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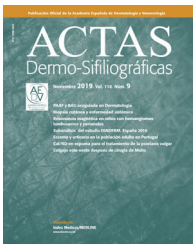

REVISIÓN

# [Translated article] Actinic Keratosis in Solid Organ Transplant Recipients: A Medical Literature Review

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**Abstract** Pharmacological immunosuppression in solid organ transplant recipients is a significant risk factor in the occurrence of actinic keratosis (AK) and later progression into squamous cell carcinomas (SCC). Treating clinical and preclinical lesions is mandatory in this group of patients due to the high changes of progression into SCC. On the other hand, prevention of AK should be considered because it plays a crucial role.

Several studies have been published on immunocompetent patients, as well as on the management and prevention of AK, but not on immunosuppressed patients.

This review aims to summarize the current knowledge on the management and prevention measures of AK in solid organ transplant recipients.


**PALABRAS CLAVE**
Queratosis actínicas;
Carcinoma escamoso;
Trasplantados de órgano sólido;
Inmunosupresión

## Queratosis actínicas en pacientes trasplantados de órgano sólido: revisión de la literatura

**Resumen** La inmunosupresión farmacológica de los pacientes trasplantados de órgano solido constituye un importante factor de riesgo tanto para la aparición de queratosis actínicas (QA) como para su progresión a carcinomas escamosos (CE). El tratamiento tanto de las lesiones clínicas como preclínicas en este grupo de pacientes es obligatorio debido a la elevada posibilidad de evolución a CE. Por otra parte, la prevención presenta también un papel importante que debemos tener en cuenta.

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Existen un gran número de estudios realizados en pacientes inmunocompetentes sobre el tratamiento y la prevención de QA, pero no en pacientes inmunosuprimidos.

Esta revisión pretende resumir el conocimiento actual sobre los tratamientos y medidas de prevención de la QA en loas pacientes trasplantados de órgano sólido.


## Introduction

Actinic keratoses (AK) are precancerous skin lesions induced by high exposure to ultraviolet (UV) radiation and, therefore, a marker of chronic sun damage.[1] Clinically, they appear as 1 mm to 2.5 cm brown-red papules and plaques with a rough, hyperkeratotic surface, mainly on sun-exposed areas such as face, lower lip, bald scalp, neck, arms, and hands.[2] Chronic sun damage triggers not only the appearance of these palpable lesions, but also to the presence of subclinical AK. The skin surface affected by actinic damage, both clinical and subclinical, is referred to as the field cancerization.[3]

Several risk factors contribute to the development of AK, including advanced age, male gender, cumulative sun exposure, fair skin (Fitzpatrick skin types I and II), baldness, and immunosuppression.[4] Solid organ transplant recipients (SOTR) experience a higher incidence of AK and non-melanoma skin cancer compared to the overall population. In these patients, there is also a greater progression of precancerous lesions from AK to squamous cell carcinoma (SCC).

AK are considered dynamic conditions that can persist, regress, recur, and progress into invasive SCC. In immunocompetent patients, the progression rate is between 0% and 0.075% per lesion/year, up to 0.89% if there is a history of non-melanoma skin cancer (whether invasive or not). When AK are part of a field cancerization, or the patient is immunocompromised, this risk increases considerably.[5] Regarding the regression of AK in transplant recipients, for specific lesions, a spontaneous resolution rate of 0% has been reported vs 28% in immunocompetent individuals. Similarly, the histopathological examination estimates that nearly 70% of SCC develop from AK.[2,4] SOTS with AK are 32 times more likely to develop SCC. Additionally, 95% of the patients with SCC also have AK.[6] Therefore, acting early on AK is crucial to prevent the development of SCC.[7]

We should also mention that after the first post-transplant skin cancer, SOTR have a risk between 45% and 57% of developing another skin cancer. The risk of developing > 10 skin cancers within the next 2 years is nearly 3% to 7%, and 25% will have synchronous lesions.[8]

## Treatment

Since SCC is the most common neoplasm in SOTR, with an incidence rate 60 to 100 times higher compared to immunocompetent individuals, and an increased rate of metastasis (8% in SOTR vs 1% to 4% in the overall population), it is mandatory to treat its precursor lesion, AK.[1,9]

Therapies of AK can be categorized into those directed at single lesions and those aimed at treating the field cancerization.

