ORIGINAL ARTICLE

Nicotinamide for Skin-Cancer Chemoprevention in Transplant Recipients

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ABSTRACT

BACKGROUND

Immunosuppressed organ-transplant recipients have an increased incidence of, and mortality from, skin cancer. Nicotinamide (vitamin B_3) enhances the repair of ultraviolet (UV) radiation–induced DNA damage, reduces the cutaneous immunosuppressive effects of UV radiation, and reduces the incidence of keratinocyte cancers (including squamous-cell and basal-cell carcinomas) and actinic keratoses among high-risk immunocompetent patients. Whether oral nicotinamide is useful for skin-cancer chemoprevention in organ-transplant recipients is unclear.

METHODS

In this phase 3 trial, we randomly assigned, in a 1:1 ratio, organ-transplant recipients who had had at least two keratinocyte cancers in the past 5 years to receive 500 mg of nicotinamide or placebo twice daily for 12 months. Participants were examined for skin lesions by dermatologists at 3-month intervals for 12 months. The primary end point was the number of new keratinocyte cancers during the 12-month intervention period. Secondary end points included the numbers of squamous-cell and basal-cell carcinomas during the 12-month intervention period, the number of actinic keratoses until 6 months after randomization, safety, and quality of life.

RESULTS

A total of 158 participants were enrolled, with 79 assigned to the nicotinamide group and 79 to the placebo group. The trial was stopped early owing to poor recruitment. At 12 months, there were 207 new keratinocyte cancers in the nicotinamide group and 210 in the placebo group (rate ratio, 1.0; 95% confidence interval, 0.8 to 1.3; P=0.96). No significant between-group differences in squamous-cell and basal-cell carcinoma counts, actinic keratosis counts, or quality-of-life scores were observed. Adverse events and changes in blood or urine laboratory variables were similar in the two groups.

CONCLUSIONS

In this 12-month, placebo-controlled trial, oral nicotinamide therapy did not lead to lower numbers of keratinocyte cancers or actinic keratoses in immunosuppressed solid-organ transplant recipients. (Funded by the National Health and Medical Research Council; ONTRANS Australian New Zealand Clinical Trials Registry number, ACTRN12617000599370.)

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Keratinocyte cancers, comprising mainly basal-cell carcinoma and cutaneous squamous-cell carcinoma, are the most common cancers in White populations.[1,2] The risk factor for these cancers, ultraviolet (UV) radiation, leads to cutaneous carcinogenesis by inducing genetic damage, suppressing antitumor immune responses, and depleting cellular ATP, thereby inhibiting DNA repair.[3-5]

The immune suppression that is required for solid-organ transplantation confers a risk of keratinocyte cancer that is 50 times as high as that in the general population.[6] Immunosuppression results in a substantial relative increase in the incidence of squamous-cell carcinoma, with the ratio of basal-cell carcinomas to squamous-cell carcinomas reversed among transplant recipients as compared with the immune-competent population.[7] Cutaneous cancers are also more frequent, aggressive, and prone to metastasis and local recurrence than those in immunocompetent persons.[8]

Sunscreen use can reduce numbers of actinic keratoses,[9] squamous-cell carcinomas,[10] and possibly basal-cell carcinomas[10] and melanomas in the general population[11] and can reduce the risk of actinic keratosis and squamous-cell carcinoma among transplant recipients.[12] However, many transplant recipients do not routinely use sunscreen.[13] Oral retinoids such as acitretin have been shown to reduce the incidence of squamous-cell carcinoma after transplantation[14] but do not prevent new keratinocyte cancers and are associated with side effects at chemopreventive doses. Clinicians may switch patients' immunesuppressant therapy to mammalian target of rapamycin (mTOR) inhibitors, the antineoplastic effects of which appear to minimize the effect that their immune suppression has on the development of squamous-cell carcinoma.[15] However, this approach is not feasible in all patients.[16]

Nicotinamide, the amide form of vitamin B_3, prevents cutaneous cancer and UV radiation–induced immune suppression in animals.[17] Nicotinamide is a precursor of nicotinamide adenine dinucleotide and reduces the decline in cellular ATP that occurs after exposure to UV radiation.[5] Consequently, nicotinamide enhances the energy-dependent process of DNA repair after exposure to UV radiation[18] and prevents UV radiation–induced immunosuppression, which is triggered by DNA damage.[5] Nicotinamide has been shown to reduce the development of actinic keratoses and keratinocyte cancers in immunocompetent persons,[19,20] but its effects in transplant recipients are unclear.[21,22] Given the affordability and safety profile of nicotinamide[23] and the related absence of changes to baseline immune responses,[24] nicotinamide has been suggested as a potential chemopreventive agent in this patient population. We conducted a phase 3, multicenter, double-blind, randomized, placebo-controlled trial, Oral Nicotinamide to Reduce Actinic Cancer after Transplant (ONTRANS), to assess the role of oral nicotinamide in the chemoprevention of keratinocyte cancers in solid-organ transplant recipients.

