation and promotion, induction of normal cellular differentiation, and immunomodulation, including increased density of Langerhans cells. Preferential retinoid-induced growth inhibition of human papillomavirus 16–immortalized keratinocytes compared with non-infected cells may also be relevant, since SCCs from OTRs are associated with a high prevalence of human papillomavirus DNA.

Although systemic retinoids have been commonly used for prevention of SCCs in high-risk OTRs, there are surprisingly few clinical studies examining this (reviewed by De Graaf et al). Shuttleworth and colleagues first reported a preventive effect from etretinate given during 6 months in 5 of 6 renal transplant recipients. Similar beneficial effects have been documented in a number of uncontrolled series of between 4 and 16 patients treated for less than 6 months to 5 years. In the only randomized, placebo-controlled trial, 19 patients received acitretin for 6 months and had significantly fewer SCCs during this time than did 19 placebo-treated patients. Eleven patients completed a randomized crossover trial in which acitretin produced a significant reduction in SCCs compared with no treatment during 12 months. In a third trial of 26 patients randomized to treatment with 2 dosages of acitretin (0.2 vs 0.4 mg/kg per day) during 12 months, a significant reduction was seen in actinic keratoses but not SCCs in both groups.

Retinoids are effective only during treatment, such that lifelong administration is potentially required for prevention of SCCs in OTRs. However, publications to date have reported treatment for only 2 years or less, with the exception of 1 study in which responses at 5 years in 7 patients were documented. In addition, the adverse effects of systemic retinoids, including mucocutaneous xerosis, alopecia, musculoskeletal complications, increased plasma triglyceride and cholesterol levels, and abnormalities of liver function, may limit their long-term use in OTRs, but this has rarely been examined in patients treated for more than 5 years. In this study we present data concerning the chemopreventive efficacy and side-effects profile of systemic retinoids in a series of 33 OTRs treated for up to 16 years.

METHODS

PATIENTS AND TUMORS

Our institution established a dedicated dermatology clinic for OTRs in the late 1980s and has a cohort of more than 800 OTRs under longitudinal study, with data on almost 8000 patient-years at risk. All OTRs are seen within 6 to 12 months of transplantation and at least annually thereafter. Since 1988 we have documented the use of systemic retinoids (initially etretinate and, since 1993, its active metabolite, acitretin) in patients who have developed at least 1 histologically proved SCC, who are predicted to be at high risk for further tumor formation (in terms of age, duration of transplantation, previous UV radiation exposure, and skin type), in whom the renal physicians consider there are no specific contraindications, and in women who are postmenopausal. A low-dosage protocol is used, starting at approximately 0.2 mg of acitretin per kilogram per day and increasing to a maximum of 0.4 mg/kg per day according to clinical response and side-effect profile. Patients are examined every 3 months, when potential adverse effects are documented and fasting lipid levels, renal and liver function, and full blood count are monitored. Routine radiographic skeletal monitoring is not performed. At each follow-up visit, advice regarding photoprotection and self-surveillance is reinforced; dysplastic lesions are treated with cryotherapy, topical fluorouracil, curettage, and cautery; and all suspicious lesions are excised.

For the purposes of this study, we included individuals who had received retinoids for at least 12 months between January 1, 1988, and December 31, 2003. Only patients in whom a complete skin cancer history was available with histologic confirmation of each tumor were studied. Patients in whom there had been an interruption in treatment for any reason during the first year were excluded from the main analysis and were analyzed separately. Patients who had received at least 12 months of treatment, but had then had an interruption in therapy, were also analyzed separately for the period after this interruption. For each individual, therapeutic benefit was assessed by comparing the numbers of SCCs before starting retinoids with annual SCC burden thereafter. The mean of this difference was calculated for all patients treated for that time interval. Information on the mean number of SCCs per year for each year after transplantation were also available. Histologically proved CIS were analyzed separately. Basal cell carcinomas, appendageal tumors, and melanomas were not included in the analysis.

