ISRCTN15719626 https://doi.org/10.1186/ISRCTN15719626

A study to investigate the immune response of the skin after application of imiquimod cream

Submission date
28/03/2022

Recruitment status
No longer recruiting

Registration date
01/04/2022

Overall study status
Completed

Last Edited
12/09/2024

Condition category
Other

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Imiquimod cream is a registered drug that causes an inflammatory response on the skin when applied to the skin of healthy volunteers. This has been shown in previous research by CHDR investigating the effects of imiquimod creme on the skin. In previous trials, CHDR has applied imiquimod for 3 consecutive days to set up a model for local skin inflammation. In this trial, we are using this creme to induce a controlled inflammation in the skin again. The aim of this study is to investigate whether a specific part of het immune system (the complement system) is activated after application of Imiquimod for 7 consecutive days. We have not previously studied the effect of 7 day exposure to the crème. Besides that, we will also be studying the response of white blood cells. These inflammatory models can be used to study the effect of (new) anti-inflammatory drugs. Part of the inflammatory response (the complement response) has not been studied in this model previously. Therefore, it is important to investigate this response further. In the future, the model could be used to study drugs that are inhibiting this part of the inflammatory response. Other than that, we also would like to investigate whether the model may be more beneficial when applying imiquimod for 7 consecutive days instead of 3 days.

Who can participate?
A total of 10 healthy Caucasian (Fitzpatrick Skin type I-III) male and female volunteers between the age of 18 and 45 will be included to undergo an imiquimod challenge. Given the pharmacodynamic exploratory character of this study, a study population with limited heterogeneity is selected.

What does the study involve?
If you participate in this study, the study will have a duration of 8 weeks maximum. In these 8 weeks, you will be visiting CHDR for 10 days. The first visit will consist of a medical screening. On the first study day, all participants will be treated with 100 mg imiquimod in 5 areas on the back. Predose measurements will be performed, and a control biopsy of untreated skin will be taken. Following the first study day, Imiquimod will be applied for another 6 consecutive days. Biopsies and skin imaging will be performed on day 3,4,6 and 8. On the other days, participants will only be treated with imiquimod. On day 14 control measurements will be performed. To measure the activation of the immune system in the skin, several skin biopsies will be taken. A biopsy is the taking of a piece of a tissue, in this instance a piece of skin. First, the biopsy spot is cleaned and

locally sedated with a local anesthetic by injection into the skin, to prevent you from experiencing pain from taking the biopsy. You will feel the needle briefly which will give a sharp, burning pain for a few seconds. A small apparatus ('apple drill') will be pushed into the skin, which causes loosening of a small fraction [of 4 mm] of the skin. The whole procedure is safe and in general people feel no big discomfort. Skin imaging will consist of digital photos, 3D photos, and a measurement where we measure the blood flow of the skin called 'Laser Speckle Contrast Imaging (LSCI)'. For the 3D photos, photos of your skin will be made to map the size of your skin, scars, redness, and pigmentation. The redness of the skin will also be evaluated by a physician.

What are the possible benefits and risks of participating?
Aldara 5% ®, on the market since 1997, is a topical cream containing 50 mg/g imiquimod. Aldara has been registered for various indications including basal cell carcinoma, actinic keratosis and genital and peri-anal warts. Please refer to the summary of product characteristics (SPC) in D2 for additional non-clinical and clinical information. CHDR has run multiple topical imiquimod challenge studies over the last 3 years, without any safety concerns. Although CHDR does not have experience yet with 7 day treatment of IMQ, studies in cancer patients have shown that 7 day treatment (both once daily and twice daily) or even 12 weeks treatment (once daily or 5 times a week) are well tolerated3,4. In the treatment of Lentigo Maligna, imiquimod is applied daily for 12 consecutive weeks. Nevertheless, there are some potential skin reactions including erythema, oedema, vesicles, erosions/ulcerations, weeping/exudate, flaking/scaling/dryness and scabbing/crusting. Because CHDR does not have previous experience with application of imiquimod for 7 consecutive days, possible skin reactions should be monitored carefully during treatment. Daily skin examination by a trained physician will take place to mitigate the risk of severe skin reactions. If signs of ulcerations appear, imiquimod treatment will be terminated immediately. Any local inflammation induced by imiquimod is expected to resolve after termination of the treatment, without long-term effects. Since psoriasis exacerbations due to imiquimod treatment have been described, psoriasis patients as well as patients with other autoimmune diseases and skin diseases are excluded to participate in this study to minimize potential risk(s).Since complement deposition can only be assessed histologically, skin biopsies are indispensable in this study. Biopsies will be taken in a minimally invasive manner. Since the diameter is only 4 mm no surgical sutures are necessary. Subjects with a dark skin type (Fitzpatrick IV – VI) have a higher risk for the development of hypertrophic scars or keloids, and will therefore not be included in this trial. Study participants will have no health benefit.

