PB-PG-0110-21244 – NIHR Research for Patient Benefit Programme – Final report

Project title: **Squamous cell carcinoma Prevention in Organ transplant recipients using Topical treatments (SPOT): a feasibility study**

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Plain language summary

Squamous cell carcinoma (SCC) is a common skin cancer in the UK, with approximately 30,000 new cases each year. SCC rates are increasing rapidly and many people affected will develop multiple SCC, usually requiring repeated surgical procedures. SCC also causes more than 20% of skin cancer-related deaths and is numerically and economically a major burden to the NHS.

Actinic keratoses (AK) are common skin lesions, estimated to affect almost a quarter of the UK population over 60y. They are potentially precancerous lesions for SCC. Although only a fraction of individual AK progress to SCC, there is a close relationship between AK numbers and SCC risk. Surprisingly, this possibility has never been properly tested until now. Organ transplant patients are an ideal patient group in whom to investigate this hypothesis as they have a very high (100-fold increased) risk of developing SCC and show an accelerated progression from AK to SCC.

The trial design was a multicentre, randomised, three arm, phase II, feasibility study comparing topical treatment of AKs. In this study, 40 transplant patients were recruited into one of 3 groups; either one of 2 commonly used cream treatments for AK (5-fluorouracil or imiquimod) or a sunscreen-only control group.

The results showed in accordance with the key feasibility criteria, that it was feasible to proceed to a phase III RCT. This has potential health and cost benefits for the NHS.

We intend to disseminate the results of this study through publications in peer reviewed scientific journals, conference presentations, and publication on clinical trial registries. The local investigators will be notified when the results are published, in order to make these available to patients who took part in this study. The results will also be published on the CancerHelp website (as specified in the Patient Information Sheet).

We are proposing a phase III, 3-arm study comparing efudix versus imiquimod and oral nicotinamide in SCC prevention. It will recruit patients with at least 1 SCC and field change AK.

Keywords: squamous cell carcinoma, actinic keratoses, cancer prevention

Summary of research findings

Background

Cutaneous squamous cell carcinoma (cSCC) is a major burden to the NHS. There are approximately 30,000 new cases per year in the UK. Immunosuppressed OTR have a more than 100-fold increased risk making them an ideal population in which to test interventions aimed at preventing cSCC. Premalignant lesions, termed actinic keratoses (AK), are present on sun-damaged skin and effective topical agents are available to treat them. The close relationship between AK and cSCC means that such topical treatment of AKs could significantly reduce subsequent risk of developing cSCC, but this assumption had never been directly tested until now.

Aims and Objectives

The aims of this project were to address the feasibility of a Phase III randomised controlled trial (RCT) in organ transplant recipients (OTR) using treatment of pre-cancerous skin lesions (actinic keratoses) as a strategy for prevention of invasive cutaneous squamous cell carcinomas (cSCC). It wasconducted most efficiently in the OTR population because they show accelerated skin carcinogenesis and the outcome of any intervention will be seen more quickly than in the general population.

Hypothesis:

That treatment of multiple (AK) using currently available topical therapies will prevent (cSCC) and become a major strategy for reducing the growing skin cancer burden in the UK.

Research question:

What is the feasibility of a Phase III RCT evaluating prevention of cSCC in OTR using two currently available and widely used topical interventions?

Study outcomes:

1. Clearance of AK from a skin 'field' over a 3-month treatment period, and persistence of clearance over a 12-month post-treatment period, in a population at high risk of developing cSCC.

2. Criteria for AK diagnosis; concordance in patient selection and clinical diagnosis; concordance in designation of skin areas/keratotic lesions to be treated.

3. Standardisation of treatment protocols across participating centres; acceptability of dose escalation design; tolerability and compliance.

4. Other feasibility issues pertinent to study design for a Phase III RCT, e.g. patient accrual;

willingness to be randomised; trial completion/attrition rates; participation in annual review.

