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

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Primary* To immunologically characterize imiquimod-induced inflammation after 7-day exposure of healthy skin;* To evaluate local complement activation/depositions after a prolonged topical imiquimod challenge;* To evaluate systemic activation of...

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

Summary

ID

NL-OMON51378

Source
ToetsingOnline

Brief title
In vivo immune activation after prolonged TLR-7 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: CHDR sponsered study

Intervention

Keyword: Complement activation, Immune activation, Inflammation, TLR7

Outcome measures

Primary outcome

* Cytokines and immune cells in skin biopsies

* Local complement factors in skin biopsies

* Complement factors and activation markers in blood samples

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 physiological 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 defence for fighting pathogens and clearing apoptotic cells. However, when hyperactivated, it is a driver of a variety of autoimmune and inflammatory diseases, making it an interesting target for drug development. An in vivo complement activation model would be of great benefit for clinical evaluation of the pharmacological activity of novel complement-targeting investigational compounds, but such a model is not readily available.

Study objective

Primary
* To immunologically characterize imiquimod-induced inflammation after 7-day exposure of healthy skin;
* To evaluate local complement activation/depositions after a prolonged topical imiquimod challenge;
* To evaluate systemic activation of complement after imiquimod challenge

Secondary
* To characterize the clinical response to prolonged imiquimod challenge over a 7-day imiquimod treatment period;

Study design

This is a single-center, inflammatory challenge study in healthy volunteers, to evaluate immune cell and complement activation by prolonged exposure to imiquimod. 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

ALDARA 5% cream

Study burden and risks

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. In these studies, imiquimod was applied at a dosage of 5 mg (100 mg Aldara®), with a maximum of 15 mg imiquimod (CHDR1430) and 60 mg (CHDR1631) a day for 2 or 3 consecutive days. In this study, imiquimod will be applied for 7 consecutive days. Five (5) areas per subject will be treated with imiquimod on the back.

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 tolerated. 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).

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 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.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

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. 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. 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

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-01-2022
Enrollment:	10
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	30-11-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-12-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	03-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-02-2022
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
EudraCT	EUCTR2021-005429-26-NL
CCMO	NL79321.056.21