The most widely used targeted therapies are cryotherapy, $CO_2$ ablative laser, or excision. Although these techniques allow for a high rate of resolution of single lesions, they lack efficacy vs the preclinical lesions found in the field cancerization, which are more likely to progress into SCC in transplant recipients. Therefore, targeted therapies are considered insufficient in SOTR, meaning that field cancerization-directed therapies are absolutely necessary.[10]

This article aims to review various field cancerization-directed therapies and strategies to prevent AK in SOTR.

## Field cancerization-directed therapies

### Conventional photodynamic therapy

Conventional photodynamic therapy (PDT) involves the application of photosensitizing agents (5-aminolevulinic acid [ALA] or methyl aminolevulinate [MAL]) to the region of interest, and use of a light source with a wavelength between 404 nm and 420 nm (blue light), or 635 nm (red light).[3] It is the most widely studied treatment in SOTR and according to the findings made so far, it has the highest complete response rate to date (40% to 89%).10 Higher response rates have been reported in patients treated with 2 cycles of PDT. We should mention that response rates are lower for AK on the hands (22% to 40%).[11] No comparative trials have ever been performed between ALA and MAL in transplant recipients. The latter offers the advantage of better skin penetration thanks to its lipophilicity and greater specificity in treating neoplastic cells.[12] However, in immunocompetent patients, there does not seem to be significant differences between the 2 photosensitizers, and even PDT with ALA may yield better results after a 1-year course of treatment.[13,14]

Despite the good results obtained, a drawback of this technique is the pain it causes in the region of interest during and after PDT sessions.[11,15] This feeling may be greater in transplant recipients, likely due to their larger field cancerization compared to that of immunocompetent patients.[11]

### Daylight photodynamic therapy

Daylight photodynamic therapy (dPDT) uses UV radiation to activate the photosensitizer, making it useful to treat a larger field cancerization. Patients treated with dPDT had fewer new-onset AK lesions at the 3-, 9-, 15-, and 21-month follow-up compared to cryotherapy. Additionally, these patients showed a preference for this field treatment.[16]

Studies have been conducted where ablative laser therapy is used prior to the application of the photosensitizer to improve the efficacy rates. This would lead to better drug absorption, especially in thicker and more hyperkeratotic lesions. Differences in the complete response after 4 months of treatment have been reported, ranging from 75.5% to 64%, respectively, depending on whether laser therapy is previously used or not,[17] being these results consistent with those from former studies.[18]

### Imiquimod

Imiquimod is a toll-like receptor 7 agonist, which triggers the activation of numerous cellular proteins, being nuclear factor kappa B a notable example. This induces the release of cytokines that will eventually activate the immune system vs antigens expressed in atypical keratinocytes, ultimately leading to their death.[3]

Despite immunosuppressive therapy in transplant recipients reduces the activity of the immune system and possibly the efficacy profile of the drug,[19] complete response rates (between 28% and 62.1%) have been reported 3 months, or 8 weeks, respectively, after completing treatment.[15,20]

Conflicting data surround sustained responses, being these responses maintained in 7% to 80% of the patients at the 1-year follow-up.[21,22] These differences may be due to variations in the therapeutic regimens across the different studies.

### 5-Fluorouracil (5-FU)

The action of 5-FU is based on the inhibition of thymidylate synthase, resulting in the inhibition of DNA synthesis and interference in the formation and function of RNA, which eventually triggers the death of target cells.[3]

Data on the efficacy profile of 5-FU treatment in immunosuppressed patients are scarce, with varying and difficult-to-compare results due to the different review times involved. Ingham et al. reported a complete response rate of 63% in patients 8 weeks into treatment, and a partial response rate of 71% at 1 year in 8 SOTR.[23] Perret et al. compared 5-FU treatment (one 3-week cycle) and MAL-PDT in 7 renal transplant recipients, with complete response rates of 11% at 6 months for 5-FU and 89% for MAL-PDT.[24] Recently, Hasan Zu et al. conducted a study that compared 3 cohorts of 40 SOTR treated with 5-FU at 5%, imiquimod, and sunscreen, with 1-year partial response rates of 58%, 29%, and 15%, respectively (the difference between imiquimod and the sunscreen was not significant), and total response rates of 17%, 7%, and 8%, being these differences also nonsignificant.[22]