A Quick Take is available at NEJM.org

Methods

Trial Participants

Eligible participants were adult solid-organ transplant recipients who had had at least two histologically confirmed keratinocyte cancers in the past 5 years. Participants had undergone kidney, liver, or heart or lung transplantation at least 12 months previously. Key exclusion criteria were impaired liver or kidney function, genetic skin-cancer syndromes, large areas of confluent skin cancer, invasive melanoma or internal cancer within the past 5 years, field treatments (large-area application of topical agents such as fluorouracil or imiquimod or large-area photodynamic therapy) for actinic keratoses within the past 4 weeks, and commencement of oral retinoids or mTOR inhibitors within the past 6 months. Participants who had begun taking these medications more than 6 months before enrollment were eligible to participate. Persons who had taken nicotinamide supplements at doses of more than 20 mg daily in the 4 weeks before enrollment or at daily doses of 500 mg or more in the 3 months before enrollment were excluded from the trial. The trial protocol is available with the full text of this article at NEJM.org.

Trial Design and Procedures

This investigator-initiated trial was conducted in Australia at Royal Prince Alfred Hospital, Westmead Hospital, St. Vincent's Hospital, and Royal North Shore Hospital in Sydney; the Skin Health Institute, the Alfred Hospital, and Royal Melbourne Hospital in Melbourne, Victoria; Royal Adelaide Hospital in Adelaide, South Australia; and Sunshine Coast University Hospital in Birtinya, Queensland. The trial adhered to the princi-

ples of the Declaration of Helsinki and was approved by the relevant human ethics committees. All the participants provided written informed consent. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Using a centralized system that implemented minimization with a random element, we randomly assigned eligible participants in a 1:1 ratio to receive either oral nicotinamide (500 mg) or matched placebo twice daily. Randomization was stratified according to sex, transplant type (heart or lung vs. kidney vs. liver), 5-year history of keratinocyte cancers (≤5 vs. >5 keratinocyte cancers), use of oral retinoids (yes vs. no), use of mTOR inhibitors (yes vs. no), and trial site.

Clinical supplies were manufactured by Blackmores (Blackmores Insolar nicotinamide 500-mg tablets and matched placebo). There was no industry involvement in the trial design or in the data analysis or reporting, and all the materials were provided to the participants free of charge. Participants were to continue the assigned regimen for 12 months, with adherence monitored by tablet counts every 6 months. Skin-cancer checks were performed at baseline and at 3-month intervals for 12 months by dermatologists who were unaware of the trial-group assignments. Any lesion not warranting immediate biopsy was reviewed at subsequent visits and if later found to be malignant on biopsy, was assigned a detection date corresponding to when it was originally observed. Actinic keratoses on the face, scalp, forearms, and hands were counted at baseline and at 3 months and 6 months by dermatology research fellows (equivalent to junior dermatology residents) who were unaware of the trial-group assignments.

Histologically based diagnosis of skin cancer was performed by specialist histopathologists (who were unaware of the trial-group assignments) at each trial site according to the routine clinical practice. All new squamous lesions (invasive squamous-cell carcinoma, keratoacanthoma, Bowen's disease [squamous-cell carcinoma in situ], and actinic keratosis) and new high-risk subtypes of basal-cell carcinoma (morpheic, infiltrating, and micronodular) were also reviewed by a single histopathologist at each trial site who was unaware of the trial-group assignments in order to ensure consistent classification of squamous-cell carcinoma differentiation and basal-cell carcinoma subtype according to the World Health Organization classification.[25]

Assessments of adverse events and medication changes, body weight, and blood pressure were recorded at visits at 1, 3, 6, 9, and 12 months. Blood samples were obtained at the same time points in order to assess blood counts, serum electrolyte (including phosphate) levels, serum immune-suppressant levels, blood-glucose control (in participants with diabetes), and renal and liver function. For kidney-transplant recipients, urine samples to monitor renal function were also obtained at the time that blood samples were obtained. Safety variables were reviewed by an independent data and safety monitoring board. Sunscreen use in the week preceding each 3-month visit as reported by the participant was recorded throughout the intervention period. Quality-of-life questionnaires (Skin Cancer Index[26] and the 36-Item Short-Form Health Survey[27]) were performed at baseline and at 12 months.

