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Personalised ultraviolet B treatment of psoriasis

Submission date
16/03/2020

Recruitment status
Suspended

Registration date
13/05/2020

Overall study status
Completed

Last Edited
13/05/2020

Condition category
Skin and Connective Tissue Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Psoriasis is a chronic inflammatory skin disease characterized by clearly defined, thick and scaly plaques that can occur anywhere on the body, causing a range of symptoms that affect quality of life, from itching and pain to physical debilitation. In addition, psoriasis may be associated with inflammatory arthritis and increased risk of heart disease. Milder forms of psoriasis typically respond well to topical therapies, but more intense treatments are necessary in severe ones. These include systemic therapies – which are effective, but often carry side effects and do not induce remission – and phototherapy. Whole-body UVB phototherapy is one of the few treatments that can clear psoriasis and induce a period of remission is the first-line phototherapy treatment modality for psoriasis. Consequently, there is a high demand for it. Nevertheless, individual patient response and length of remission is variable and currently unpredictable. Further, this equates to an annual cost of ~£101M across the UK. Narrow-band UVB (NbUVB) is as effective as broad-band UVB (BbUVB), but has few side effects and is thought to have a low risk of skin cancer if used according to published guidelines. At present, therapeutic approaches in the management of psoriasis are not curative. Phototherapy can induce disease remission, but this is variable, with remission in some patients after a course of NbUVB ranging from months to years, however in other patients clearance is not achieved at all. As a result, patients may require repeated courses to control their symptoms but typically are not given a course of phototherapy more than annually. The aim of this study is to develop clinical markers and biomarkers that predict which patients will do well with UVB and which patients are likely to remain clear for longer. The researchers will then use computer modelling to develop personalised UVB treatment regimes for individual patients.

Who can participate?
Participants aged 18 years or older with chronic plaque psoriasis who have been prescribed NbUVB phototherapy

What does the study involve?
All participants are treated with whole-body NbUVB phototherapy in a stand-up cabinet. Participants will be seen at the start of the study and up to week 8 of treatment to measure their vital signs, complete questionnaires, and provide blood samples, punch biopsies and skin swabs. Once patients complete all of the treatment sessions they will be provided with a diary to monitor any flares of their psoriasis. The research team will call patients every month to ask about any flare of their psoriasis. If their psoriasis flares, then they will be asked to come to the

hospital. This will be performed on a monthly basis until their psoriasis score is 50% or more of their pre-treatment level (defined as a relapse).

What are the possible benefits and risks of participating?
There are no perceived short-term benefits to the patients. The data and samples collected will form part of the subsequent analysis which the study team hope will lead in time to better management and treatment of psoriasis with ultraviolet light and allow this to be personalised. Collection of biological samples may be a burden to some patients. All procedures will be carried out by trained members of the study team in a clinical area within dermatology in order to minimise participant discomfort and pain. In the case of biopsy samples, local anaesthetic will be administered prior to the procedure to minimise pain and discomfort. All biopsies will be performed by a trained, experienced, and qualified clinician or nurse. Interview of patients for the collection of clinical data will take place in a private consulting room within dermatology to maintain patient confidentiality, dignity, and privacy. Potential risks of the skin biopsy include local discomfort, bleeding, and/or rarely infection. The procedure will leave a small scar and sometimes a small area of local hyperpigmentation. After injection of a local anaesthetic, intolerance reactions are possible in very rare cases. Taking blood samples might cause discomfort and bruising. The collection of samples for this study will be scheduled to coincide with patients' routine clinical visits in as many cases as possible. Narrowband UVB treatment will be administered as per the usual hospital protocol. Patients will also be asked for an additional three research visits outside of their standard clinical care. If as a result of computer modelling, the researchers increase the doses of UVB at a greater rate than currently or increase the frequency of UVB treatments, then there is a small risk of burning the skin. The risk of burning the skin would only be marginally more than the standard use of narrowband UVB. In case patients experience any burning during or after treatment, the treatment will be suspended and all appropriate medical intervention will be performed as per the usual hospital protocol.

Where is the study run from?
Royal Victoria Infirmary (UK)

When is the study starting and how long is it expected to run for?
December 2015 to October 2021

Who is funding the study?
Teresa Rosenbaum Golden Charitable Trust, matching funding by Newcastle University and NIHR Newcastle Biomedical Research Centre (BRC) funding (UK)

Who is the main contact?
Prof. Nick Reynolds
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Contact information

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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
217936

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 33725, IRAS 217936

Study information

Scientific Title
Personalised ultraviolet B (UVB) treatment of psoriasis through biomarker integration with computational modelling of psoriatic plaque resolution

Acronym
ROSETREES

Study objectives
At present, therapeutic approaches in the management of psoriasis are not curative. Phototherapy can induce disease remission, but this is variable, with remission in some patients after a course of NbUVB ranging from months to years, however in other patients clearance is not achieved at all. As a result, patients may require repeated courses to control their symptoms but typically are not given a course of phototherapy more than annually.

