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Feasibility of a trial to evaluate nicotinamide for chemoprevention of skin cancers in organ transplant recipients in the UK

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Dear Editor,

Keratinocyte cancers (KC) are the commonest malignancies in the UK population, with rates increasing annually.[1] Nicotinamide (vitamin B3) has recently been reported to reduce the incidence of KC in high-risk patients.[2] It is a precursor of nicotinamide adenine dinucleotide (NAD+) which replenishes cellular energy levels and enhances efficient repair of ultraviolet light (UV) induced DNA damage within keratinocytes.[3] Solid organ transplant recipients (OTRs) are at particularly high risk of KC, with 150 times increased risk of cutaneous squamous cell carcinoma (cSCC) compared with the immunocompetent general population.[4] Recent randomised controlled trial (RCT) data from Australia suggest that oral nicotinamide reduces cSCC by approximately 30% over a 12-month period in immunocompetent individuals with a past history of KC.[2]

Although trials investigating the role of nicotinamide in OTRs are planned or underway in Australia and Canada (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=372709; https://clinicaltrials.gov/ct2/show/NCT03769285), to date, there have been no trials evaluating the chemopreventative role of nicotinamide in a UK OTR population.

We propose a randomised controlled trial (RCT) comparing nicotinamide versus placebo in risk reduction of cSCC in high-risk OTRs in the UK. To explore feasibility of undertaking this RCT we assessed willingness of UK clinicians and OTRs to participate and their potential concerns. An electronic Survey Monkey™ questionnaire was sent to Dermatologists and Transplant Units (August 2018 – April 2019). Anonymised paper-based surveys were self-completed by OTRs when attending dedicated Transplant Dermatology Clinics (January 2019 – May 2019). Data were entered and analysed using Microsoft Excel.

Clinician survey: 99 clinicians (1 male:1.4 female) from 40 UK National Health Service (NHS) Trusts (in England, Scotland, Wales and Northern Ireland) responded (79% consultants: 87% dermatologists, 12% transplant physicians; response rate approximately 10%). 38% of respondents reviewed an average of 1-2 OTR/week, with 50% reviewing > 2 OTRs/week. 67 of 99 replied to questions on systemic chemoprevention. 49 of 67 (73%) respondents had initiated systemic chemoprevention, with acitretin the most frequent first-line choice (40/67, 60%); 24% (16/67) had used nicotinamide previously. 72 respondents replied to the question of whether they would be willing to recruit patients to this study; of these 59 (82%) would be willing. Specific concerns included optimising the definition of high-risk OTRs in order to maximise event rate.

OTR survey: 271 of 301 OTRs from 11 NHS Trusts (England, Scotland and Wales) responded (response rate 90%), 1 male:1.6 female; mean age 57 years (y), range 18 – 83y; mean time from first transplant 14.4 y (range 0 – 51y). The majority were renal transplant recipients (65%) with 14% lung, 12% heart, 4% liver, 1% pancreas and 0.4% bowel transplant recipients. 66 (24%) reported a prior cSCC history, with 50% of this cohort (n=33) reporting > 5 KC. 6% of respondents had previously received systemic chemoprevention: 4% (10/271) with acitretin and 3% (7/271) nicotinamide. Topical chemoprevention used at least once included 5% 5-fluorouracil cream (15%), 5% imiquimod cream (2%) and diclofenac in hyaluronic acid gel (1%). Overall, 71% (193/271) were willing to participate in the proposed trial. For patients with a past history of cSCC, and therefore eligible for recruitment to the proposed RCT, this increased to 85% (56/66). Specific concerns raised included the need for additional hospital visits and blood tests and potential interactions between nicotinamide and regular medications.

Skin cancers in OTRs are more frequent and aggressive, with a greater risk of tumour recurrence, local invasion and metastasis than in the immunocompetent population.[4, 5] This feasibility survey has confirmed that the systemic chemoprevention strategy used most frequently in the UK is oral acitretin, a drug with significant adverse effects, and that current use of nicotinamide is limited. It is important that chemoprevention is safe, inexpensive and has few side effects. Nicotinamide fulfils these criteria and, if effective in OTRs, has the potential to be a more appropriate first line chemopreventative agent than

acitretin, but could also be used in conjunction with acitretin in the highest-risk patients. These feasibility surveys demonstrated support for a UK-based trial amongst both clinicians and in OTRs. Given the low-cost and low toxicity of oral nicotinamide, confirmation of its efficacy in a UK OTR population has the potential to transform chemopreventative practice in this growing high-risk patient population.

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