During the course of this retrospective study, it was our policy to reduce immunosuppression only in the presence of metastatic disease. However, immunosuppression may be altered by transplant physicians for a number of other reasons, eg, coincident posttransplant lymphoproliferative disease, Kaposi sarcoma, or gout (azathioprine is greatly reduced or stopped if allopurinol sodium therapy is started). The medical records of all patients included were carefully scrutinized for evidence of any coincident reduction in immunosuppression that may have influenced the development of cutaneous SCC.

STATISTICAL ANALYSIS

The differences in numbers of SCCs between the pretreatment period and each year after the start of treatment were calculated for each patient. Confidence intervals (CIs) and P values for the mean of the differences were determined by 1-sample t tests. When the responses to acitretin of the 2 age groups at transplantation and the 2 age groups at start of retinoid treatment were compared, independent-sample t tests were used. The statistical package used was SPSS 11.00 (SPSS Inc, Chicago, III).

RESULTS

Forty-two patients received systemic retinoids for chemoprevention of skin cancer at our institute between 1988 and 2003. Ten individuals were excluded from further analysis, as they did not fulfill all study criteria (4 were treated for less than 1 year in total; 2 were transferred from other hospitals and skin cancer data were incomplete; 2 were treated for vulval intraepithelial neoplasia only; 2 started treatment with retinoids for viral warts or acne rather than skin cancers, but subsequently developed SCCs while taking retinoids). Four patients had received treatment for longer than 1 year but with inter-
ruptions in treatment within the first 12 months, leaving 28 patients who had received continuous treatment (Table 1). Two patients (patients 24 and 26) were included in both the series of 28 patients receiving continuous treatment and the analysis of effects of interruptions in treatment, as they received treatment for longer than 1 year but then experienced an interruption in treatment. Patient 1 also discontinued treatment (because of alopecia) after 19 months but did not experience a rebound in SCC numbers in the first 2 months after stopping treatment; he was then lost to follow-up and was not included in the analysis of interruptions.

One of the 28 OTRs had received a cardiac transplant, and the remainder were renal transplant recipients. Their mean age at transplantation was 44.6 years (range, 17-67 years), and 26 were male. Immunosuppressive drug regimens consisted of azathioprine and prednisolone (n=7); azathioprine, prednisolone, and cyclosporine (n=19); prednisolone and cyclosporine (n=1); and azathioprine and cyclosporine (n=1). All had had at least 1 documented SCC before retinoid therapy, with the exception of patient 12 (Table 1). This individual had had 3 severe CIS lesions with probable microinvasion and was considered very high risk (he had already had a basal cell carcinoma before transplantation, was skin type I, and had spent many years as an outdoor worker in the Middle East, and his older brother [patient 13] had had multiple SCCs). He therefore started treatment with retinoids before a frankly invasive SCC occurred. The mean number of years from transplantation to first SCC was 7.5 (range, 3-17 years), and the mean number of SCCs before the start of treatment with retinoids was 5.37 (range, 1-12). In the 12-month pretreatment interval, the mean number of SCCs was 2.9 (range, 0-9). Acitretin was used in 25 patients, but 3 patients treated before 1993 started treatment with equivalent doses of etretinate, and 2 were subsequently changed to acitretin.