Where is the study run from?
Centre for Human Drug Research (The Netherlands)

When is the study starting and how long is it expected to run for?
December 2021 to June 2022

Who is funding the study?
Centre for Human Drug Research (The Netherlands)

Who is the main contact?
J.A. (Juliette) van den Noort, PharmD, MSc, jvdnoort@chdr.nl
M. (Matthijs) Moerland, PhD, mmoerland@chdr.nl

Contact information

Type(s)
Public

Contact name
Miss Juliette van den Noort

ORCID ID
http://orcid.org/0000-0001-7356-6847

Contact details
Zernikedreef 8
Leiden
Netherlands
2333 CL
+31 71 5246 400
jvdnoort@chdr.nl

Type(s)
Principal Investigator

Contact name
Mr Matthijs Moerland

Contact details
Zernikedreef 8
Leiden
Netherlands
2333 CL
+31 71 5246 400
mmoerland@chdr.nl

Additional identifiers

EudraCT/CTIS number
202100542926

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CHDR2135

Study information

Scientific Title
Immunological characterization of TLR-7 mediated inflammation and complement activation after prolonged Imiquimod exposure in healthy volunteers

Acronym
TLR-7

Study objectives
In this study, we aim to characterize TLR7-mediated inflammation, including complement involvement, after 7-day imiquimod exposure in healthy volunteers.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 15/12/2021, Stichting BEBO (Doctor Nassaulaan 10, 9401 HK Assen, The Netherlands; +31 592-405871; info@stbebo.nl), ref: NL79321.056.21

Study design
Single-center inflammatory challenge study in healthy volunteers

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Other

Study type(s)
Other

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Imiquimod induced inflammation

Interventions
10 volunteers will receive imiquimod as a challenge agent on tape-stripped skin, followed by serial biopsies of the challenge sites. In addition, one area will treated with imiquimod for 7 days and only be followed non-invasively over time (local perfusion and erythema).

Intervention Type
Other

Primary outcome measure
1. Immunological characterization of imiquimod-induced inflammation after 7-day exposure of healthy skin by analysis of cytokines and immune cells in skin biopsies taken at baseline, 48h, 72h 120h and 168h after application.
2. To evaluate local complement activation/depositions after a prolonged topical imiquimod challenge by analysis of local complement factors in skin biopsies taken at baseline, 48h, 72h 120h and 168h after application.

3. To evaluate systemic activation of complement after imiquimod challenge by analyzing complement factors and activation markers in blood samples taken baseline, 48h, 72h 120h, 168h and 312h after application.

Secondary outcome measures
To characterize the clinical response to prolonged imiquimod challenge over a 7-day imiquimod treatment period by measuring perfusion by laser speckle contrast imaging, erythema by Antera 3D and clinical evaluation at baseline, 48h, 72h, 120h, 168h and 312h after application.

Overall study start date
15/12/2021

Completion date
30/06/2022

Eligibility

Key inclusion criteria
1. Healthy male and female subjects, 18 to 45 years of age, inclusive. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, blood serology and urinalysis. In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects
2. Body mass index (BMI) between 18 and 30 kg/m2 and a minimum weight of 50 kg, inclusive
3. Fitzpatrick skin type I-III (Caucasian)
4. Female subjects of childbearing potential must use effective contraception for the duration of the study
5. Able and willing to give written informed consent and to comply with the study restrictions

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
45 Years

Sex
Both

Target number of participants
10

Total final enrolment
10

Key exclusion criteria
1. History of pathological scar formation (keloid, hypertrophic scar) or keloids or surgical scars in the target treatment area that in the opinion of the investigator, would limit or interfere with dosing and/or measurement in the trial;
2. Diagnosed with psoriasis or family history of psoriasis
3. History of skin cancer (basal cell carcinoma, squamous cell carcinoma, melanoma);
4. Have any current and / or recurrent clinically significant skin condition at the treatment area (e. g. atopic dermatitis); including tattoos;
5. Using immunosuppressive or immunomodulatory medication within 30 days prior to enrolment or planned to use during the course of the study;
6. Use of topical medication (prescription or over-the-counter [OTC]) within 30 days of study drug administration, or less than 5 half-lives (whichever is longer) in local treatment area;
7. Participation in an investigational drug or device study within 3 months prior to screening or more than 4 times a year;
8. Loss or donation of blood over 500 mL within three months prior to screening or donation of plasma within 14 days of screening;
9. Any (medical) condition that would, in the opinion of the investigator, potentially compromise the safety or compliance of the patient or may preclude the patient's successful completion of the clinical trial;
10. Any vaccination within 30 days prior to initial IMQ dosing or planned during the course of the study with exception of vaccination for SARS-CoV-2;
11. Vaccination for SARS-CoV-2 within 14 days prior to initial IMQ dosing, or planned during the course of the study;
12. Chronic infection with HIV, hepatitis B (HBV) or hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test at screening excludes a subject;
13. A history of ongoing, chronic or recurrent infectious disease;
14. Current smoker and/or regular user of other nicotine-containing products (e.g., patches);
15. History of or current drug or substance abuse considered significant by the PI (or medically qualified designee), including a positive urine drug screen.
16. Previous use of Aldara (imiquimod cream) 3 months prior to the baseline visit;
17. Volunteers with clinically relevant infections
18. Hypersensitivity for dermatological marker at screening
19. Tanning due to sunbathing, excessive sun exposure or a tanning both within 3 weeks of enrollment.
20. Pregnant, a positive pregnancy test, intending to become pregnant, or breastfeeding

Date of first enrolment
30/12/2021

Date of final enrolment
03/03/2022

Locations

Countries of recruitment
Netherlands

Study participating centre

Centre for Human Drug Research
Zernikedreef 8
Leiden
Netherlands
2333 CL

Sponsor information

Organisation
Centre of Human Drug Research

Sponsor details
Zernikedreef 8
Leiden
Netherlands
2333 CL
+31 71 5246 400
clintrials@chdr.nl

Sponsor type
Industry

Website
https://chdr.nl/

Funder(s)

Funder type
Not defined

Funder Name
Centre for Human Drug Research

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact-peer-reviewed journal

Intention to publish date
31/07/2024

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication

IPD sharing plan summary

Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 3	01/02/2022	05/10/2022	No	No
Results article		26/08/2024	12/09/2024	Yes	No