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CHAPTER 5

Systemic and topical retinoids in the management of skin cancer in organ-transplant recipients

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Systemic and Topical Retinoids in the Management of Skin Cancer in Organ Transplant Recipients

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BACKGROUND. Nonmelanoma skin cancers are the most frequent malignancies in organ transplant patients. Patients who develop multiple new skin cancers may benefit from retinoid chemoprevention.

OBJECTIVE. The objective of this study was to advise on the use of retinoids in organ transplant recipients.

METHODS. A summary was performed of the existing literature regarding experience with retinoid chemoprevention for skin cancer in organ transplant patients.

RESULTS. Systemic retinoids, specifically acitretin, are effective in inhibiting tumor development in organ transplant patients.

This effect is only present during therapy, however. Topical retinoids have some effect in the treatment of actinic keratoses.

CONCLUSIONS AND RECOMMENDATIONS. Systemic retinoids can be used for chemoprevention of skin cancer. For a good result, long-term treatment with acitretin is necessary. Side effects, however, limit the use of retinoid chemoprevention. It is advised that treatment be started at a low dose, and patients should be monitored regularly for triglyceride and cholesterol levels and transaminases.

Y. G. L. DE GRAAF, MD, S. EUVRARD, MD, AND J. N. BOUWES BAVINCK, MD, PHD HAVE INDICATED NO SIGNIFICANT INTEREST WITH COMMERCIAL SUPPORTERS.

Skin Cancer in Organ Transplant Recipients

NONMELANOMA SKIN cancers, especially squamous cell carcinomas, are the most frequent malignancies in organ transplant recipients.^{1,2} The frequency of skin cancers increases progressively with time after transplantation. In temperate climates such as in the Netherlands, 40% of the renal transplant recipients will develop skin cancer 20 years after transplantation.³ In sunny climates like Australia these percentages are even higher.⁴

Furthermore, in this particular population squamous cell carcinomas tend to be multiple and may have a more aggressive course with frequent recurrences compared to the immunocompetent host. Often there is an association with warts, premalignant keratoses, Bowen's disease, and keratoacanthomas.²

Prevention and Management of Skin Cancer

In organ transplant recipients, intensive surveillance and treatment of precancers and cancers in an early stage is necessary.⁵ This consists mainly of multiple

sessions of cryotherapy, curettage and coagulation, and repeated surgical excisions of tumors. Resurfacing the dorsum of the hand may also be useful in selected patients.⁶

Organ transplant recipients who may benefit from retinoid chemoprevention are those who are actively developing large numbers of skin cancers.^{7,8} In this overview we will summarize the most important literature regarding the experience with systemic and topical retinoids in the chemoprevention of skin cancer in organ transplant recipients.

Mechanism of Action

Retinoids are structural and functional analogs of vitamin A that display a wide range of biologic activity.⁹ Results of basic investigations suggest that retinoids act chemopreventively by inducing growth arrest or apoptosis of tumor cells, by modulating the immune response or differentiation of keratinocytes, or a combination of these events.¹⁰⁻¹²

Intracellularly, retinoids interact with cytosolic proteins and two families of nuclear receptors, the retinoic acid receptors and retinoid X receptors. As a result, specific genes are expressed.¹² It has also been shown that retinoic acid is more effective in inhibiting the growth of human papillomavirus (HPV)-infected human keratinocytes than that of normal

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keratinocytes, probably by suppressing the early transcription of HPV genes.^{13,14}

Rook et al.¹⁵ reported a marked increase of Langerhans cells within the epidermis in three patients after treatment with etretinate and topically applied tretinoin. The increase of Langerhans cells was correlated with duration of therapy. This may indicate a possible immunologic mechanism. In addition, a (statistically not significant) trend was reported for an increase in Langerhans cell density in squamous cell carcinomas during etretinate therapy.¹⁶