### Tirbanibulin

Tirbanibulin is a recently approved therapy vs non-hyperkeratotic and non-hypertrophic AK (Olsen I). Tirbanibulin is a synthetic antiproliferative agent which by binding to tubulin, inhibits its polymerization and disrupts Src signaling in actively dividing cells. This mechanism of action leads to cell cycle arrest, abnormal mitosis, and eventually apoptosis.[25]

No data have been published to this date on the efficacy and safety profile of tirbanibulin therapy in immunosuppressed patients. To date, only 2 stage III clinical trials have been conducted in immunocompetent patients, achieving a nearly 50% complete response on day 57, with 53% of them remaining recurrence-free at the 1-year follow-up.[26]

The most common side effects are local and transient, being redness and scaling notable and happening after completing therapy.[26]

### Diclofenac

Diclofenac is a non-steroidal anti-inflammatory drug that inhibits cyclooxygenase-2 and the synthesis of prostaglandins. The exact mechanism by which diclofenac acts in the management of AK remains unclear. However, it is believed to be due to its anti-inflammatory and antiangiogenic properties, leading to antiproliferative and apoptotic effects.3

Only 1 clinical trial has ever been conducted in SOTR comparing diclofenac at 3% in hyaluronic acid vs a vehicle. In the trial, on week 20, the complete response rate reported was 41% in patients on a 16-week course of diclofenac, a response that was maintained in 45% of patients at the 2-year follow-up.[27]

## What therapy should be selected in each case?

There are numerous studies on the management of AK among immunocompetent patients. However, evidence on the most effective therapy to treat AK and field cancerization in SOTR is still scarce. Therefore, there is uncertainty on what the best practices are for different patients. However, recommendations have been made based on expert dermatologist consensus on the management of AK in SOTR based on the presence of actinic damage and the past medical history of non-melanoma skin tumors.[28]

Based on these recommendations, the treatment of choice for isolated AK is cryotherapy, being necessary to treat field cancerization when AK appears clustered in a certain anatomical area. Field cancerization-directed therapies can be challenging due to patient compliance issues. Given the higher incidence and recurrence of AK in SOTR, they are more likely to require multiple cycles, and a combination of different therapeutic alternatives.

We should mention the need to make regular follow-up appointments with the dermatologist to screen for new-onset lesions, at least, every 6 to 12 months.[29]

## Prevention

The primary goal of AK prevention techniques is to avoid and reduce the number of these lesions and, consequently, the risk of SCC. Primary prevention through patient education and the use of sunscreen should be recommended for all SOTR. Regarding secondary and tertiary prevention, different options are advised for high-risk patients only.

### Sunscreen

Sun exposure is the most important modifiable risk factor for the development of AK and SCC in SOTR. However, routine use of sunscreen in this population is simply not enough.[1] Significant differences have been reported in the occurrence of AK and SCC when comparing the regular and the intermittent use of sunscreen over a 2-year span.[30]

Some sunscreens have been specifically designed for chronic sun damage to prevent the appearance of

premalignant and malignant skin lesions. Supplementation with DNA repair enzymes helps protect against the damage caused by UV light. These enzymes include photolyase, T4 endonuclease V, UV endonuclease, and OGG1 endonuclease.[31]

The incidence of low levels of vitamin D in SOTR should also be taken into consideration following the recommendation of avoiding sun exposure, and using glucocorticoids in some patients. Glucocorticoids can increase the breakdown of 25-hydroxyvitamin D. Therefore, lab tests should be conducted among this population, and supplementation administered when necessary, as it is safe and effective to do so.[1]

### Immunosuppression

The immunosuppression used in SOTR promotes the development of new AK and SCC. The most widely used drugs are calcineurin inhibitors (tacrolimus and cyclosporine), antiproliferatives (azathioprine, mycophenolate mofetil), and recently, mTOR inhibitors (sirolimus and everolimus). In addition to the differences reported in the intensity and duration of immunosuppression, not all immunosuppressants carry the same risk.1 Tacrolimus and azathioprine are 2 immunosuppressants most commonly associated with the development of SCC.[1,28] In contrast, mTOR inhibitors have proven capable of reducing the number of non-melanoma skin cancers in SOTR when added to, or in lieu of older immunosuppressants.[1,32,33] Additionally, it has been reported that sirolimus delays the development of AK, and even induces regression and slows down the incidence of new SCC.[34,35] These can often start right after transplantation, and are often associated with the use of prednisone and mycophenolate mofetil.[35]

The conversion from azathioprine to mycophenolate mofetil should be considered whenever possible.1 Substituting calcineurin inhibitors with mTOR inhibitors and reducing immunosuppression are also valid strategies to minimize the incidence rate of AK and SCC. It is recommended to make these immunosuppression changes in SOTR with > 10 SCCs/year, or in those with high-risk SCC. The immunosuppression regimen should always be discussed with the transplant team.[1,28]

Despite the decreased incidence of AK and SCC, mTOR inhibitors have side effects that can limit their use and lead to drug discontinuation. Common adverse events include mouth ulcers, edema, acneiform reactions, hyperlipidemia, thrombocytopenia, leukopenia, delayed wound healing, and postoperative complications.[35]

Currently, topical sirolimus has various indications without the severe adverse events associated with this drug. Recently, its potential efficacy profile to reduce keratinocytic lesions has been reported, with a 3-fold reduction in in situ SCCs at 24 weeks vs placebo, with no differences being reported in the overall number of SCCs.[36]

### Retinoids

Retinoids are the most effective strategy to prevent AK and SCC in high-risk populations.[37] Acitretin can prevent both premalignant and malignant skin lesions at skin level.[38] A difference in the number of premalignant keratotic lesions of up to 43% has been reported in 6-month comparisons of SOTR on acitretin vs placebo.[39] Additionally, low-dose acitretin (10 mg to 30 mg) for a longer period of time has been shown to reduce the occurrence of skin cancer by up to 50% in SOTR with tolerable adverse events.[40] Other retinoids such as isotretinoin could be used in patients who remain intolerant to acitretin, or have near-term pregnancy plans requiring higher doses to reach the desired effects with a poorly established efficacy.[37]

Systemic treatment should be maintained because rebound effects have been reported shortly after drug discontinuation.[38,39,41]

Topical retinoids might be a future option, but their efficacy has not been sufficiently demonstrated to date.[37]

### Capecitabine

Capecitabine is a prodrug of 5-FU. Its potential preventive therapeutic effect to reduce AK and, consequently, SCC in SOTR has been reported anecdotally.[42,43] In a case series, the impact of low-dose capecitabine (1 g/m$^2$/day, with a 1-week break every 14 days) in the management of AK in 15 SOTR was examined. More than half of the patients reduced their incidence of AK, while 20% remained stable.[44]

Adverse events associated with this treatment include fatigue, nausea, hand-foot syndrome, gout, or an impaired kidney function. Sometimes, these adverse events can lead to down-titration, or drug discontinuation, so the risk-benefit ratio should always be taken into consideration prior to using this therapy.[42–44]

### Nicotinamide

Nicotinamide is a form of vitamin $B_3$ that could reduce UV radiation-induced immunosuppression and enhance DNA repair, thereby reducing both the field cancerization and the number of skin cancers.[45]

Unlike in immunocompetent patients, in whom there seems to be fewer skin neoplasms (but not AK).[45,46], recent reports have shown no significant differences in transplant recipients after comparing nicotinamide (500 mg/12 hours) to placebo, both in skin neoplasms and AK.[47]

### Expert recommendations

According to the consensus of expert dermatologists, acitretin therapy and changing the immunosuppressive regimen should be spared for patients with multiple, or high-risk skin cancer.[28]

## Conclusions

SOTR require special attention from dermatologists. Due to the risk of progression to SCC, patient education, regular screenings, prevention, and ongoing treatment of AK are mandatory. Transplant recipients should be treated holistically. Single lesions and the field cancerization need to be treated as well. Also, recurrent treatment cycles and the combination of various therapies will often be required. Regarding new lesion prevention in high-risk patients, the use of oral retinoids and change of immunosuppression should be considered.

## Conflicts of interest

None declared.

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