Development of a dermal TLR4 challenge in healthy volunteers.

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To characterize the response to intradermal LPS by:- Clinical measures- Biophysical measures- Imaging- Molecular and cellular responses- Routine safety measures

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Epidermal and dermal conditions
Study type	Interventional

Summary

ID

NL-OMON46799

Source
ToetsingOnline

Brief title
Skin inflammation challenge with TLR4 agonist

Condition

- Epidermal and dermal conditions

Synonym
Skin inflammation

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Skin inflammation, TLR4 agonist

Outcome measures

Primary outcome

Tolerability / safety endpoints

• Monitoring Adverse events (AEs)

• Monitoring BP, HR and T

• Local tolerance (Numeric Rating Scale (NRS) pruritus and pain)

• Circulating cytokines (TNFα, IL-6, IL-8, IL-1β), complement activation

Pharmacodynamic endpoints

Non-invasive measures:

• Perfusion by Laser speckle contrast imaging (LSCI)

• Erythema by Antera 3D camera

• Erythema by clinical evaluation (erythema grading scale)

• Temperature by thermography

Invasive measures:

• Biopsies:

o Cytokines and chemokines (mRNA, TBD)

o Histology (HE)

o Immunohistochemistry:

- Neutrophils

- Monocytes/macrophages

- CD4+ lymphocytes

- CD8+ lymphocytes

- CD56+ lymphocytes

- CD1c dendritic cells

• Suction blister exudates:

o Cytokines and chemokines (protein, TBD)

o Flow cytometry:

- Neutrophils

- Monocytes/macrophages

- CD4+ lymphocytes

- CD8+ lymphocytes

- CD56+ lymphocytes

- CD1c dendritic cells

Secondary outcome

N.A.

Study description

Background summary

Inflammation is a response to damaged tissue and/or pathogens resulting a release of cytokines and subsequent cellular activation. 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 belongs to the family of pattern recognition receptors (PRRs). These highly conserved receptors recognize pathogen-associated molecular patterns (PAMPs) and danger associated molecular patterns (DAMPs). Upon recognition PRRs induce the activation of a strong inflammatory response and thereby kick starting the innate immune response. Toll-like receptor 4 (TLR4) is able to recognize several exogenous ligands of which

lipopolysaccharides (LPS) found on gram-negative bacteria is best known (Molteni et al. 2016).

Systemic LPS administration in humans is a widely used, safe and well tolerated method to study a controlled systemic inflammatory response (Andreasen et al. 2008, Van Poelgeest et al. 2018). This inflammatory response offers a platform for the investigation of pharmacodynamic and potentially clinically significant effects in early drug development. The disadvantage of a systemic LPS challenge is that it is relatively burdensome for the volunteer, and that it cannot be repeated over time. A local LPS challenge model could be an interesting drug development tool, since it would allow repeated or multiple LPS stimulations over time within one volunteer. However, a local dermal response to LPS in healthy humans has only been studied once (Basran et al. 2013). Their interest was mainly in neutrophil recruitment, therefore a more in depth characterization of the TLR4 response to LPS in human skin is still lacking.

In 2016 Motwani et al. presented a challenge model in which they injected UV-killed E. coli (a Gram-negative bacterium and thus containing LPS) intradermally in healthy volunteers. Although UV-killed E. coli led to a strong but transient local inflammatory response, the downside is that E. coli contains multiple different PAMPs, which makes the subsequent inflammatory response less specific.
Specific knowledge on the TLR4 response in human skin is of interest because TLR4 signaling is indicated in several skin diseases such as psoriasis and acne vulgaris.

The aim of this study is to characterize the inflammatory response upon intradermal LPS injection in healthy volunteers. By doing so we create a challenge model that temporarily induces skin inflammation via a specific pathway which enables future application as proof-of-pharmacology or drug profiling in drug developmental programs.