TRIAL END POINTS

The primary end point was the number of new keratinocyte cancers (defined as basal-cell carcinoma, squamous-cell carcinoma in situ, or invasive squamous-cell carcinoma) at 12 months. Prespecified secondary end points included the following: the numbers of new basal-cell carcinomas and new squamous-cell carcinomas at 12 months, squamous-cell and basal-cell carcinoma histologic subtypes and differentiation, the number of keratinocyte cancers across different transplant types, the number of recurrent keratinocyte cancers at 12 months, the number of actinic keratoses at month 6, quality of life at month 12, and safety (adverse events and changes in body weight, blood pressure, and laboratory variables, including a basic metabolic panel, complete blood counts, and drug levels of routinely measured immunosuppressants such as calcineurin and mTOR inhibitors).

STATISTICAL ANALYSIS

In our phase 2 trial involving kidney-transplant recipients, a mean of 4.2 keratinocyte cancers per participant developed within 6 months among the participants in the placebo group.[21] We therefore estimated that in the high-risk population of transplant recipients in the current trial,

the mean count of new keratinocyte cancers per participant during the 12-month intervention period would be 7. We calculated that a target sample size of 254 would provide the trial with 80% power at a two-sided 5% level of significance to detect a 30% difference in the keratinocyte cancer count to 12 months (i.e., 7 keratinocyte cancers per participant in the placebo group vs. 4.9 in the nicotinamide group), assuming a negative binomial distribution with a dispersion parameter of 0.75 and allowance for nonadherence (assuming that 10% of the participants would discontinue the assigned regimen by 12 months).

Analyses were prespecified in the statistical analysis plan (which is available with the protocol), and further details of the analysis approaches are provided in the Supplementary Appendix, available at NEJM.org. A modified intention-to-treat approach was used to construct the primary analysis set for the analysis of efficacy end points. The modified intention-to-treat data set comprised all the data available from the participants who had undergone randomization and had at least one postbaseline skin assessment. Data from the participants who underwent randomization and received at least one dose of nicotinamide or placebo were used in the safety analysis.

The primary analysis was a comparison of the number of new keratinocyte cancers per person at 12 months between the two trial groups and was performed with the use of a negative binomial regression model with the number of previous keratinocyte cancers in the 5 years before randomization included as a covariate. Participants with a missing count of keratinocyte cancers at 12 months had their last postbaseline count included in the analysis, and an offset term was added to the model to account for the shortened length of follow-up. The widths of confidence intervals for secondary end-point analyses were not adjusted for multiple comparisons, and no definite conclusions can be drawn from these data. Therefore, these results are presented as point estimates with 95% confidence intervals but no P values. The sensitivity of the conclusions to adjustment for stratification factors and no covariates (other than trial group) in the model was examined for the primary end point. The consistency of the treatment effect on the primary end point was evaluated across transplant types. As a sensitivity analysis, we set the keratinocyte cancer count for any patient who was not followed to the 12-month assessment to missing, and we repeated the analysis using multiple imputation.

Counts of actinic keratoses were analyzed with the use of a repeated-measures model specified within a general linear-mixed model framework, with the baseline value and trial-group assignment fitted as covariates. We tested for an interaction between trial group and time point. Quality-of-life end points were analyzed with the use of an analysis of covariance model with the baseline value as the covariate. We repeated the actinic keratosis counts and quality-of-life analyses using multiple imputation and after applying a normal score transformation to investigate the sensitivity of the results to missing data and any departures from normality in the distribution of residuals.

RESULTS

PARTICIPANTS

From May 2017 through August 2019, a total of 288 persons were assessed for eligibility, and 158 participants (58 at Royal Prince Alfred Hospital, 10 at Westmead Hospital, 10 at St. Vincent's Hospital, 6 at Royal North Shore Hospital, 19 at the Skin Health Institute, 29 at the Alfred Hospital, 7 at Royal Melbourne Hospital, 9 at Royal Adelaide Hospital, and 10 at Sunshine Coast University Hospital) underwent randomization. A total of 79 participants were randomly assigned to the nicotinamide group and 79 to the placebo group (Fig. 1). Recruitment was slower than anticipated and ceased in August 2019, which was 12 months before the expiration of our available supply of nicotinamide and placebo.

