Oral Nicotinamide Reduces Actinic Keratoses in Phase II Double-Blinded Randomized Controlled Trials

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TO THE EDITOR

Nicotinamide (vitamin B3) prevents photocarcinogenesis in mice (Gensler *et al.*, 1999) and photoimmunosuppression in humans (Damian, 2010). Actinic keratoses (AKs) strongly predict nonmelanoma skin cancer risk (Green and Battistutta, 1990). These phase II studies aimed to determine whether oral nicotinamide, at different doses, reduced AKs in sun-damaged individuals.

Healthy, immune-competent volunteers with ⩾4 palpable AKs (face, scalp and upper limbs) were recruited from Royal Prince Alfred Hospital Dermatology Clinics, Sydney, Australia. The study protocols (ACTRN12609000490279; ACTRN12610000689077; http://www.anzctr.org.au) adhered to Helsinki Guidelines and were approved by the Sydney South West Area Health Service and University of Sydney ethics committees. All volunteers provided written informed consent.

Participants were randomly assigned (1:1) to take nicotinamide 500 mg (Nature's Own, Virginia, Queensland, Australia) or matched placebo (Australian Custom Pharmaceuticals, Sydney, New South Wales, Australia) twice daily (Study 1) or once daily (Study 2) for 4 months. The treatment allocation sequence was determined by a computer-generated randomization list prepared using a permuted blocks method (block size 6) by an investigator (DLD) not involved in AK assessment. Participants underwent complete skin examination before randomization, were encouraged to use daily sunscreen, and remained blinded throughout the study.

At baseline, 2 and 4 months, palpable AKs were identified visually and by touch by a blinded observer (DS), counted and documented on a body grid chart. At baseline and 2 months, full blood count, creatinine, and liver function were assessed.

A target of 36 patients was selected for Study 1 based on clinical judgement as this was our first pilot trial of oral nicotinamide. A conservative

Table 1. Baseline characteristics and AKs during treatment with nicotinamide or placebo

	Study 1 (500 mg b.d.)		Study 2 (500 mg o.d.)	
	Placebo	**Nicotinamide**	**Placebo**	**Nicotinamide**
Patients enrolled	17	18	20	21
Men:women	10.7	15.3	14:6	14:7
Mean age (years; range)	**72** (52–90)	**71** (59–82)	**72** (48–89)	**67** (52–80)
Total AKs at baseline				
Mean (SD)	**31.5** (21.1)	**29.3** (23.5)	**40.3** (26.5)	**30.6** (16.3)
Range (median)	9–92 (23)	6–89 (19)	7–101 (37)	12–73 (27)
Total AKs at 2 months				
Mean (SD)	**28.2** (20.7)	**18.1** (16.8)	**35.5** (23.1)	**24.3** (14.6)
Range (median)	6–91 (20)	3–65 (11)	5–99 (34)	4–60 (21)
LS mean (95% CI)[1]	**20.9** (18.5-23.5)	**13.6** (12.1-15.3)	**26.1** (23.2–29.4)	**22.1** (19.7–24.8)
Relative reduction (95% CI)[1]		**35%** (23–45%)		**15%** (0–28%)
P-value		**<0.0001**		**0.046**
Total AKs at 4 months				
Mean (SD)	**27.1** (19.9)	**16.6** (13.9)	**34.8** (20.9)	**21.6** (14.7)
Range (median)	6–89 (20)	2–54 (10)	5–89 (32)	3–60 (18)
LS mean (95% CI)[1]	**19.9** (16.9–23.4)	**12.9** (11.0–15.2)	**25.9** (21.9–30.6)	**18.3** (15.6–21.6)
Relative reduction (95% CI)[1]		**35%** (18–48%)		**29%** (11–44%)
P-value[2]		**0.0006**		**0.005**

Abbreviations: AKs, actinic keratoses; CI, confidence interval; LS, least squares.
Bold values indicate means and significant *P*-values.
[1]Back-transformed estimates from an analysis of covariance performed on the $\log_e$(AK count) data at the time point indicated with treatment group included as a factor and the baseline $\log_e$(AK count) as a covariate. The absolute difference between the groups on $\log_e$(AK count) corresponds to the relative difference between the groups on AK count.
[2]Very similar *P*-values were obtained in a sensitivity analysis when the groups were compared on percentage change from baseline at month 4 in AK count (statistical problems associated with using percentage change as an endpoint and rationale for statistical adjustment of baseline scores via analysis of covariance as the optimal analysis approach reviewed in Bonate (2000)).