5. Feasibility issues pertinent to the design of a health economic component to the Phase III RCT, e.g. testing the sensitivity of QoL instruments to measure the impact of these interventions or their failure on health-related quality of life

6. Assessment of patient preferences using discrete choice questionnaires; develop user involvement in design of the Phase III RCT based on these findings.

Methods

The SPOT trial was designed as a multi-centre, randomised, three arm, open-label, phase 2 feasibility trial comparing field-directed topical treatment of Actin Keratoses (AK) in Organ transplant Recipients (OTRs) using two currently licensed topical interventions – 5-fluorouracil or 5% imiquimod – plus discretionary sunscreen and a control arm using discretionary sunscreen alone, as per standard care. It was proposed that Sixty OTRs with multiple AK would be recruited into the trial.

40 patients were randomised to the OTR arm across three sites, Royal Free (5), Royal London (21) and Manchester Royal Infirmary (14).

The study took 31 months longer to complete than anticipated. There were two main reasons for this:

1.As this is a very under-researched field, at the start of the study there were few protocols available regarding scoring of AKs. We therefore undertook a detailed pre-trial phase of developing and testing a clinical scoring system that could be used consistently across all clinical sites. This involved 4 assessment exercises in London and Manchester in which all clinical assessors met and screened 4-6 patients on two occasions. We evaluated intra- and interobserver consistency in scoring after the first exercise to refine the scoring protocol. This was then evaluated in subsequent exercises until sufficiently robust consensus was achieved in both intra- and inter-observer scores. This was an essential pre-trial phase which guaranteed the highest possible consistency in clinical evaluations across sites.

2.We had intended to have 2 clinical sites in Manchester – Salford and Manchester Royal Infirmary (PI Dr John Lear). Unfortunately, there were major delays in opening the first site (Salford). We therefore elected not to open the second site. However, the site opened was then relocated with very little advance warning as the dermatology department in the hospital was closed and relocated. This caused major disruption to the progress of the trial and meant that recruitment in the Manchester site was both delayed and significantly restricted as patients were reluctant to travel to the new location. Ultimately, it was only possible to recruit 14 of the anticipated 40 patients in Manchester. We therefore had to keep the trial open for much longer than planned in order to recruit additional patients in London.

Findings

The main objective of this phase II trial was to determine the feasibility of performing a phase III RCT Reference Number PB-PG-0110-21244 using topical treatment of AK as a strategy for prevention of invasive cSCC.

Success guidelines to indicate the feasibility study could proceed to a phase III RCT include:

1. At least 30% of eligible patients were willing to be randomised

2. At least 70% of patients complete Treatment Cycle 1, for each active treatment arm

3. At least 70% who require treatment Treatment Cycle 2 complete it, for each active arm

4. At least 70% of participants would be willing to use the treatment again. This will be evaluated by patient responses to the question asked during the completion of the Long Q at the end of the trial

Feasibility 1:

Eligibility was assessed for 74 patients out of 76 patients. Out of the 74 that eligibility was assessed for, 72 patients were found to be eligible. Out of these 72 eligible patients, 72 were invited to take part. 48 of these patients accepted to take part by giving their consent and 40 patients were entered into the study.

By using the number of eligible patients invited to take part into the study as the denominator and the number of patients that accepted and gave consent as the numerator, this gives a proportion of 67% and a 95% CI of (55%, 77%).

Feasibility 2:

The Arm 1 proportion for cycle 1 is 11/13. Giving a percentage of 85% and a 95% CI of (55%, 98%).

The Arm 2 proportion for cycle 1 is 13/14. Giving a percentage of 93% and a 95% CI of (66%, 100%).

Feasibility 3:

The Arm 1 proportion for cycle 2 is 10/12. Giving a percentage of 83% and a 95% CI of (52%, 98%).

The Arm 2 proportion for cycle 2 is 13/14. Giving a percentage of 93% and a 95% CI of (66%, 100%).

