Local complement activation after dermal inflammatory challenge

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON23725

Source
Nationaal Trial Register

Brief title
CHDR2036

Health condition

Inflammation

Sponsors and support

Primary sponsor: CHDR
Source(s) of monetary or material Support: Sponsor

Intervention

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 tapestripped 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

Baseline till EOS

Intervention

Imiquimod
UV-B

Contacts

Public
Centre for Human Drug Research
M. Moerland

+31 71 5246 400
Scientific
Centre for Human Drug Research
M. Moerland

+31 71 5246 400

Eligibility criteria

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

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

Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	19-02-2021
Enrollment:	15
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Plan description
N.A.

Ethics review

Positive opinion

Date:	05-03-2021
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 50971
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL9304
CCMO	NL76227.056.20
OMON	NL-OMON50971

Study results

Summary results
N.A.