Warts in renal transplant recipients showed pronounced K13 expression in contrast to warts in the immunocompetent host. This may reflect an important molecular event inherent in the malignant degeneration of warts in renal transplant recipients. Retinoid treatment significantly correlated with a specific pattern of K13 expression in skin lesions of renal transplant recipients. It has been suggested that by keeping keratinocytes in this esophageal-type differentiation, retinoids might act chemopreventively.¹⁷ Six months of treatment with topical tretinoin resulted clinically in an increased skin thickness. Histologic and ultrastructural examination of retinoic acid treated "normal skin" of renal transplant recipients revealed epidermal and dermal changes evoking increased cellular metabolism in the treated sites.¹⁸

Use of Retinoids in Nonimmunosuppressed Individuals

Systemic Retinoids

Systemic retinoids can be administered to treat precancers and cancers, but more often are used as chemopreventive agents. Treatment of actinic keratoses and Bowen's disease in immunocompetent patients was effective with the use of various retinoids.¹² Treatment of basal cell carcinomas and squamous cell carcinomas, however, showed no clear beneficial effects.¹²

In most trials, retinoids have been administered to prevent skin cancer. These trials were performed in immunocompetent individuals and in patients with xeroderma pigmentosum.¹⁹

Xeroderma pigmentosum is a rare recessive disease of defective DNA repair, in which patients have a 1000-fold increased risk of developing skin cancers.²⁰ In a 3-year controlled prospective study of oral isotretinoin at a dose of 2 mg/kg/day in five xeroderma pigmentosum patients, a reduction of 63% of tumors ($p = 0.02$) was reported in the treatment period compared to the pretreatment interval.²⁰ With these high doses, however, severe adverse effects were

reported. As a result two of the seven patients were unable to complete the protocol.²⁰

In a double-blind, randomized controlled trial of retinol versus placebo in 2297 immunocompetent individuals with actinic keratoses, daily retinol was associated with a statistically significant reduction in the risk of developing squamous cell carcinomas.²¹ In contrast, low doses of isotretinoin were not effective in reducing basal cell carcinomas.²²

The adverse effect profile of synthetic retinoids resembles the symptoms associated with hypervitaminosis A and may hamper the use of these agents.¹² The most frequent systemic side effect is an increase in plasma triglycerides. Increases of total and LDL cholesterol levels are also frequently observed.²³ Other adverse effects are abnormalities of liver function tests, arthralgias, mucocutaneous xerosis, and alopecia.¹² In addition, treatment at high doses or for a long term has been associated with various skeletal abnormalities such as calcifications of tendons and ligaments around joints, hyperostosis of the spine, and osteoporosis.^{7,12} Retinoids are highly teratogenic if given orally during embryogenesis.¹² Isotretinoin's link to psychiatric disorders such as depression is still controversial.²⁴

Topical Retinoids

The advantage of topical retinoids is the avoidance of systemic toxicity. Good results were obtained in the treatment and chemoprevention of actinic keratoses in immunocompetent patients using topical retinoids, in particular isotretinoin and tretinoin.¹² Topical retinoids have not been systematically tested in the treatment or prevention of nonmelanoma skin cancer in immunocompetent individuals.¹²

Retinoid Chemoprevention in Organ Transplant Recipients

Systemic Retinoids

The tables provide a summary of the clinical studies with retinoids in organ transplant recipients that are discussed in this overview.

Initially, studies were performed with etretinate. Later etretinate was replaced by its active metabolite, acitretin.

The four studies summarized with etretinate were all without an explicit control group and showed a reduction of new skin cancers, compared to the pretreatment period (Table 1). The well-known side effects of retinoids were observed but were well manageable (Table 1). Specifically no deterioration of renal function was noted.^{15,25-27}

Table 1. Clinical Studies With Etretinate in Organ Transplant Recipients

<i>Study</i>	<i>Technical Details of Study*</i>	<i>Treatment Result</i>	<i>Side Effects</i>
Shuttleworth et al. ²⁵	NCG, <i>n</i> = 6, 1 mg/kg/day, 6 months	5 patients, no new skin cancers; 1 patient, 2 new SCCs after 6 months.	Cheilitis, increased triglycerides (<i>n</i> = 3), increased cholesterol (<i>n</i> = 2); no deterioration in renal function.
Kelly et al. ²⁶	NCG, <i>n</i> = 4, 50 mg/day, 8–13 months	Considerable reduction new SCCs.	Mild mucocutaneous side effects, thrombocytopenia (<i>n</i> = 1); renal function unchanged.
Rook et al. ¹⁵	NCG, <i>n</i> = 11, 10 mg/day in combination with topically applied 0.025% tretinoin (<i>n</i> = 7) or tretinoin alone (<i>n</i> = 4), 9 months	3 of 4 patients, no new SCCs after 9 months of etretinate + topical tretinoin (2 of 3 patients, no new SCCs after 9 months of topical tretinoin alone); 4 patients, nonevaluable.	Mild mucocutaneous side effects.
Gibson et al. ²⁷	NCG, <i>n</i> = 11, 0.3 mg/kg/day, 17 months	10 patients, significant reduction of new skin cancer after 3 + 6 months compared to pretreatment period; 1 patient, nonevaluable.	Mild mucocutaneous side effects, increased triglycerides (<i>n</i> = 3), increased cholesterol (<i>n</i> = 1).

*Respectively, the type of trial (NCG, study without any explicit control group), the study size, the dose of etretinate, and the duration of the study are depicted. Abbreviation: SCC, squamous cell carcinoma.

Table 2. Clinical Studies With Acitretin in Organ Transplant Recipients

<i>Study</i>	<i>Technical Details of Study*</i>	<i>Treatment Result</i>	<i>Side Effects</i>
Vandeghinste et al. ³⁹	CR, <i>n</i> = 1, 0.5 mg/kg/day, 15 months	No new dysplastic skin lesions observed.	Mild mucocutaneous side effects.
Bouwes Bavinck et al. ²⁸	RCT (compared with placebo), <i>n</i> = 38, 30 mg/day, 6 months	Statistically significantly fewer patients with new skin cancers compared to placebo reduction of number of actinic keratoses.	Side effects: mild mucocutaneous, hair loss, increased cholesterol + triglycerides (<i>n</i> = 3); renal function unchanged.
Yuan et al. ³⁰	NCG, <i>n</i> = 15, 10–50 mg/day, <6 to >12 months	Variable effects on skin cancer.	Mild mucocutaneous side effects.
McKenna et al. ³¹	NCG, <i>n</i> = 16, 0.3 mg/kg/day, 5 years	Statistically significant reduction of new skin cancers after 4 years compared to pretreatment period.	Mild mucocutaneous side effects, increased triglycerides (<i>n</i> = 1), increased cholesterol (<i>n</i> = 1).
McNamara et al. ³²	NCG, <i>n</i> = 5, 10–25 mg/day, 10–24 months	3 patients, significant decrease in new tumors compared to pretreatment period; 2 patients, moderate decrease in new tumors.	Mild mucocutaneous side effects.
George et al. ³³	RCT (compared to no therapy), <i>n</i> = 23, 25 mg/day, 2 year	Number of SCCs significantly lower on acitretin compared to drug-free period.	Cheilitis, headache, increase of musculoskeletal symptoms, gastritis, increased triglycerides.
de Sévaux et al. ²⁹	RCT (0.4 mg/kg/day compared to 0.2 mg/kg/day), <i>n</i> = 26, 0.4 or 0.2 mg/kg/day, 1 year	Decrease of actinic keratoses by 50% in both groups; no effect on development of skin cancers in both groups compared to pretreatment period.	Mild mucocutaneous side effects, mild hair loss.

*Respectively, the type of trial (CR, case report of single cases; RCT, randomized controlled trial; NCG, study without any explicit control group), the study size, the dose of acitretin, and the duration of the study are depicted. Abbreviation: SCC, squamous cell carcinoma.