The characteristics of the participants at baseline were similar in the two groups (Table 1). The representativeness of the trial participants is described in Table S1 in the Supplementary Appendix. Adherence to the assigned regimen was similar in each group (approximately 78%). At least one postbaseline skin assessment was available for all the participants but 1. Three participants died (1 in the nicotinamide group and 2 in the placebo group), and 11 other par-

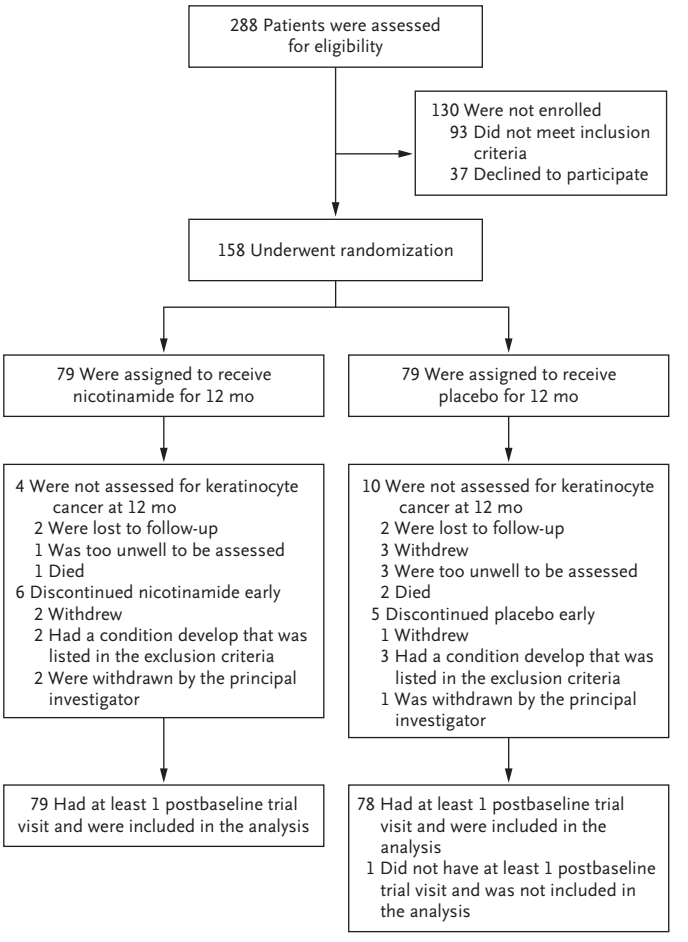

Figure 1. Randomization and Follow-up of the Participants.

ticipants withdrew, were lost to follow-up, or were too unwell to be assessed.

END POINTS

The mean (±SD) number of keratinocyte cancers per participant during the 12-month intervention period was 2.6±3.2 in the nicotinamide group and 2.7±3.4 in the placebo group. The rate ratio of keratinocyte cancers per participant (with adjustment for previous keratinocyte cancers) was 1.0 (95% confidence interval [CI], 0.8 to 1.3; P=0.96). The results for all keratinocyte cancers, basal-cell carcinomas, and squamous-cell carcinomas are summarized in Table 2 and Table S2. The numbers of squamous-cell carcinomas and basal-cell carcinomas alone were similar in the two groups at 12 months. The rate ratio was estimated at 1.4 (95% CI, 0.8 to 2.3) for basal-cell carcinomas and 0.9 (95% CI, 0.6 to 1.2) for squamous-cell carcinomas. There was no evidence that transplant type influenced outcome (Table S3), nor did other characteristics that were examined post hoc, such as sex, age, and previous keratinocyte cancer (Table S4). Five recurrent keratinocyte cancers were observed during the trial: 1 squamous-cell carcinoma in the nicotinamide group and 4 cancers (1 basal-cell carcinoma and 3 squamous-cell carcinomas) in the placebo group.

A baseline count and at least one postbaseline count of actinic keratoses were obtained for 153 participants. The mean count of actinic keratoses over the trial as estimated from the repeated-measures model was 13.1 in the nicotinamide group and 12.8 in the placebo group (difference, 0.4; 95% CI, −3.0 to 3.7) (Table S5). The two groups had similar outcomes with regard to the quality-of-life scales and the use of sunscreen (Tables S6 and S7).

SAFETY

The numbers and types of adverse events were similar in the two groups (Tables S8 through S14). The most frequent adverse events were infections and infestations (predominantly respiratory, urinary tract, and skin infections). Three systemic cancers were diagnosed in the placebo group (metastatic squamous-cell carcinoma, lung cancer, and liver angiosarcoma) and one in the nicotinamide group (renal-cell carcinoma with fatal postnephrectomy complications). In the placebo group, one participant received a diagnosis of chronic antibody-mediated rejection of the kidney transplant. Changes in body weight, blood pressure, and laboratory variables were similar in the two groups (Table S15). Blood levels of immune suppressants remained within therapeutic ranges (Table S16).

DISCUSSION

Keratinocyte cancers contribute to disease and death in solid-organ transplant recipients. The ONTRANS trial did not show a significant effect of nicotinamide therapy on the primary end point of the number of keratinocyte cancers at 12 months. The numbers of basal-cell carcinomas, squamous-cell carcinomas, and actinic keratoses were also similar in the two trial groups. These results are in contrast to the findings of

the Oral Nicotinamide to Reduce Actinic Cancer (ONTRAC) trial of nicotinamide to prevent skin cancers in immunocompetent high-risk participants, which showed a 23% lower rate of keratinocyte cancers among participants taking nicotinamide than among those taking placebo.[19] Examination of basal-cell carcinomas and squamous-cell carcinoma in that trial showed that the effects of nicotinamide therapy on the tumor immune environment did not differ among tumor types.[28] A phase 2 trial examining the effect of nicotinamide in 22 kidney-transplant recipients showed nonsignificant trends toward rate reductions in keratinocyte cancers and actinic keratoses at 6 months.[21] A case–control study involving 30 kidney-transplant recipients and 8 liver-transplant recipients showed a significant difference in the area of actinic keratoses at 6 months with 250 mg of nicotinamide taken three times daily as compared with placebo.[22]

Although sunscreen is effective in the prevention of actinic keratosis and squamous-cell carcinoma in transplant recipients,[12] the percentage of participants who had used any sunscreen in the past week did not reach 50% at any point in the current trial. Poor adherence to this preventive measure in recipients of organ transplants is a persisting impediment to the effectiveness of sunscreen in preventing sun damage that can lead to neoplastic lesions, despite reasonable levels of knowledge regarding sun protection as a preventive measure.[13]

Our trial has limitations. First, the sample size of 158 was below the target of 254 owing to slow recruitment and the expiration date of the trial drugs. The trial was underpowered, but no signal of efficacy was observed in the sample size achieved. Second, the number of keratinocyte cancers that were detected during the trial was lower than anticipated. The mean number of keratinocyte cancers per participant during the 12-month intervention period was 2.6, which was below the estimated mean count of 7 over a 12-month period, as informed by the mean rates observed in the ONTRAC trial in an immunocompetent cohort (2.4 keratinocyte cancers per person during the 12-month intervention period)[19] and a phase 2 trial involving kidney-transplant recipients (4.2 keratinocyte cancers per person during a 6-month period).[21]

A survey of dermatologists and transplantation physicians in the United Kingdom showed that 24% of those who had previously initiated systemic chemoprevention of keratinocyte cancers in their patients had prescribed nicotinamide.[29] Similarly, a survey of surgeons who perform Mohs surgery revealed that 76.9% recommended nicotinamide for the prevention of keratinocyte cancers.[30] Although there are no available data regarding recommendations by Australian clinicians for nicotinamide treatment, it may be hypothesized that some transplant recipients with a high burden of keratinocyte cancers are already

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Nicotinamide (N=79)	Placebo (N=79)
Mean age — yr	62.2±11.5	61.9±12.1
Male sex — no. (%)	59 (75)	57 (72)
Type of transplant — no. (%)		
Heart or lung	21 (27)	21 (27)
Kidney	36 (46)	35 (44)
Liver	22 (28)	22 (28)
Other†	0	1 (1)
Never smoked — no. (%)	38 (48)	35 (44)
No. of skin cancers in past 5 yr		
Keratinocyte cancer		
Mean	7.2±7.4	7.6±7.5
Range	2–44	2–41
Basal-cell carcinoma		
Mean	2.2±3.2	2.8±4.2
Range	0–16	0–24
Squamous-cell carcinoma‡		
Mean	5.0±5.9	4.8±5.6
Range	0–35	0–29
No. of actinic keratoses at baseline§		
Mean	13.2±17.4	14.6±18.8
Range	0–115	0–85
Any sunscreen use in past week — no. (%)	30 (38)	35 (44)
Oral retinoid use — no. (%)	5 (6)	6 (8)
mTOR inhibitor use — no. (%)	13 (16)	14 (18)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. The term mTOR denotes mammalian target of rapamycin.
† One participant in the placebo group had undergone both hepatic and pancreatic transplantation. Stratification during randomization was with regard to the liver transplant.
‡ Squamous-cell carcinoma included squamous-cell carcinoma in situ (Bowen's disease) and keratoacanthoma.
§ Data on the number of actinic keratoses were missing for one participant in the placebo group.

Table 2. Keratinocyte Cancers and Basal-Cell and Squamous-Cell Carcinomas.*

End Point	Nicotinamide (N=79)	Placebo (N=78)	Rate Ratio (95% CI)	P Value
	no. of cancers (mean no. per participant)			
Primary end point: keratinocyte cancer	207 (2.6)	210 (2.7)	1.0 (0.8–1.3)	0.96
Basal-cell carcinoma				
Total	69 (0.9)	59 (0.8)	1.4 (0.8–2.3)	
Subtype				
Superficial	35 (0.4)	26 (0.3)		
Nodular	26 (0.3)	29 (0.4)		
Micronodular	3 (<0.1)	1 (<0.1)		
Infiltrating	2 (<0.1)	2 (<0.1)		
Other	2 (<0.1)	0		
Unknown	1 (<0.1)	1 (<0.1)		
Squamous-cell carcinoma†				
Total	138 (1.7)	151 (1.9)	0.9 (0.6–1.2)	
Subtype				
Squamous-cell carcinoma in situ	85 (1.1)	79 (1.0)		
Keratoacanthoma	0	2 (<0.1)		
Invasive squamous-cell carcinoma	53 (0.7)	70 (0.9)		
Well differentiated	22 (0.3)	35 (0.4)		
Moderately differentiated	22 (0.3)	26 (0.3)		
Poorly differentiated	5 (0.1)	6 (0.1)		
Other	1 (<0.1)	1 (<0.1)		
Unknown	3 (<0.1)	2 (<0.1)		

* The median follow-up was 12 months in each group, with data on the duration of follow-up available for 79 participants in each group. One participant in the placebo group did not undergo a postbaseline assessment and was not included in the end-point analyses. A negative binomial regression model with the number of previous keratinocyte cancers in the 5 years before randomization was included as a covariate and an offset term to adjust for length of follow-up.
† Squamous-cell carcinoma included squamous-cell carcinoma in situ (Bowen's disease) and keratoacanthoma.

using nicotinamide. This situation may have resulted in a population of lower-risk participants and may have had an effect on participant recruitment. Few of our participants were taking retinoids, a finding that reflects that this group was not as severely affected by keratinocyte cancers as our overall Australian transplantation-clinic population. Although this trial excluded participants with extreme field cancerization, in which contiguous cancers covering large surface areas precluded accurate counts of keratinocyte cancers, such patients are uncommon. We sought and enrolled extreme-risk participants with large numbers of quantifiable keratinocyte cancers, including those who had had more than 40 keratinocyte cancers in the previous 5 years.

Mycophenolate mofetil, azathioprine, cyclosporine, and tacrolimus impede DNA repair and have carcinogenic effects beyond immunosuppression.[31,32] Nicotinamide may be unable to overcome this pharmacologic suppression of both antitumor immunity and DNA-repair enzymes, despite its ability to reduce UV radiation–induced immunosuppression and enhance DNA repair in the absence of these agents.[24] Future studies, such as international collaborations that are able to enroll a larger patient population or to focus on patients taking mTOR inhibitors, which do not have the same effect on DNA repair, could be designed to address the effect of nicotinamide on the chemoprevention of keratinocyte cancers.

The safety profile of nicotinamide therapy in our trial was similar to that in published series and remained similar through the 12-month intervention period.[19,21,33] The numbers of adverse events was similar in the nicotinamide group and the placebo group, with no meaningful differences in blood pressure, body weight, blood counts, serum electrolyte levels, or liver or renal function between the two groups.

In this trial of oral nicotinamide in transplant recipients that was stopped early because of limited recruitment, the rates of skin cancers over a 12-month period were similar in the intervention group and the placebo group.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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