Feasibility 4:

The Overall proportion is 25/31. Giving a percentage of 81% and a 95% CI of (63%, 93%). The Arm 1 proportion is 8/11. Giving a percentage of 73% and a 95% CI of (39%, 94%). The Arm 2 proportion is 9/11. Giving a percentage of 82% and a 95% CI of (48%, 98%).

The Arm 3 proportion is 8/9. Giving a percentage of 89% and a 95% CI of (52%, 100%).

Conclusions

Although AK treatment is undertaken at least partly with the aim of cSCC prevention. This trial was the first step in this process. Results of this trial indicate (in accordance with the feasibility objectives) that it would be possible to perform a phase III RCT evaluating efficacy of AK treatment in preventing cSCC.

Implementation of the resulting research findings will be a priority for Skin Cancer Services throughout the NHS, given the very common nature and escalating incidence of AK and cSCC.

We intend to disseminate the results of this study through publications in peer reviewed scientific journals (specialist, general medical, primary care, nursing and health services), conference presentations (including those held by dermatologists, transplant clinicians, primary care clinicians specialist nurses, health economists and patient groups), and publication on clinical trial registries (clinicaltrials.gov, ISRCTN, and EudraCT) as appropriate. The local investigators will be notified when the results are published, in order to make these available to patients who took part in this study. The results will also be published on the CancerHelp website (as specified in the Patient Information Sheet).

Since this project was developed with the benefit of comments from patients attending our clinics, the Kidney Patient Associations at the recruiting sites and consumer representatives from the UK Dermatology Clinical Trials Network, NCRI Melanoma Clinical Studies group

and the NCRI Non Melanoma Skin Cancer Subgroup, the results will be shared with these patient groups and associated national charities.

There are many websites which provide information for the public and healthcare professionals regarding skin cancer prevention in the general population and in organ transplant recipients. These will be a potentially useful means of disseminating results. For example: British Association of Dermatology website; CR-UK Sunsmart website (and the CRUK/DoH SunSmart Campaign in which both Dr Proby and Dr Harwood have been actively involved since its launch); Skin Cancer Hub website; SCOPE (Skin Care in Organ Transplant Recipients, Europe); ITSCC (International Transplant Skin Reference Number PB-PG-0110-21244 Cancer Collaborative) and the AT-RISC Alliance.

The definitive results of the Phase III study will be of particular importance to disseminate amongst primary care (general practitioners, community skin cancer practitioners), dermatologists and clinical nurse specialists. These data are also likely to inform revision of guidance produced on AK treatment and SCC prevention by several bodies including the British Association of Dermatologists and NICE.

Patient and public involvement

This project was developed with the benefit of comments from patients attending our clinics, the Kidney Patient Associations at the recruiting sites and consumer representatives from the UK Dermatology Clinical Trials Network, NCRI Melanoma Clinical Studies group and the NCRI Non Melanoma Skin Cancer Subgroup, the results will be shared with these patient groups and associated national charities.
The study is included on the UKCRN and CancerHelp websites, where patients and the public can view information about the study.
Members of the Lay Reference Panel and other trial participants have been invited to provide formal and informal feedback to patient groups and to specialist groups such as BSSCII, SCOPE and at other appropriate meetings.
PPI representatives were also active members on the trial steering committee, advising and recommending on certain aspects of development and conduct of a trial.

Data sharing statement

See link [https://www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253] for the NIHR position of the sharing of research data. The NIHR strongly supports the sharing of data in the most appropriate way, to help deliver research that maximises benefits to patients and the wider public, the health and care system and which contributes to economic growth in the UK. All requests for data should be directed to the award holder and managed by the award holder.

Disclaimer

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This project was carried out between 01 December 2014 and 03 July 2019. This final report has not been peer-reviewed. The report was examined by the Programme Director at the time of submission to assess completeness against the stated aims.