This study aims to develop clinical markers and biomarkers that predict which patients will do well with UVB and which patients are likely to remain clear for longer. The researchers will then aim to use computer modelling to develop personalised UVB treatment regimes for individual patients.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 06/04/2017, North East - Tyne & Wear South Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; 0207 104 8084, 0207 104 8265; tyneandwearsouth.rec@hra.nhs.uk), REC ref: 17/NE/0045

Study design
Non-randomised; Interventional; Design type: Treatment, Diagnosis, Process of Care, Device, Management of Care, Active Monitoring

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Psoriasis

Interventions
Research conducted by us and others has informed the initial doses of UVB, incremental dose increases during the course of therapy (to account for photoadaption) and the frequency of delivery of phototherapy. However, such pragmatic clinical trials require large numbers of patients and the potential for personalisation of therapy (apart from the initial starting dose) has not been realised. Recently, the researchers established a research collaboration between dermatology (Institute of Cellular Medicine) and Computing Science and built a computational model of psoriasis and its response to phototherapy. They have previously shown that apoptosis is a key mechanism in the resolution of psoriatic plaques and this can be induced by NbUVB radiation. The current research builds on these novel findings to refine scalable biomarkers and clinical determinants of response to UVB. This will inform the further refinement and

personalisation of treatment protocols. By combining systems biology modelling with powerful formal verification techniques, the researchers will ultimately develop optimised and individualised psoriasis treatments.

The proposed study aims at developing clinical and biomarkers that predict patient response to NbUVB phototherapy, using computer models to optimise protocols for the delivery of NbUVB phototherapy and performing a pilot study of modified and personalised NbUVB phototherapy regimes. Patients with psoriasis who have been prescribed NbUVB phototherapy as part of routine standard care will be given the opportunity to participate.

There will be three main groups of patients in the study and patients will be recruited sequentially into the groups. The pathway for the first group of patients (group one) in this study aims to derive biomarkers in skin and blood predictive of clinical response. These will be validated in group 2. Clinical, histological and biomarker data derived from these studies will be fed into our computer models, enabling systematic study in silico of the contribution of key biological parameters on psoriasis clearance. The researchers will then model the effects of key parameters, including escalation of UVB doses and time intervals between phototherapy, in the context of individual patient data, and develop algorithms that compute more efficient, effective and personalised UVB treatment regimes. These newly derived regimes will then be tested in a pilot clinical study. In practice the researchers envisage the derivation of two principle regimes for testing: a) optimised variation in dosimetry (including incremental dose increase during course) and/or frequency of NbUVB delivery – applied to all patients in the group, and b) personalised variation in dosimetry and/or frequency of delivery of NbUVB based on baseline demographics/characteristics.

Visit schedule
Baseline visit
To be eligible to participate, patients in all groups will have been prescribed NbUVB in a phototherapy clinic and are waiting to start treatment. Following this, they will have the opportunity to learn about this study and if they meet the eligibility criteria they will be invited to participate and provide informed consent. What follows is a description of each patient group' s potential path through the study.

Day 1
As part of standard care, all patients have their Minimal Erythema Dose (MED) measured. This allows the team to optimize the starting dose of phototherapy taking into account individual skin sensitivity. In clinical practice, this increases gradually from 0.7 MEDs. Briefly, MED testing involves applying a range of doses of NbUVB using a hand-held device to uninvolved skin (typically the lower back) and assessing the erythemal response 24 hours later (Day 2).

Day 2
As in routine standard care, 24 hours later the smallest dose of NbUVB that results in just perceptible erythema is recorded as the MED. The researchers will also measure skin redness with an erythema meter. For more detailed information about MED testing.

Once MED testing is completed, two small, similar plaques (ideally around 0.5 cm in diameter) will be selected on the patient's back. Using a handheld device, two small areas at the edge of each plaque will be irradiated with 0.75 MED or 3.0 MED of NbUVB.

Day 3
24 hours later punch biopsies or micro-biopsies will be taken from each plaque and also a site- and size-matched plaque that has not been irradiated. Skin swab samples will also be taken from adjacent to biopsy sites and uninvolved psoriasis skin for mtDNA analysis.

In the discovery group (group 1), 4 x ≤5 mm punch biopsies will be performed. These biopsies will be bisected for immunohistology, RNA and DNA analysis. In the validation and feasibility groups (groups 2 and 3 respectively) smaller biopsies will be performed.3 x ≤4 mm punch biopsies in group 2 and 3 x ≤3 mm micro-biopsies in group 3.

Phototherapy regime
The patients will then commence whole body NbUVB phototherapy in a stand-up cabinet. For groups 1 and 2, NbUVB phototherapy will be delivered as per normal clinical practice, three times a week for approximately 8 weeks (~24 treatments in total). The initial dose of NbUVB is based on the patient's MED (0.75 MED) and doses are escalated according to a pre-determined protocol and clinical response. Because previous studies have shown that doses close to the MED clear psoriasis more effectively and the adaption of psoriasis skin to NbUVB differs from adaption to broad-band UVB, the researchers will study the time course of adaption during NbUVB (at weeks 2, 4 and 8). These data will feed into our computer modelling and may for example permit personalisation of dosimetry during a course of NbUVB.

