A dermal inflammatory challenge study to evaluate complement activation in healthy volunteers

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Primary objectives• To evaluate complement activation after topical imiquimod challenge• To evaluate complement activation after local UV-B challenge

Ethical review	Approved WMO
Status	Completed
Health condition type	Immune disorders NEC
Study type	Interventional

Summary

ID

NL-OMON50971

Source
ToetsingOnline

Brief title
Local complement activation after dermal inflammatory challenge

Condition

- Immune disorders NEC
- Epidermal and dermal conditions

Synonym
complement activation, Inflammation

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Q32bio

Intervention

Keyword: Challenge, Imiquimod, Inflammation, UV-B

Outcome measures

Primary outcome

• Complement factors in skin biopsies following imiquimod challenge

• Complement factors in skin biopsies following UV-B challenge

Secondary outcome

• Perfusion by LSCI

• Erythema by Antera 3D and clinical evaluation

Study description

Background summary

Inflammation is a response to damaged tissue and/or pathogens resulting in cellular activation and a release of cytokines. Although inflammation is in principle a healthy process, in some cases an excessive and/or poorly regulated inflammatory response can be harmful to the host, which is the case in many inflammatory disorders.
Toll-like receptors belong to the family of pattern recognition receptors (PRRs). These highly conserved receptors recognize pathogen-associated molecular patterns (PAMPs) and danger associated molecular patterns (DAMPs). Detection of PAMPs by mediators of innate immunity brings multiple components of immunity into play, including the complement system. One part of the complement system is a collection of proteins (C5-C9) that, when activated, form aggregates that punch holes in the cell membranes of targeted microbes, killing the cells by lysis. The complement system also includes serum glycoproteins that, when activated, promote uptake of microorganisms by phagocytes (opsonization). As such, the complement system is a first line of defense for fighting pathogens and clearing apoptotic cells. However, when hyperactivated, it is a driver of a variety of autoimmune and inflammatory diseases. Investigational products are under development for regulation of complement, preferably directly to diseased tissues without long-term systemic blockade, minimizing the risk of serious infections and other complications. An in vivo complement activation model would be of great benefit for the early clinical evaluation of the pharmacological activity of novel

complement-targeting investigational compounds, but such a model is not readily available. The current study will evaluate the capacity of 2 common and clinically well-characterized innate immune triggers (UV-B and imiquimod) to drive complement activation in vivo.
Imiquimod is an imidazoquinolone drug acting as TLR7 agonist, exhibiting tumoricidal and anti-viral effects both in vitro and in vivo (Hanna et al, 2016). Aldara® (imiquimod 5%) cream is on the market for treatment of (pre)malignant and HPV-induced skin lesions (see SPC Aldara). CHDR has extensive experience with the topical imiquimod challenge model in which repeated exposure of tape-stripped skin to Aldara results in the development of psoriasis-like inflammatory lesions. 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 increase into the skin. CHDR has applied this model frequently in the field of inflammatory pain studies.
In this study, we aim to evaluate complement activation after local imiquimod and UV-B exposure in healthy volunteers. Readouts will be based on non-invasive measures (local erythema, perfusion, temperature) and invasive measures (IHC and mRNA analysis of skin punch biopsies, for cytokines/chemokines, immune cells, and complement factors).

Study objective

Primary objectives
• To evaluate complement activation after topical imiquimod challenge
• To evaluate complement activation after local UV-B challenge

Study design

This is a single-centre, two-part inflammatory challenge study in healthy volunteers, to evaluate complement activation by imiquimod and UV-B in two parallel groups of healthy volunteers. In the first study part, two cohorts of 5 volunteers will undergo a topical UV-B or imiquimod challenge, accompanied by non-invasive imaging and serial biopsies of the challenge sites. In the second study part, one of both challenges may be repeated in a group of 5 additional volunteers to confirm the outcomes of the first study part, and optimize the timing of assessments, if necessary.

Intervention

Imiquimod
Aldara 5% is a cream containing the active ingredient imiquimod (50 mg/g). In general use, maximum application duration is up to 16 weeks with 3-5 applications per week depending on the indication (see SPC). A dosage of 5 mg imiquimod (100 mg Aldara®) per treatment site will be applied, for 3 days.

UV-B
As part of the screening assessments, the subject*s Fitzpatrick skin photo type is determined (type I - VI). The subject is first exposed to 6 different doses of UV-B, to determine the Minimal Erythemic Dose (MED) expressed in J/cm2, using the six different slots of the UV-B lamp. Twenty-four hours (± 2 hours) after the exposure of the 6 doses, the erythemic response of the skin to UV-B is assessed by two observers. The MED is determined visually, by observing which dose produces the first clearly discernible erythema. On the treatment days, the subject*s skin is exposed to two minimal erythema doses (2MED) of UV-B.

Study burden and risks

Aldara / imiquimod
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 (SmPC) in D2 for additional non-clinical and clinical information. Treatment with imiquimod appears to be safe and reasonably tolerated. Nevertheless, there are some potential skin reactions including erythema, oedema, vesicles, erosions/ulcerations, weeping/exudate, flaking/scaling/dryness and scabbing/crusting. Therefore, possible skin reactions should be monitored carefully during treatment. 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). CHDR has run multiple topical imiquimod challenge studies over the last 3 years, without any safety concerns. Imiquimod exposure in this study will be within the normal therapeutic range, at a limited duration.
UV-B
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 2 x MED. 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.
Skin punch biopsies
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 3 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

1. Healthy male subjects, 18 to 65 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, coagulation, 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. Subjects and their partners 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.

Exclusion criteria

Eligible subjects must meet none of the following exclusion criteria at screening:
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. History of skin cancer (basal cell carcinoma, squamous cell carcinoma, melanoma);
3. Have any current and / or recurrent clinically significant skin condition at the treatment area (i.e. atopic dermatitis); including tattoos;
4. History or presence of post-inflammatory hyperpigmentation.
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. Chronic infection with HIV, hepatitis B (HBV) or hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test at screening excludes a subject;
11. A history of ongoing, chronic or recurrent infectious disease;
12. Current smoker and/or regular user of other nicotine-containing products (e.g., patches);
13. History of or current drug or substance abuse considered significant by the PI (or medically qualified designee), including a positive urine drug screen.

14. Previous use of Aldara (IMIQUIMOD cream) 3 weeks prior to the baseline visit;
15. Tanning due to sunbathing, excessive sun exposure or a tanning booth within 3 weeks of enrollment.
16. A minimal erythema dose (MED) higher than 355 mJ/cm2 at screening.
Applicable for the participants in the UVB-MITT population only.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	19-02-2021
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aldara 5% ®
Generic name:	Imiquimod
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	11-01-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	11-02-2021
Application type:	First submission
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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 23725
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2020-005595-35-NL
CCMO	NL76227.056.20

Study results

Date completed:	16-04-2021
Results posted:	01-08-2022

First publication
09-03-2022