Abbreviations: AKs, actinic keratoses; BCC, basal cell carcinoma; CI, confidence interval; LS, least-squares; SCC, squamous cell carcinoma

interpretation of the Study 1 results was used to inform the assumptions used in the sample size calculation for Study 2, where a sample size was selected to provide $\geqslant$80% power to detect a standardized effect size of 0.4 at the two-sided 5% level of significance, based on an analysis of covariance model given a correlation of 0.90 between baseline and follow-up assessments (Borm *et al.*, 2007), allowing for 5% withdrawal.

All randomized patients were eligible for inclusion in the efficacy analysis (intention to treat). The primary endpoint obtained for each patient was the AK count at 4 months. We also noted all histologically confirmed skin cancers during the study. The right-skewed distribution of the AK data was rectified by applying a $\log_e$ transformation (with results back-transformed for reporting). The relative difference between groups on AK count was estimated using an analysis of covariance adjusting for baseline (Bonate, 2000). Logistic and Poisson regression was used to compare treatment groups from both studies combined on skin cancer incidence with the number of previous cancers and study designation fitted as covariates.

A total of 35 patients were enrolled in Study 1 (June–October 2009) (Table 1). One withdrew (nicotinamide) at 2 months because of invasive squamous cell carcinoma (SCC), but returned for his 4-month AK count. A total of 41 patients were enrolled in Study 2 (August–November 2010); two withdrew from treatment (placebo) soon after their baseline counts because of nursing-home placement, but agreed to follow up AK counts. Two nicotinamide participants withdrew from follow-up for personal reasons soon after enrolment; their baseline AK counts were carried forward and included in the primary analysis (Figures 1 and 2).

AK counts at baseline and follow-up are shown in the Table 1. A 35% relative reduction in AK count at 4 months (95% confidence interval (CI): 18–48%; $P=0.0006$) was estimated from Study 1 (with similar results at 2 months). A 29% relative reduction in AK count at 4 months (95% CI: 11–44%; $P=0.005$) was estimated from Study 2 (with smaller but significant differences observed at 2 months). There was no evidence that the relative effect of nicotinamide was modified by baseline AK count (treatment-by-baseline interaction *P*-value was non-significant).

For Studies 1 and 2 combined, 37 patients were randomized to placebo and 37 to nicotinamide. Eighty-one and 79% of placebo and nicotinamide patients, respectively, had previous, histologically confirmed skin cancers. During the 4-month trials, 11 placebo patients developed 20 new skin cancers (12 basal cell carcinoma (BCC) and 8 SCC) and 2 nicotinamide patients developed 4 cancers (2 BCC and 2 SCC). The odds of developing at least one skin cancer was significantly lower with nicotinamide (odds ratio = 0.14; 95% CI: 0.03–0.73, $P=0.019$) as was the rate of new skin cancers (relative rate = 0.24; 95% CI: 0.08–0.71, $P=0.010$) as estimated, respectively, by Logistic and Poisson regression models