With acitretin, one placebo-controlled trial and two other randomized controlled trials were performed (Table 2). In addition, three studies without an explicit control group and one case report were published (Table 2). The randomized, double-blind, placebo-

controlled trial showed a significant effect on the prevention of skin cancer at a acitretin dose of 30 mg/day. During a 6-month period, 2 of 19 patients (11%) in the acitretin group reported a total of two new squamous cell carcinomas, compared with 9 of 19

patients (47%) in the placebo group who developed a total of 18 new carcinomas ($p = 0.01$).²⁸ Furthermore, the relative decrease of keratotic skin lesions was 13% in the acitretin group, compared to a relative increase of 28% in the placebo group ($p < 0.01$). After the end of treatment, however, skin cancers and keratotic skin lesions relapsed.²⁸ The other studies generally confirmed the favorable effect of acitretin on the reduction of development of new skin cancers and actinic keratoses.^{29–33} In the Australian open randomized crossover trial, 25 mg acitretin/day was prescribed to 14 patients, and 9 patients received no retinoid treatment. They crossed over after 1 year. A significantly lower number of squamous cell carcinomas was shown in patients while on acitretin compared to the drug-free period ($p = 0.002$).³³ A recent randomized study with low-dose acitretin was performed by de Sévaux et al.²⁹ in 26 renal transplant patients of whom 13 were treated with 0.4 mg/kg/day acitretin and 13 with 0.2 mg/kg/day for 1 year. A decrease in actinic keratoses of 50% was reported in both groups. Nevertheless, no effect on the development of non-melanoma skin cancer was reported in the two low-dose groups of patients when compared to the pretreatment period.²⁹

As far as we know, there are a few reports about the use of isotretinoin in transplant patients with skin cancer.^{8,34} In one study with one patient a 50% reduction of new lesions compared to the pretreatment period was observed.³⁴

Side effects of retinoids in organ transplant recipients are identical to those reported in the immunocompetent host. In organ transplant recipients there is a theoretical concern of immunostimulation caused by the systemic retinoids, which theoretically could lead to rejection of the transplanted organ.⁸ Osteoporosis is also a particular problem for the posttransplant recipient, who is already at risk for osteoporosis from

glucocorticoid exposure.⁵ Furthermore, elevation of serum lipids is more common in organ transplant recipients also without systemic retinoids. This problem is usually manageable by the use of antihyperlipemics.³⁵

Topical Retinoids

Two studies with topically applied tretinoin and one with topically applied adapalene are summarized in Table 3. A statistically significant reduction of actinic keratoses was observed in two studies.^{36,37} Side effects were generally mild.^{36–38} No significant effect was shown in the study of Smit et al.,³⁸ possibly because of the smaller sample size, the lower concentration of tretinoin, the shorter study duration, the complexity of the study, the focus on immunohistochemical and histologic parameters, or a combination of these factors. As far as we know, no studies with topically applied retinoids were performed to study the effect on the development of new skin cancers.

Personal Experience With Acitretin in Organ Transplant Recipients

Acitretin in a dose between 10 and 30 mg per day has, in our experience, a clear effect on the number and thickness of the hyperkeratotic skin lesions and the number of new skin cancers. Most of the approximately 75 patients we have treated in Leiden (The Netherlands) and Lyon (France) together could tolerate this regimen for a 4- to 6-month period. Approximately one-third of these patients were able to continue this regimen for at least 5 years without significant side effects. About half of the patients, however, have preferred to discontinue this treatment after 4 to 6 months because of dry skin, dry lips, significant hair loss, pruritus, or arthralgias. With

Table 3. Clinical Studies With Topical Retinoids in Organ Transplant Recipients

Study	Technical Details of Study*	Treatment Result	Side Effects
Euvrard et al. ³⁶	RCT (vs. placebo), $n = 22$, 0.05% tretinoin once daily, 3 months	Statistically significant reduction of keratotic lesions after 3 months compared to placebo (45% vs. 23%).	Local tolerance generally good.
Euvrard et al. ³⁷	RCT (vs. placebo), $n = 40$, 0.3% vs. 0.1% adapalene, 6 months	Significant decrease in actinic keratoses in 0.3% group compared to placebo (32% vs. 21%).	Skin irritation ($n = 1$).
Smit et al. ³⁸	CT (four treatment modalities), $n = 13$, 0.02% tretinoin vs. calcipotriol vs. both vs. emollient twice daily, 6 weeks	Treatment of actinic keratoses, alone or in combination with calcipotriol, showed no effect on clinical, immunohistochemical, and histologic measures.	Pruritus in all test areas (number unknown).

*Respectively, the type of trial (RCT, randomized controlled trial; CT, controlled trial), the study size, the dose of the topical retinoids, and the duration of the study are depicted.

regard to objective adverse effects, we have observed liver toxicity in two kidney transplant recipients necessitating treatment discontinuation, although we have not observed significant renal dysfunction or allograft rejection. Elevated serum triglycerides and cholesterol levels have been easily manageable. We have utilized intermittent therapy in some patients with alternating 1 to 3 months, with and without acitretin. This regimen seems to be effective, but randomized-controlled trials should be performed to prove the efficacy of this treatment regimen.

Recommendations and Conclusion

Systemic retinoids, specifically etretinate and acitretin, have shown to be effective in inhibiting the development of new dysplastic skin lesions and skin cancers in organ transplant recipients. Because etretinate is not marketed anymore, acitretin is the medication most often utilized and the recommendations in this overview therefore only pertain to acitretin. Experience with isotretinoin in organ transplant patients is limited. Nevertheless, it is probably the most widely studied retinoid in the chemoprevention of skin cancers in nonimmunosuppressed patients. The results in transplant patients are expected to be similar as compared to nonimmunosuppressed patients. We have no data to compare the antitumoral effect of either drug in transplant or in nontransplant patients. Isotretinoin could be useful in female patients because of the shorter time required to avoid pregnancy (1 month after the discontinuation of the treatment compared to acitretin (2 years)).

Systemic retinoids are variably tolerated by organ transplant patients. Because the benefit of acitretin is present only during treatment, long-term treatment usually is necessary. Long-term use of systemic retinoids, however, may be limited by the occurrence of side effects in individual patients. Specifically, subjective side effects, such as dry skin, dry lips, and hair loss, may be reason to discontinue therapy with acitretin, despite treatment with topical moisturizers.

Although no patients were reported in whom retinoid therapy affected the transplanted organ, the possible immune-stimulating effect of retinoids causes some theoretical concern for rejection of the transplanted organ. Use of acitretin therefore should in our opinion be limited to patients with dozens of hyperkeratotic skin lesions and/or at least one squamous cell carcinoma in the medical history, but other levels of involvement of the skin have also been suggested.

Because the minimal effective dose varies greatly between patients, it may be best to start at a low dose

(between 10 and 30 mg/day), which can be increased as tolerated if insufficient benefit is observed.⁵ In our experience a dose of 30 mg/day acitretin or less was sufficiently effective. When treatment is limited by subjective side effects, intermittent acitretin treatment could be considered with periods on acitretin therapy intermingled with treatment-free periods. In addition to the intermittent acitretin regimen, lowering the dose of acitretin is an alternative method of decreasing the side effects.

Patients should be monitored for the usual measures when using oral retinoids. Triglyceride levels, cholesterol levels, and transaminases should be tested before the start of the treatment and at regular intervals during treatment, initially monthly and later at 3-month intervals. In renal transplant recipients, renal function should be monitored. Radiologic examination of the spine and long bones could be performed in patients with long-term use of retinoids but, in our opinion, is not useful in organ transplant recipients, because osseous side effects of treatment with corticosteroids can be expected.

Although topical retinoids seem effective in the treatment of actinic keratoses and warts in organ transplant patients, the effect is clearly less than with treatment with systemic retinoids. Topical retinoids may be warranted as first-line therapy in high-risk patients once actinic keratoses begin to develop, but before a critical threshold necessitating oral retinoids is reached.

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