**EFFECT OF RETINOIDS ON THE NUMBER OF SCCS PER YEAR**

Twenty-eight patients received continuous retinoids for at least 1 year (Table 1). The mean of the differences in numbers of SCCs in the pretreatment compared with the
posttreatment 12-month intervals confirmed a mean reduction of 1.46 SCCs per year \((P=0.006; 95\% \text{ CI}, −0.45 \text{ to } −2.47)\). A total of 25 patients received retinoid therapy for at least 2 complete years, with a mean reduction of 2.20 SCCs per year \((P<0.001; 95\% \text{ CI}, −1.37 \text{ to } −3.03)\). Fourteen patients received 3 complete years of treatment, with a mean reduction of 2.14 SCCs \((P=0.02; 95\% \text{ CI}, −0.47 \text{ to } −3.82)\). Eleven patients were treated for at least 4 years, and although the mean reduction was still 1.63 SCCs, this did not quite achieve statistical significance \((P=0.09; 95\% \text{ CI}, 0.32 \text{ to } −3.59)\). For individuals who had received at least 5, 6, 7, 8, 9, and 16 years of continuous treatment \((n=6, 6, 4, 4, 2, \text{ and } 1, \text{ respectively})\), the mean difference in SCCs continued to show an overall reduction, but this was no longer statistically significant (Table 2, Figure 1). Responses for selected individual patients are shown in Figure 2.

The mean number of SCCs per year after transplantation and before the start of retinoid treatment was also calculated. There was a gradual increase in the annual SCC number each year after transplantation, reaching a maximum in the 12-month interval immediately before retinoid therapy was started. As expected, there was a strong correlation between the number of SCCs in the 12 months preceding acitretin treatment and the total number of SCCs from time of transplantation to start of acitretin therapy (Figure 1).

### EFFECT OF INTERRUPTION IN RETINOID THERAPY

Six patients received retinoids for more than 18 months but had experienced an interruption in therapy, in all cases inadvertently rather than as the result of adverse effects.

<table>
<thead>
<tr>
<th>Years After Starting Retinoid Treatment</th>
<th>No. of Patients</th>
<th>Mean Difference, Pretreatment and Posttreatment SCCs</th>
<th>95% Confidence Interval</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>−1.46</td>
<td>−0.45 to −2.47</td>
<td>0.006</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>−2.20</td>
<td>−1.37 to −3.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>−2.14</td>
<td>−0.47 to −3.82</td>
<td>0.02</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>−1.63</td>
<td>0.32 to −3.59</td>
<td>0.09</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>−0.83</td>
<td>1.09 to −2.76</td>
<td>0.32</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>−0.67</td>
<td>1.88 to −3.21</td>
<td>0.53</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
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<td>1.54 to −4.55</td>
<td>0.22</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>−1.00</td>
<td>3.12 to −5.11</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Abbreviation: SCC, squamous cell carcinoma.

Figure 1. Annual numbers of squamous cell carcinomas (SCCs) before and after the start of systemic retinoid treatment. Only patients in whom there had been continuous retinoid treatment are included.

Table 2. Effects of Retinoid Treatment on SCC Development

- **Figure 2:**

- **Table 2:**

- **Figure 1:**
In 2 cases (patients 24 and 26, Table 1) this interruption did not occur during the first 12 months of retinoid therapy, and these individuals were therefore also included in the analysis of continuous treatment up until the time at which this interruption occurred. The remaining 4 cases were not included in the main analysis because an interruption had occurred within the first year of treatment. There was a significant difference in SCC numbers in the 12-month interval before and after an interruption in treatment, with a mean increase of 4.67 SCCs (95% CI, 1.3-8.03; \( P = .02 \)). This “rebound” increase in SCCs was most marked in patients taking retinoids for longer than 12 months (Table 3). Individual data for patient 24 are given in Figure 3.

**METASTATIC SCC AND RETINOID THERAPY**

Metastases from cutaneous SCC were recorded in 4 of the 28 patients receiving continuous retinoid treatment. Two patients (cases 9 and 11) were diagnosed as having metastatic SCC in the 2 weeks before treatment started, and 2 patients (cases 18 and 21) developed metastatic disease while already taking retinoids. Patient 9 had local lymph node metastases from a spindle cell SCC arising on the right cheek, as well as bony metastases to ribs and sacrum, and was treated with radical surgery and radiotherapy. He survived for 57 months without further metastases and died of unrelated causes (Figure 4A). Patient 11 had right axillary lymph node metastases presumed to have originated in a primary SCC on the dorsum of the hand, despite complete histological resection 6 months previously. He was treated with surgery and radiotherapy and had no further metastases in 36 months of follow-up. Patient 21 had lymph node metastases from a recurrent SCC situated on the dorsum of the left hand 66 months after starting acitretin. In the preceding 2 years his annual number of SCCs had increased above pretreatment levels, despite an increase in acitretin dose (Figure 4B). He was treated with surgery but died 6 months later of apparently unrelated causes. Patient 18 had a rather similar course in that his annual SCC numbers were well controlled with acitretin treatment for 14 years, but this control appeared to be lost in the year before development of metastases. He had both local lymph node involvement and pulmonary metastases from poorly differentiated SCC arising on the scalp and remained under follow-up.
EFFECT OF RETINOIDS ON CIS

