A Phase 0, single-center study to characterize the response of a UV-B skin challenge on the skin of healthy volunteers and cutaneous lupus erythematosus (CLE) patients.

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Primary Objectives- To characterize the dermal immune response of healthy volunteers following a UV-B skin challenge- To characterize the dermal immune response of CLE patients following a UV-B skin challenge on non-lesional skin- To evaluate the…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Epidermal and dermal conditions
Study type	Observational invasive

Summary

ID

NL-OMON56266

Source
ToetsingOnline

Brief title
UV-B challenge in healthy volunteers and CLE patients

Condition

- Epidermal and dermal conditions

Synonym
cutaneous lupus erythematosus, lupus affecting the skin

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Industry

Intervention

Keyword: CLE patients, UV-B skin challenge

Outcome measures

Primary outcome

- To characterize the dermal immune response of healthy volunteers following a UV-B skin challenge

- To characterize the dermal immune response of CLE patients following a UV-B skin challenge on non-lesional skin

- To evaluate the test-retest variability of the UV-B challenge in healthy volunteers and CLE patients

Secondary outcome

- To evaluate disease-related characteristics and biomarkers in patients with CLE compared to healthy volunteers

- To evaluate time-related changes in disease-related characteristics in patients with CLE

Study description

Background summary

Cutaneous lupus erythematosus (CLE) is an autoimmune disease that can occur isolated to the skin or as a manifestation of Systemic Lupus Erythematosus (SLE) (Stannard et al., 2016). Subtypes of CLE, which differ in lesion morphology and histopathology, include acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE), and chronic cutaneous LE (CCLE). CCLE can be further

subdivided into various subtypes including (but not limited to) cutaneous discoid LE (CDLE) and LE profundus (LEP).
The pathogenesis and pathophysiology of CLE is not fully understood. The current concept regarding the onset of the disease comprises a genetic background predisposing to CLE triggered by factors such as UV light, which leads to cellular stress and eventually to the release of DNA components in keratinocytes (Fetter et al., 2022). Activation of both Toll-like receptor (TLR)-dependent and TLR-independent inflammatory signalling cascades leads to increased expression of several cytokines, in particular type I interferon (IFN). Type I interferon mediates increased expression of proinflammatory chemokines via the JAK-STAT pathway, leading to recruitment of cells, release of cytokines and a chronic reactivation of innate immune pathways.
The UV-B *sun burn* model is an inflammatory pain model in which erythema is induced on the skin by radiating the skin with UV-B light in a well-controlled and reproducible manner. UV-B exposure drives an increase in skin perfusion, followed by infiltration of immune cells into the skin. CHDR has applied this model frequently in the field of inflammatory pain studies. UV-B causes keratinocyte apoptosis by damaging DNA via strand breaks and pyrimidine dimer formation. In addition, UV-B induces immunologic function and attracting of inflammatory cells including IL-1, TNFa, ICAM-1 and histocompatibility II molecules (e.g. HLA-DR) (Kim et al. 2013).
UV provocation in patients with SLE and/or CLE has been reported frequently in literature to study photosensitivity. The last comprehensive literature review was performed by Kim and Chone (2013) summarizing more than 700 patients and up to a dose of 2xMEDx6 days. Minimal side effects were reported in a large multicenter trial *Photoprovocation in cutaneous lupus erythematosus: a multicenter study evaluating a standardized protocol of 1.5 MED*, Kuhn et al. 2011, where a general good tolerability was observed when a 4.5 cm2 section of skin was irradiated with 1.5x MED for a total of three times over three consecutive days.
Although there are some studies investigating the inflammatory response of the skin to UV-B, the in-depth characterization of the immune response in healthy volunteers as well as validation in a patient cohort with the purpose of developing a rapid inflammatory model for drug development programs is still lacking.
Therefore, the objective of this phase 0 study is to characterize the dermal immune response of healthy volunteers and CLE patients following a UV-B skin challenge on non-lesional skin compared to healthy volunteers, for later integration into a phase 1 proof-of-mechanism study with a novel immunomodulatory agent.

Study objective

Primary Objectives
- To characterize the dermal immune response of healthy volunteers following a UV-B skin challenge
- To characterize the dermal immune response of CLE patients following a UV-B

skin challenge on non-lesional skin
- To evaluate the test-retest variability of the UV-B challenge in healthy volunteers and CLE patients
Secondary Objectives
- To evaluate disease-related characteristics and biomarkers in patients with CLE compared to healthy volunteers
- To evaluate time-related changes in disease-related characteristics in patients with CLE

Study design

This is a single-center study in which 10 healthy volunteers and 6 cutaneous lupus patients will be included to characterize the dermal immune response following a UV-B challenge. After 5 healthy volunteers completed challenge period 1, an interim analysis will commence to determine the optimal time point for skin biopsy sampling focusing on the type I interferon response. This time point will be implemented in the patient part.