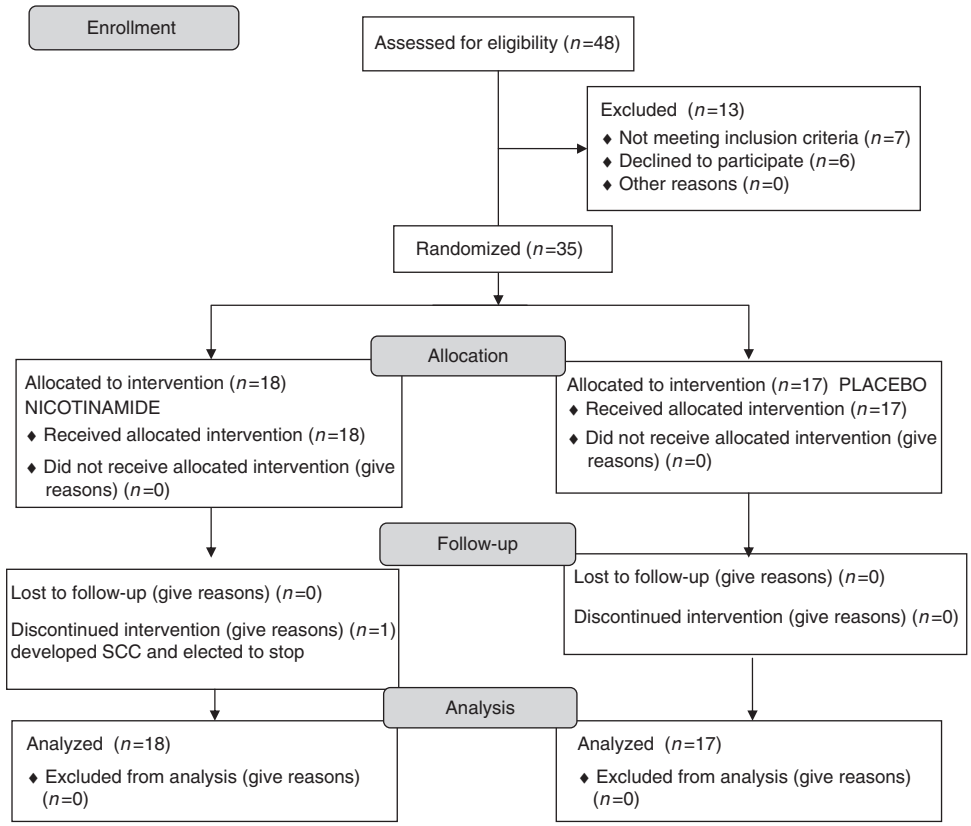

Figure 1. CONSORT 2010 flow diagram, study 1: nicotinamide 500 mg b.d. versus placebo. SCC, squamous cell carcinoma.

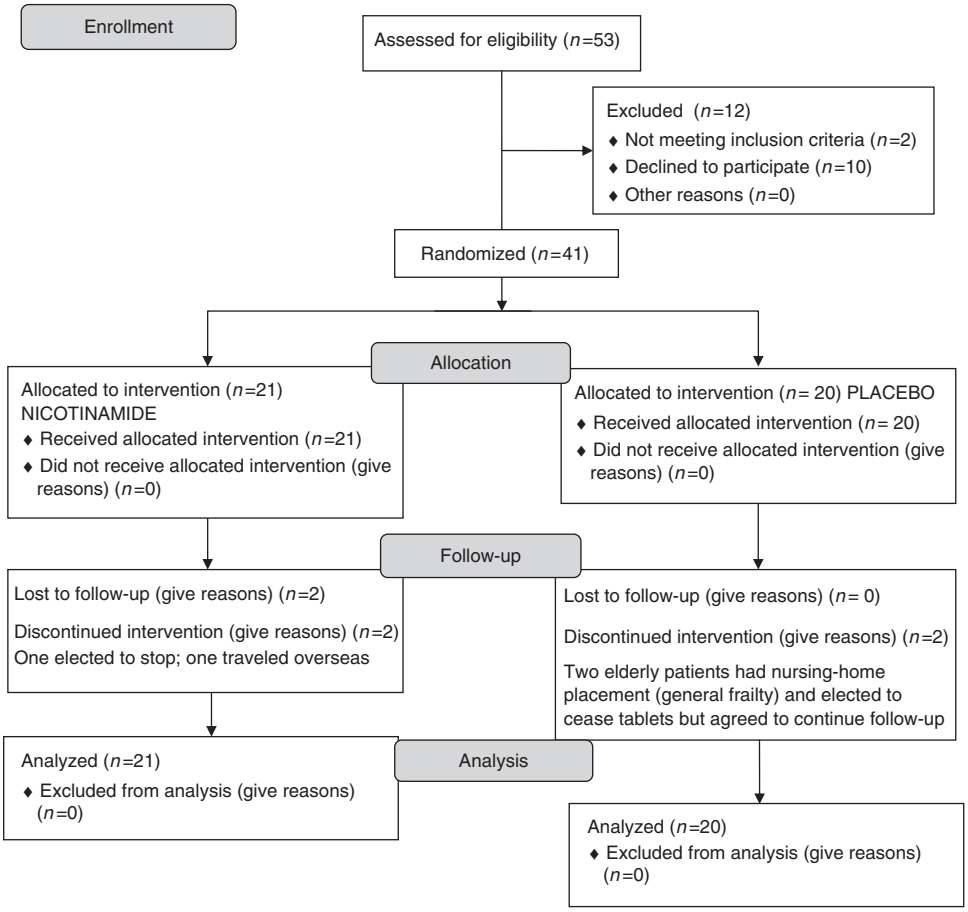

Figure 2. CONSORT 2010 flow diagram, study 2: nicotinamide 500 mg daily versus placebo.

and adjusting for study and number of previous skin cancers. The treatment effect remained significant when analysis of skin cancer rates was repeated using a negative binomial model ($P = 0.038$), although we note the unplanned nature of this combined analysis. Compliance, measured by counts of returned tablets, was 94–98%. One patient, who was also taking aspirin, described nausea while taking nicotinamide. No other potential side effects were reported and no clinically significant changes in blood profiles were observed.

The mechanisms by which nicotinamide might prevent skin cancer or reduce progression of subclinical lesions are unclear. Nicotinamide is a substrate and inhibitor of the nuclear enzyme poly-ADP-ribose polymerase, which is centrally involved in DNA repair (Virag and Szabo, 2002). As a precursor of nicotinamide adenine dinucleotide, nicotinamide prevents the decline in cellular energy observed after UV exposure (Park *et al.*, 2010), and could therefore maintain efficient DNA repair. Immunosuppression has a key role in the malignant transformation of AKs (Frost and Green, 1994), and nicotinamide is highly immune protective in humans (Damian *et al.*, 2008). Hence, nicotinamide protection from photoimmunosuppression (Yiasemides *et al.*, 2009) may be a key mediator of the reduction in AKs observed here.

Spontaneous fluctuation in AK counts has been previously reported (Criscione *et al.*, 2009; Moloney *et al.*, 2010), consistent with the 13–15% reduction from baseline observed in our placebo groups. Our randomized, double-blinded design enabled detection of AK reductions with nicotinamide relative to any background variations in AKs due to seasonal and behavioral fluctuations in UV doses.

Nicotinamide is well tolerated and costs $5–$10 per month at the doses used here. The results of these phase II studies suggest nicotinamide is effective in reducing AKs and shows promise for skin cancer chemoprevention. A longer phase III trial in a larger cohort, with new skin cancers as the primary endpoint, is now warranted.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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REFERENCES

Bonate PL (2000) *Analysis of Pretest-Postest Designs*. Chapman & Hall/CRC: Boca Raton, Florida, USA

Borm GF, Fransen J, Lemmens WAJG (2007) A simple sample size formula for analysis of covariance in randomized clinical trials. *J Clin Epidemiol* 60:1234–8

Criscione VD, Weinstock MA, Naylor MF *et al.* (2009) Actinic keratoses natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. *Cancer* 115:2523–30

Damian DL (2010) Photoprotective effects of nicotinamide (invited review). *Photochem Photobiol Sci* 9:578–85

Damian DL, Patterson CRS, Stapelberg M *et al.* (2008) Ultraviolet radiation-induced immunosuppression is greater in men and prevented by topical nicotinamide. *J Invest Dermatol* 128:447–54