When histologically proved CIS were included in the analysis, the reduction in annual lesion numbers remained significant in years 1 to 3 of retinoid therapy. Although similarly reduced in year 4 and later, this was no longer significant. Many patients treated with retinoids also had widespread epidermal dysplasia and/or viral warts. Most experienced considerable subjective and objective improvement in these lesions, although such effects were not specifically quantified in this study.

COINCIDENT ALTERATIONS IN IMMUNOSUPPRESSION

Immunosuppression was reduced at the time systemic retinoid treatment was started in the 2 patients (patients 9 and 11) in whom it was being administered as part of treatment for metastatic SCC. Careful examination of the medical records of all patients revealed no other changes in immunosuppression in the 12 months before or after starting retinoid therapy, with the exception of patient 2, in whom a posttransplant lymphoproliferative disorder was diagnosed 8 months after acitretin was started, and azathioprine therapy was gradually reduced and stopped during the subsequent 2 years.

EFFECT OF AGE AT TRANSPLANTATION AND AGE AT STARTING RETINOID TREATMENT

For the 25 patients who had been treated for at least 2 years, the influence of age at transplantation on response to retinoids was analyzed. Patients were divided into 2 groups: those who underwent transplantation before 45 years of age and those who were at or above 45 years. There was no significant difference between these groups in mean reduction of SCCs in either the first or second years of treatment. The mean age at which retinoids were started was 55.3 years. The influence of age at start of treatment on efficacy was analyzed by dividing patients into 2 approximately equal groups: those 55 years or older and those younger than 55 years. There was no significant difference between these 2 groups in mean reduction of SCCs during the first 2 years of treatment.

EFFECT OF TIME AND CUMULATIVE TUMOR NUMBERS BEFORE THE START OF RETINOID TREATMENTS

Retinoid treatments were started a mean of 2.82 years (range, 1-9 years) after first SCC. The effect of this time interval on efficacy of treatment was assessed by considering patients in 2 groups: those in whom retinoids were started less than 3 years and 3 or more years after the first SCC. This time interval had no significant influence on subsequent efficacy of retinoids in reducing SCCs. A mean of 5.37 SCCs were diagnosed before retinoid therapy was started; there was no difference in reduction of SCCs in individuals with fewer than 5 and those with 5 or more SCCs before starting treatment.

Table 3. Effects of Interruptions in Retinoid Therapy on SCC Numbers

<table>
<thead>
<tr>
<th>Patient No. *</th>
<th>Duration of Retinoid Treatment Before Interruption, mo</th>
<th>Duration of Interruption, mo</th>
<th>12-mo Preinterruption Interval</th>
<th>12-mo Postinterruption Interval</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>48</td>
<td>5</td>
<td>6</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>26</td>
<td>16</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>29</td>
<td>12</td>
<td>6</td>
<td>0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>30</td>
<td>32†</td>
<td>6</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
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<td>6</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>32</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviation: SCC, squamous cell carcinoma.

*Patients 24 and 26 were also included in the series of 28 patients receiving continuous treatment (Table 1) up to the time at which there was an interruption in treatment. Patients 29 to 33 were not included in that series, as the interruptions occurred within the first 12 months of treatment. All patients subsequently had at least 18 months of total retinoid therapy and were therefore taking retinoids in the postinterruption 12-month interval. Patient 1 (Table 1) also discontinued treatment (because of alopecia) after 19 months but did not experience a rebound in SCC numbers in the first 2 months after stopping treatment; he was then lost to further follow-up in our department and is not included in this analysis.