For group 3, based on computer modelling, the delivery of NbUVB phototherapy will be modified to enable testing of optimised variation in dosimetry and/or frequency of NbUVB delivery. The potential for personalised variation in dosimetry and/or frequency of delivery of NbUVB based on baseline demographics/characteristics will also be explored. Limited in part by practical and logistical considerations, irradiation frequency will be limited to between x1 to x5 per week and patients will receive a maximum of 24 NbUVB treatments in total.

During phototherapy, blood and skin swab (lesional skin lower back) samples will be taken twice weekly 24 h and 48 h after NbUVB during weeks 2, 4 and 8 to determine the time course of key biomarkers and how these reflect treatment response. The 48h post-irradiation samples will be taken just prior to the next NbUVB treatment minimising the need for extra visits.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Clinical markers and biomarkers as determinants of UVB phototherapy response for clinical application. Specific measures include:
1. Rate of apoptosis and biomarkers in skin biopsies taken after NbUVB phototherapy; rate of apoptosis is measured by manual and automated counts of histology slides at 24 hours after irradiation with narrowband UVB light (day 3)
2. Psoriasis severity measured using Psoriasis Area Severity Index (PASI) (score ranges: 0-72) at baseline, during phototherapy and at end of treatment. Follow- up by phone monthly for 6 months to assess length of remission

Key secondary outcome(s))
Integration of clinical and biomarker data using computer modelling to predict the outcome of UVB phototherapy in individual patients and develop personalised phototherapy regimes. Specific measures include:
1. Physician’s global assessment, demographics including assessment of handgrip strength,

weight (kg), waist (cm), height (cm), blood pressure (mm/Hg) measured at baseline/within 6 months of recruitment
2. DNA and RNA extraction and analysis (serum isolation for sequencing and genotyping, reverse-transcriptase polymerase chain reaction (RT PCR), microarray transcriptome analysis, RNA sequencing, and epigenetic analysis), trace mineral and serological analysis, analysis of blood cell free DNA to look for DNA damage, all performed in blood samples collected at day 2, day 3, week 2, week 4 and week 8. These samples will enable assessment and refinement of potential biomarkers including but not limited to apoptotic biomarkers in blood/serum (fragmented cytokeratin-18, DNA nucleosomes, cytochrome c, serum fortilin, mtDNA (mtDNA) damage). These biomarkers will be quantified by ELISA, qPCR or similar techniques.
3. Mitochondrial DNA analysis of skin swab samples (non-invasive site-matched swab sampling will be collected from non-lesional plus lesional skin [ideally lower back] of psoriasis patients), measured at day 2, day 3, week 2, week 4 and week 8
4. Minimal erythema dose (skin's sensitivity to narrowband UV light) measured visually with the aid of an erythema meter, in line with current clinical practice, at 24 hours after test irradiation and performed at baseline, week 2, week 4 and week 8
5. Impact of skin disease on quality of life measured using Dermatology Life Quality Index (DLQI) (score ranges: 0-30) at week 1 and week 8

Completion date
31/10/2021

Eligibility

Key inclusion criteria
1. Aged 18 years or older (no upper age limit)
2. Able to speak English
3. Able to provide informed consent
4. Has chronic plaque psoriasis
5. Prescribed NbUVB phototherapy
6. Able and willing to attend the phototherapy department regularly

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Able to control their psoriasis or already controlled by topical therapy
2. Pregnant

3. Have had significant sun exposure, sun-bed use or previous NbUVB within the last month or be planning significant sun exposure or sun-bed use in the next month
4. Have previously taken, in the last three months any of the following: methotrexate, azathioprine, ciclosporin, biological therapy or systemic steroids for treatment of psoriasis
5. Have previously taken, in the last month, any oral photosensitising medications, including: thiazide diuretics, antibiotics such as tetracyclines and quinolones, non-steroidal anti-inflammatory drugs, phenothiazines, retinoids, sulphonylureas, quinine and St John's Wort
6. Also suffer from diseases where phototherapeutic treatment is contraindicated: xeroderma pigmentosum, lupus erythematosus

Date of first enrolment
04/07/2017

Date of final enrolment
28/02/2021

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Royal Victoria Infirmary
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Newcastle upon Tyne
United Kingdom
NE1 4LP

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Charity

Funder Name
Teresa Rosenbaum Golden Charitable Trust; Grant Codes: A1175

Funder Name
Newcastle University

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

Funder Name
NIHR Newcastle Biomedical Research Centre

Alternative Name(s)
Newcastle Biomedical Research Centre, Newcastle NIHR Biomedical Research Centre

Funding Body Type
Private sector organisation

Funding Body Subtype
Research institutes and centers

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository. Study datasets will be stored in Newcastle University secured server. Data will be available upon request to Prof. Nick Reynolds (nick.reynolds@ncl.ac.uk) following peer-review publication. Some of the data (e.g. RNAseq) will be deposited and made available in publicly available databases following peer-review publication.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes