A randomized, evaluator-blind, vehicle controlled, parallel group study to explore the effects of the anti-inflammatory drug prednisolone in a TLR4 and TLR7 challenge model in healthy volunteers

Published: 30-09-2019
Last updated: 15-05-2024

Primary Objectives* To assess the pharmacodynamic effects of systemic prednisolone on the LPS- or IMQ-induced inflammatory response* To assess safety & tolerability of intradermal LPS and topical IMQ in combination with prednisoloneSecondary...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin and subcutaneous tissue disorders NEC
Study type	Interventional

Summary

ID

NL-OMON55304

Source
ToetsingOnline

Brief title
Anti-inflammatory drugs in TLR4 and TLR7 topical challenge model

Condition

- Skin and subcutaneous tissue disorders NEC

Synonym
Dermatological challenge model, skin inflammation model

Research involving

Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: CHDR-funded study

Intervention

Keyword: Imiquimod, LPS, Prednisolone, TLR4 and TLR7 challenge

Outcome measures

Primary outcome

Tolerability / safety endpoints

* Adverse events (AEs)

* Vital signs

* 12-leads ECGs

* Local tolerance (erythema grading scale, numeric rating scale (NRS) pruritus

and pain)

Pharmacodynamic endpoints

Non-invasive measures:

* Perfusion by Laser speckle contrast imaging (LSCI)

* Erythema by Antera 3D camera

* Erythema by clinical evaluation (erythema grading scale)

* Optical Coherence Topography (OCT) (part A only)

* 2D photography by ATBM for photo documentation only (part A only)

Invasive measures:

* Suction blister exudates, including but not limited to

o Cytokines and chemokines

o Flow cytometry (for example: neutrophils, monocytes/macrophages, CD4+

lymphocytes, CD8+ lymphocytes, CD56+ lymphocytes, CD1c dendritic cells)

* Skin punch biopsies

o Local biomarkers, may include but is not limited to,: IL-8, IFN-*, IL-1*,

IFN-*, MXA, MX1, IL-6, IL-10, CCL20 and HBD-2

o Immunohistochemistry: CD1a, HLADR, CD8+, CD4+, CD14+, CD11c complement

factors, iNOS, Gasdermin, IRAK4

o Histology (HE)

* Ex vivo blood assay

o Ex vivo cytokine release assay (imiquimod, part A only)

o Ex vivo cytokine release assay (LPS, part B only)

o Ex vivo NET assay (Part B only)

Secondary outcome

N.A.

Study description

Background summary

Inflammation is a response to damaged tissue and/or pathogens resulting in 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 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). Upon recognition PRRs induce the activation of a strong inflammatory response and thereby kick starting the innate immune response. Toll-like receptor 7 (TLR7) is an intracellular, endosomal TLR and is able to recognize single stranded (ss)RNA from viruses and the class of imidazoquinolone drugs such as imiquimod (IMQ). Toll-like receptor 4 (TLR4) is a transmembrane TLR to recognize lipopolysaccharide (LPS), a large molecule found on the outer membrane of Gram-negative bacteria. Activation of TLR4 or TLR7 leads to the activation of the central transcription factor, nuclear factor-kB and induces secretion of pro inflammatory cytokines such as tumor necrosis factor alpha (TNF-*), interferon gamma (IFN-*), IFN-*, interleukin(IL)-6, IL-1a, IL-1b, IL-8, IL-12, IL-17, IL-22, IL-23 granulocyte macrophage colony-stimulating factor and granulocyte colony-stimulating factor (innate immunity). All cytokine elevations and local effects have been reported to be reversible. Imiquimod (a TLR7 agonist) has shown to exhibit tumoricidal and anti-viral effects both in vitro and in vivo (Hanna et al, 2016). Aldara (imiquimod 5%) cream is an immune response modifier for topical administration and is currently on the market for (pre)malignant and HPV-induced skin lesions (see SPC Aldara).

Study objective

Primary Objectives
* To assess the pharmacodynamic effects of systemic prednisolone on the LPS- or IMQ-induced inflammatory response
* To assess safety & tolerability of intradermal LPS and topical IMQ in combination with prednisolone

Secondary Objectives
* To explore pharmacodynamic biomarkers determined in blister exudate compared to skin punch biopsies in LPS or IMQ-induced inflammation.

Study design

A placebo controlled, interventional study to assess the anti-inflammatory effects oral prednisolone in an LPS or IMQ skin challenge model in healthy volunteers.

In part A of this study, IMQ will be applied on a tape-stripped skin area on the upper back in combination with oral administration of prednisolone.
In part B of this study subjects will receive a two day pretreatment with oral prednisolone (0.25mg/kg BID) or placebo. At day 1 subjects will receive either two or four intradermal LPS injections on the volar forearm (10ng LPS per injection)

Intervention

Part A ; Imiquimod and Prednisolone
Part B ; LPS and Prednisolone (or placebo)

Study burden and risks

The overall aim of this study is to evaluate the anti-inflammatory and immunomodulatory properties of oral prednisolone in an LPS and IMQ skin challenge model in healthy volunteers. Prednisolone is known for the side effects when used in a high dose for a longer period, however in this study this product is only used for a limited amount of days (up to 4 days) and therefore no lasting effects are likely to occur. We refer to the SPC in D of the submission dossier for more information. No medical benefit can be expected from this study for the participating subjects.

Contacts

Public
Centre for Human Drug Research

Zernikedreef 8
Leiden 2333CL
NL
Scientific
Centre for Human Drug Research

Zernikedreef 8
Leiden 2333CL
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

1. Healthy male or female subjects (part B males only), 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 maximum weight of 100 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. Any vaccination within the last 3 months; COVID19 vaccination is allowed up until 4 weeks prior to the first prednisolone/placebo dosing, and from 2 weeks after the last prednisolone/placebo dosing.
2. Family history of psoriasis;
3. History of pathological scar formation (keloid, hypertrophic scar);
4. Have any current and / or recurrent pathologically, clinical significant skin condition at the treatment area (i.e. atopic dermatitis); including tattoos
5. Previous use of Aldara (IMQ cream) 3 weeks prior to the baseline visit (part A only)
6. Known hypersensitivity to the (non)investigational drug, drugs of the same class, or any of their excipients;
7. Hypersensitivity for dermatological marker at screening;
8. Requirement of immunosuppressive or immunomodulatory medication within 30 days prior to enrollment or planned to use during the course of the study;
9. 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
10. Tanning due to sunbathing, excessive sun exposure or a tanning booth within 3 weeks of enrollment;
11. Participation in an investigational drug or device study within 3 months

prior to screening or more than 4 times a year.
12. Loss or donation of blood over 500 mL within three months prior to screening (part A and B), or donation of plasma within 14 days of screening (part B only)
13. 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.
14. Latent Diabetes Mellitus
15. Volunteers with clinically relevant infections
16. Current smoker and/or regular user of other nicotine-containing products (e.g., patches); or positive urine cotinine test at screening (part B only)
17. History of or current drug or substance abuse considered significant by the PI (or medically qualified designee), including a positive urine drug screen.
18. Subjects that test positive for a SARS-CoV-2 infection
19. Subjects with a BMI > 30 and/or cardiovascular, respiratory or immune system disorders

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-02-2020
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Aldara 5% creme
Generic name:	imiquimod
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Prednisolone solution 5 mg/ml
Generic name:	prednisolone

Ethics review

Approved WMO Date:	30-09-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-12-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-04-2020

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-08-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-03-2021
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

ID: 28349
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2019-003567-21-NL
CCMO	NL71422.056.19
OMON	NL-OMON28349