Healthy volunteers

After the screening visit, in which the minimal erythema dose (MED) will be determined, the skin of the upper back will be challenged with two-times MED UV-B irradiation on three 1cm2 squares on the back in challenge period 1. Skin punch biopsies of 4mm will be taken 3h, 6h and 24h post challenge. The site that will be biopsied 24h post challenge will serve as imaging site to characterize the inflammatory response following UV-B irradiation with several non-invasive imaging tools. Imaging will also be performed on unchallenged skin as control. Additionally, one control biopsy will be taken from unchallenged skin of the upper back before the challenge at day 1. Two weeks after the first challenge period, the second challenge period will commence in which one 1cm2 square on the back will be challenged with two-times MED UV-B irradiation and biopsied 24h after the challenge to test repeatability. In total, five skin punch biopsies will be taken from healthy volunteers.

CLE patients

After the screening visit, in which the MED will be determined, the skin of the upper back will be challenged with two-times MED UV-B irradiation on one 1cm2 square on the back. This site will be biopsied at the optimal time point determined after an interim analysis of data of five healthy volunteers. Two weeks later, the same challenge will be performed to determine test-retest variability. The inflammatory response following UV-B irradiation will also be characterized with several non-invasive imaging tools. As control, imaging will also be performed on unchallenged skin. One control biopsy will be taken from unchallenged skin of the upper back during the first challenge period.
In total, three skin punch biopsies will be taken from the CLE patients.

Study burden and risks

Benefit
No medical benefit can be expected for the participants during the study.

Risk assessment
UV irradiation from sunlight is associated with an increased incidence of skin cancer. UV irradiation contains a spectrum of wavelengths with UV-B being one of the risk factors for skin cancer. The UV-B wavelength range used in this study is the narrow band (NB) range 310-315nm, which is also used for phototherapy of skin conditions such as psoriasis. In general, UV-B phototherapy is a very safe treatment modality [Lee, 2005]. In a large study aiming to define the long*term carcinogenic risk of NB*UV-B treatment in humans, no significant association was found between NB*UV-B treatment and basal or squamous cell carcinomas, or melanoma [Hearn, 2008]. Participants with pre-existing risk factor for skin cancer will be excluded.

The UV-B test may induce post-inflammatory hyperpigmentation (PIH) in some cases [Siebenga, 2019]. Typically, at centres performing the UV-B inflammatory test, 3xMED (Minimum Erythemal Dose) of UV-B irradiation is applied to induce sensitisation, however, long-lasting PIH has been associated with 3xMED. As risk mitigation, participants with Fitzpatrick skin type IV, V or VI will be excluded. Dose of UV irradiation will be at max 2xMED. The potential occurrence of hyperpigmentation will be carefully monitored. Before study participation, study participants will be thoroughly informed the potential risk of PIH at the UV irradiation sites. CHDR has run multiple UV-B challenge studies over the last 10 years, without any safety concerns. In only one of these studies, the UV-B challenge was combined with a second inflammatory challenge. In the present study, it could be argued that this is also the case: biopsies will be collected from UV-B-inflamed skin. The biopsy will drive a wound healing response comprising an inflammatory component. It is unknown whether the biopsy procedure on UV-B-inflamed skin increases the risk for PIH. However, based on in-house historical data CHDR has no indications for this.. In the public domain, there are no reports of punch biopsy-driven PIH that the investigators are aware of.

UV provocation in patients with SLE and/or CLE has been reported frequently in literature to study photosensitivity. The last comprehensive literature review was performed by Kim and Chone (2013) summarizing more than 700 patients and up to a dose of 2xMEDx6 days. Minimal side effects were reported in a large multicenter trial *Photoprovocation in cutaneous lupus erythematosus: a multicenter study evaluating a standardized protocol of 1.5 MED*, Kuhn et al. 2011, where a general good tolerability was observed when a 4.5 cm2 section of skin was irradiated with 1.5x MED for a total of three times over three consecutive days. The UV-B exposed skin areas in this study will be limited to 1x1 cm squares on the back.

Study procedures
Albeit all study procedures are considered minimal invasive, participants can experience pain and/or haematoma and in rare cases local infection during and after a skin punch biopsy and/or venepuncture. For characterization of the dermal immune response, skin biopsies are indispensable in this study. A skin punch biopsy can possibly leave a lasting mark on the skin, therefore subjects with a history of hypertrophic scarring or keloid will be excluded. Biopsies will be taken in a minimally invasive manner. Since the diameter is only 4 mm no stitching is necessary.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Eligible healthy volunteers must meet all the following inclusion criteria at

screening:
1. Signed informed consent prior to any study-mandated procedure.
2. Male or female subjects,18-65 years of age at the time of signing informed consent; in general, stable good health as per judgement of the investigator based upon the results of a medical history, physical examination, vital signs, ECG, and laboratory assessments performed at screening. Repeated laboratory testing may be performed at the discretion of the clinical investigator.
3. Body mass index (BMI) > 18.0 and < 32.0 kg/m2.
4. Fitzpatrick skin type I-III (Caucasian).
5. No clinically significant skin disease as judged by the investigator.
6. No history of hypertrophic scarring or keloid.
7. Subject is willing to refrain from application of any topical product (e.g., ointments, cream or washing lotions) on the skin 24 hours prior to every study visit day.
8. Subject is willing to refrain from any direct sun contact to the area being challenged (back) for the duration of the study.
9. Subject has the ability to communicate well with the investigator in the Dutch language and is willing to comply with the study requirements.