Study objective

To characterize the response to intradermal LPS by:
- Clinical measures
- Biophysical measures
- Imaging
- Molecular and cellular responses
- Routine safety measures

Study design

A saline controlled, interventional study to characterize the inflammatory response to intradermal LPS in healthy volunteers.

Intervention

LPS, purified lipopolysaccharide prepared from Escherichia Coli: 113: H10:K negative (U.S. Standard Reference Endotoxin)

Study burden and risks

No medical benefit can be expected from this study for the participating subjects.
Risk assessment
Expected adverse events related to LPS administration
Intravenous administration of LPS can lead to influenza-like symptoms (e.g. chills, headache, eye sensitivity to light, nausea, myalgia and arthralgia), increase in core temperature and pulse rate, and decline in mean arterial pressure. Most symptoms are dose-related and resolve within 2-6 hours. (Andreasen et al., 2008). As with any study involving administration of exogenous substance, rare side effects cannot be excluded beforehand. Reports of a decrease in cardiac contractility have been made following administration of 4 ng/kg bodyweight (Suffredini et al., 1989), but were temporary and were resolved after 8 to 12 hours. Noteworthy, CHDR has extensive experience with both in vivo and ex vivo LPS challenges (Dillingh et al., 2014; Monnet et al., 2017; van Poelgeest et al., 2018) and will not administer a LPS dosage of more than 0.5 ng/kg - 0.8 ng/kg (based on body weight of 50 kg - 80 kg), thereby minimizing the chance of stated adverse events ever happening Basran et al. have administered up to 45 ng LPS divided over 3 intradermal injections and this led a localized painless erythema, and no adverse effects deemed to be related to systemic LPS exposure were observed. A related study by Gilroy et al. used UV-killed E. coli to induce an intradermal inflammatory response. This inflammatory response peaked at 4-6 hours and subsided over a period of approximately 48 hours. In this current study the LPS challenge will provide a safer and more controlled alternative when compared to the UV-killed E. coli challenge.

Expected adverse events related to the suction blister device
During the study suction blisters will be induced on the LPS and saline injected skin. The suction blister device (NP-4, Electric Diversities, Maryland, USA) is widely used in dermatological research settings. Using negative pressure (up to 8 in/Hg) a 10mm diameter blister is formed in approximately 60 to 90 minutes. The blister formation process is not painful. Once the blister is formed the roof is pierced with a needle and the blister fluid is aspirated, after which the blister is dressed with a small gauze. Rare complications of a the blister include infection and post inflammatory hyperpigmentation. To minimize the risk of post inflammatory hyperpigmentation Fitzpatrick skin types 4-6 are excluded.

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 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;
2. Body mass index (BMI) between 18 and 30 kg/m2, inclusive, and with a minimum weight of 50 kg;
3. Fitzpatrick skin type I-III (Caucasian);
4. 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. Any disease associated with immune system impairment, including auto-immune diseases, HIV and transplantation patients;
2. Any vaccination within the last 3 months;
3. Family history of psoriasis;
4. History of pathological scar formation (keloid, hypertrophic scar);
5. Have any current and / or recurrent pathologically, clinical significant skin condition at the treatment area (i.e. atopic dermatitis);
6. Hypersensitivity for dermatological marker at screening;
7. Requirement of immunosuppressive or immunomodulatory medication within 30 days prior to enrollment or planned to use during the course of the study;
8. Excessive sun exposure or a tanning booth within 3 weeks of enrollment;
9. Participation in an investigational drug or device study within 3 months prior to screening or more than 4 times a year;
10. Loss or donation of blood over 500 mL within three months prior to screening. Or the donation of plasma within 14 days prior to screening;
11. Current smoker and/or regular user of other nicotine-containing products (e.g., patches);
12. History of or current drug or substance abuse considered significant by the PI (or medically qualified designee), including a positive urine drug screen.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-08-2018
Enrollment:	18
Type:	Actual

Ethics review

Approved WMO Date:	16-05-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-08-2018
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	NL65297.056.18