Frost CA, Green AC (1994) Epidemiology of solar keratoses. *Br J Dermatol* 131:455–64

Gensler HL, Williams T, Huang AC *et al.* (1999) Oral niacin prevents photocarcinogenesis and photoimmunosuppression in mice. *Nutr Cancer* 34:36–41

Green A, Battistutta D (1990) Incidence and determinants of skin-cancer in a high-risk Australian population. *Int J Cancer* 46: 356–61

Moloney FJ, Vestergaard ME, Radojkovic BL *et al.* (2010) Randomised, double-blinded, placebo controlled study to assess the effect of topical 1% nicotinamide on actinic keratoses. *Br J Dermatol* 162:1138–9

Park J, Halliday GM, Surjana D *et al.* (2010) Nicotinamide prevents ultraviolet radiation-induced cellular energy loss. *Photochem Photobiol* 86:942–8

Virag L, Szabo C (2002) The therapeutic potential of poly(ADP-ribose) polymerase inhibitors. *Pharmacol Rev* 54:375–429

Yiasemides E, Sivapirabu G, Halliday GM *et al.* (2009) Oral nicotinamide protects against ultraviolet radiation-induced immunosuppression in humans. *Carcinogen* 30:101–5

Interpretation of Skindex-29 Scores: Response to Sampogna and Abeni

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TO THE EDITOR

Until recently, little was known about the interpretability of scores of the Skindex-29, a well-established, dermatology-specific health-related quality of life (HRQoL) instrument (Chren *et al.*, 1997a, b). Nijsten *et al.* (2009) and Prinsen *et al.* (2010, 2011) were the first to identify the clinical meaningfulness of Skindex-29 scores by estimating a categorization of Skindex-29 scores, denoting mildly, moderately, and (very) severely impaired HRQoL (Nijsten *et al.*, 2009; Prinsen *et al.*, 2010, 2011).

In their thoughtful commentary in the *Journal of Investigative Dermatology,* 131, (9) September 2011, Sampogna and Abeni persuasively showed how different methods, a distribution-based and an anchor-based method, respectively, result in different categorizations of scores (Sampogna and Abeni, 2011). They applied the distribution-based ranges of scores found by Nijsten *et al.* and the anchor-based cutoff scores found by Prinsen *et al.* to an Italian sample of inpatients diagnosed with psoriasis, and to another Italian sample of dermatological outpatients. By means of this comparison, differences between the two categorizations were shown; in general, the ranges of scores presented by Nijsten *et al.* were lower than the cutoff scores presented by Prinsen *et al.* Sampogna and Abeni also explored the clinical implications of these differences, for instance the consequence of using different categories in determining patient's eligibility for systemic treatment.

Unfortunately, a misinterpretation leading to an incorrect categorization

Table 1. An overview of the Skindex-29[1] cutoff scores derived by an anchor-based method (Prinsen *et al.*)[2] and the ranges of scores derived by a distribution-based method (Nijsten *et al.*)[3]

	Symptoms		Emotions		Functioning		Overall	
Categorization	**Prinsen *et al.***	**Nijsten *et al.***	**Prinsen *et al.***	**Nijsten *et al.***	**Prinsen *et al.***	**Nijsten *et al.***	**Prinsen *et al.***	**Nijsten *et al.***
Very little	—	<3	—	<5	—	<3	—	<5
Mild	⩾39	4–10	⩾24	6–24	⩾21	4–10	⩾25	6–17
Moderate	⩾42	11–25	⩾35	25–49	⩾32	11–32	⩾32	18–36
Severe	⩾52	26–49	⩾39	>50	⩾37	>33	⩾44	>37
Very severe	—	>50	—	—	—	—	—	—

[1]The domain scores and the overall score are expressed on a 100-point scale, with higher scores indicating a lower level of quality of life.
[2]Skindex-29 cutoff scores are derived from the original articles (Prinsen *et al.*, 2010, 2011).
[3]Categorization of Skindex-29 scores are derived from the original article (Nijsten *et al.*, 2009).

Abbreviations: HRQoL, health-related quality of life