Eligible CLE patients must meet all the following inclusion criteria at screening:
1. Signed informed consent prior to any study-mandated procedure.
2. Male or female CLE patients, 18-65 years of age at the time of signing informed consent; in general, stable good health as per judgement of the investigator based upon the results of a medical history, physical examination, vital signs, ECG, and laboratory assessments performed at screening. Repeated laboratory testing may be performed at the discretion of the clinical investigators.
3. Body mass index (BMI) > 18.0 and < 35.0 kg/m2.
4. Fitzpatrick skin type I-III (Caucasian).
5. Patient has the ability to communicate well with the investigator in the Dutch language and is willing to comply with the study requirements.
6. Subject is willing to refrain from application of any topical product (e.g., ointments, cream or washing lotions) on the skin 24 hours prior to every study visit day.
7. Subject is willing to refrain from any direct sun contact to the area being challenged (back) for the duration of the study
8. Participants must have a diagnosis of CLE that fulfils the following:
* Confirmed diagnosis by clinicopathological correlation.
* Receiving one of the following treatments for CLE (stable for a minimum of 8 weeks):
* None
* Hydroxychloroquine
* Methotrexate
* Topical corticosteroids (for the target lesion there will be a wash

out of 2 weeks before the first challenge period)

Exclusion criteria

Eligible healthy volunteers must meet none of the following exclusion criteria at screening:
1. (History of) immunological abnormality (e.g., immune suppression by medication, auto-immune disease, auto-inflammatory disease) that may interfere with study objectives, in the opinion of the investigator.
2. History of skin cancer (basal cell carcinoma, squamous cell carcinoma, melanoma);
3. Diagnosis of systemic lupus erythematosus (SLE) according to the EULAR-ACR criteria (2019) or substantial indication for systemic involvement.
4. Have any current and/or recurrent clinically significant skin condition, including tattoos, in the skin area of interest (back).
5. Antibiotic use, operation, or intervention by surgeon/dentist within one month before Day 1.
6. Positive hepatitis B surface antigen (HbsAg), hepatitis C antibody (HCV ab), or human immunodeficiency virus antibody (HIB ab) at screening.
7. Participation in an investigational drug study within 3 months prior to screening or more than 4 times a year.
8. Loss or donation of blood over 500mL within three months prior to screening.
9. The use of any medication within 28 days prior to Day 1 (apart from the allowed CLE-medication in patients), if the investigator judges it may interfere with the study objectives.
10. History of alcohol abuse or consumption exceeding 5 standard drinks per day on average within 3 months of screening. Alcohol consumption will be prohibited from at least 24 hours preceding each study visit.
11. Positive urine test for drugs or history of drug abuse at screening. Urine drug test may be repeated at the discretion of the investigator.
12. Pregnant, a positive pregnancy test, intending to become pregnant during the study conduct, or breastfeeding.
13. (A history of) any clinically significant medical condition, factor or abnormality that might interfere with study conduct or interpretation, as judged by the investigator.
14. A minimal erythema dose (MED) higher than 355 mJ/cm2 at screening.
15. Any active or chronic and/or uncontrolled condition that, in the opinion of the investigator, may influence study conduct or interpretation.

Eligible CLE patients must meet none of the abovementioned and following exclusion criteria at screening:
1. Presence of a relevant skin infection or disease in the target areas other

than the observational disease (CLE), inclusively, but not limited to atopic dermatitis, psoriasis vulgaris and dermatomycosis.
2. Having received treatments for CLE or any other disease within the following intervals prior to Day 1:
a. < 2 weeks for topical treatment, e.g., corticosteroids at target area(s).
b. < 6 weeks for systemic therapy with immunosuppressive agents (other than hydroxychloroquine).
c. < 12 weeks for biologics.
d. < 8 weeks procedure or surgery in or close to the target areas.
e. < 3 months for chemotherapeutical treatment.
3. Low complement (C3 and/or C4) levels at screening (< ULN).
4. Positive ANA and anti-dsDNA and/or anti-SM antibodies at screening.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-10-2023
Enrollment:	16
Type:	Actual

Ethics review

Approved WMO

Date:	29-09-2023
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-02-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL85040.056.23