†Patient 30 was not included in the main analysis, as he had had an interruption in retinoid therapy within the first 12 months, although this was for just 1 month. He continued with therapy but had a longer interruption after 32 months of therapy, and it is the effect of this interruption that is recorded here.
Figure 4. Effects of systemic retinoids on the course of metastatic cutaneous squamous cell carcinoma (SCC). A, Patient 9. Retinoid treatment was started at the time of diagnosis; no further metastases occurred and SCC development was significantly reduced. B, Patient 21. Metastases developed during retinoid treatment; the annual number of SCCs and carcinomas in situ (CIS) increased shortly before the diagnosis of metastases.

ADVERSE EFFECTS OF RETINOIDS

Among the subjective side effects reported, dry lips, dry skin, and palmoplantar desquamation were common and dose limiting in 5 patients (18%) (Table 4). Hair loss occurred in 2 patients and led to discontinuation of treatment by 1 patient. Arthralgia was reported by 2 individuals; in 1 patient a dose reduction was required, but in the other, arthralgia was transient and not clearly related to treatment, and in neither case were there accompanying radiographic abnormalities. Other symptomatic side effects included dry eyes (n=3), headache (n=1), epistaxis (n=1), nail fragility (n=2), and pseudoporphyria (n=1). Elevated serum triglyceride and cholesterol levels had been present in 15 (54%) of the 28 patients before starting treatment, of whom 9 were already taking lipid-lowering drugs. Overall, 10 (36%) of the 28 patients had an increase in lipid levels above pretreatment values while taking retinoids; 3 were already taking lipid-lowering drugs, and the dose was increased. In 6 patients, elevation of lipid levels during treatment necessitated introduction of lipid-lowering drugs, but lipid levels had been elevated in 4 of these patients before retinoid treatment was started. Only 2 patients with normal pretreatment lipid levels had to start taking lipid-lowering drugs during treatment. In 2 patients with chronic renal impairment before the start of treatment, renal function slowly deteriorated, but this deterioration was not considered to be due to retinoids. Results of hematologic and liver function tests were not adversely affected in any patient.

COMMENT

This is, to our knowledge, the first study to provide information on both short-term (<5 years) and long-term (>5-16 years) use of systemic retinoids in the prevention of cutaneous SCCs in OTRs. Of 28 OTRs receiving continuous retinoid treatment, a significant mean reduction of 1.46 SCCs occurred in the first year of treatment, 2.24 SCCs by the second year, and 2.14 SCCs in year 3. This reduction was sustained, but nonsignificant, at years 4 and later. In 2 patients, retinoids appeared to halt progression of documented metastatic disease. In 2 other individuals, metastases developed during treatment and, in both cases, loss of chemopreventive efficacy had already been noted in the preceding 12 months. Most adverse effects were mild, and treatment was discontinued in only 1 patient because of these. In 6 patients, interruption of therapy was associated with a significant rebound increase in tumors.

RETINOID CHEMOPREVENTIVE EFFICACY

Although we demonstrated a significant annual reduction in SCCs after introduction of retinoids by comparison with the 12-month pretreatment interval, it is likely that this approach may have underestimated the true chemopreventive efficacy of retinoids. Data on the mean numbers of SCCs before retinoid treatment confirmed a steady annual increase for each year after transplantation. Thus, the projected tumor numbers for each year after treatment might have been expected to far exceed the baseline taken in the 12-month pretreatment interval. In these circumstances, the annual reduction in tumor numbers with retinoid treatment may well have been even greater and may also have continued to be highly significant at years 4 and above. A carefully designed case-control study would be necessary to investigate such a possibility. A possible confounding factor in interpreting these data is that more frequent monitoring and intensive treatment of premalignant lesions may have accounted for some of the reduction in SCC numbers during retinoid treatment. However, all of these patients had been under regular surveillance since the time of their transplantation and had received regular advice concerning photoprotection, and all of them had been treated for dysplastic lesions before starting retinoid therapy.

In a previous study, retinoids appeared to have a significantly better chemopreventive effect in patients with...
5 or more tumors before starting treatment, although only 2 cases were followed up for 5 years. In contrast, we found no difference in the benefits of retinoids in patients with fewer than 5 SCCs or 5 or more SCCs before treatment, both groups showing a significant response. There was also no major effect of age, duration of transplantation, and interval between first SCC and starting retinoid therapy on their efficacy. These data would appear to indicate a possible beneficial role for retinoids whatever the burden of skin malignancy, age, and time since transplantation.

Four (14%) of 28 patients had SCC metastases, highlighting the potentially aggressive nature of SCCs in these high-risk patients. In 2 patients, metastases arose just before the introduction of retinoid treatment, and in both cases no further metastases were detected after follow-up of 57 and 36 months. While this may have resulted from radical surgery and radiotherapy as well as reduction in immunosuppression, it is possible that retinoids also had a significant therapeutic effect. The 2 patients who developed metastases while receiving treatment both followed a similar pattern of prolonged control of SCCs over several years while taking retinoids, and then apparent loss of this control in the year before metastasis occurred. It is possible that the chemopreventive efficacy of retinoids is only partial and temporary in such high-risk individuals, and that a sudden increase in SCCs may herald imminent metastatic disease. In a recent multicenter study, 6 of 8 similar patients with SCC metastases before or after starting retinoid treatment had to stop because of adverse side effects. Martinez et al suggested that such patients are less able to tolerate systemic retinoid therapy, but this was not our experience in that all 4 patients continued treatment, and 2 appeared to benefit significantly in terms of subsequent disease progression.

ADVERSE EFFECTS OF RETINOIDS

In patients without metastatic disease, low-dose retinoids appeared to be well tolerated and adverse effects were easily managed. Only 1 patient discontinued treatment because of symptomatic side effects. In addition 7 patients (25%), retinoid dose was limited by symp-
Effect of retinoids on renal function. More than half of all patients had increased lipid levels before starting retinoids, and most were already receiving treatment for this, reflecting the rigorous optimization of lipid levels required in these individuals, given their increased risk of cardiovascular disease. Only 2 individuals with normal lipid levels before retinoid therapy had an increase in lipid levels while taking retinoids that required the introduction of lipid-lowering drugs. Retinoid dose was limited in an additional 2 individuals to control elevated lipid levels. Two patients with chronic renal failure and graft rejection documented before the start of retinoid treatment progressed to end-stage renal failure (after 24 and 33 months). Despite the theoretical possibility of allograft rejection associated with their immunopotentiating effects, it was considered unlikely that retinoids significantly contributed to this progression. No deterioration in renal function was observed in any other patient. Previous studies have also failed to demonstrate an adverse effect of retinoids on renal function.13

“REBOUND” SCC DEVELOPMENT DURING INTERRUPTION OF THERAPY

A significant increase in SCCs was seen in the 12 months after interruption of treatment in 6 patients. Previous studies have also shown such a relapse in tumor development,6,13,18,19,22 such that continuous treatment appears to be required to maintain a chemopreventive effect. It therefore seems most appropriate to regard retinoid chemoprevention as a potentially lifelong treatment in OTRs, and this must be considered before the patient embarks on such treatment. However, an alternative strategy of intermittent retinoid treatment coupled with periods of intensive surgery during the subsequent rebound remains a possibility that has not yet been investigated.

In conclusion, low-dose retinoids significantly reduce SCC development in high-risk OTRs for at least 3 years and probably as long as 9 years, with an acceptable side-effect profile. Case-control studies over extended periods, including investigation of appropriate timing of intervention and dosing regimens, are now required to optimize use of this important chemopreventive strategy in the management of skin cancer after organ transplantation.

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